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DES CHOIX SCIENTIFIQUES ET TECHNOLOGIQUES**

RAPPORT

sur

LES ENJEUX DE LA BIOLOGIE DE SYNTHÈSE

Tome 2 : annexes

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Déposé sur le Bureau de l'Assemblée nationale
par M. Claude BIRRAUX,

Premier Vice-Président de l'Office

Déposé sur le Bureau du Sénat
par M. Bruno SIDO,

Président de l'Office

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INTRODUCTION

PRESIDENCE DE MME GENEVIEVE FIORASO, DEPUTEE, RAPPORTEURE

Mme Geneviève Fioraso, députée de l'Isère, rapporteure. Au nom de l'Office parlementaire d'évaluation des choix scientifiques et technologiques, et de son président, Claude Birraux, qui vous prie d'excuser son absence du fait de sa participation à une table ronde de l'ensemble des présidents des offices au niveau européen, j'ai l'honneur de vous souhaiter la bienvenue. Cette audition publique fait suite à un colloque scientifique sur le thème de la biologie de synthèse. Cette procédure, tout à fait caractéristique de l'OPECST, illustre parfaitement l'ambition qui a présidé à sa création. Il s'est agi en effet, à travers la participation du public et de la presse, de promouvoir le principe de transparence, puisque l'un et l'autre se voient reconnaître le droit d'être présents et de poser des questions, d'échanger. À cet égard, l'OPECST peut être considéré au sein de l'institution parlementaire comme un pionnier, car c'est seulement postérieurement à sa création que les autres commissions se sont vues également conférer la faculté de procéder à des auditions ouvertes à la presse. À travers la promotion du principe de transparence, le législateur a souhaité permettre à l'OPECST de jouer le rôle d'interface entre la communauté scientifique et la société civile, selon une expression chère au président Birraux. À cet égard, cette audition publique répond à cette exigence en étant jumelée à un colloque franco-américain, organisé par la mission scientifique de l'Ambassade de France à Washington. Je tiens à remercier de nouveau cette mission, en particulier Mireille Guyader et Marc Magaud, et également les scientifiques, le professeur François Képès et toute son équipe. Ce colloque s'est tenu hier et ce matin sur ce thème émergent de la biologie de synthèse.

Pour en revenir à l'OPECST, au terme d'une trentaine d'années d'existence, il serait assez présomptueux d'affirmer que l'OPECST est parvenu à rapprocher complètement la communauté scientifique, les médias et la société civile, et à instaurer ce que certains appellent de leurs vœux, et j'en fais partie, la démocratie scientifique ou la démocratie technologique. Le débat parlementaire, trop caricatural sur les OGM – c'est mon point de vue –, ou l'échec récent du débat national sur les nanotechnologies – c'est un point de vue relativement partagé –, montre, s'il en était besoin, que les positions binaires, et la violence parfois, avec laquelle elles peuvent s'exprimer, s'opposent à l'évidence à une approche rationnelle des risques et des avantages des nouvelles technologies, a fortiori des sciences ou technologies émergentes. Mais il ne faudrait pas pour autant méconnaître ou minimiser les possibilités offertes par les auditions publiques. Le thème qui nous réunit aujourd'hui en fournit la démonstration.

La biologie de synthèse se définit par la conception de systèmes biologiques artificiels, qui combinent la modélisation mathématique et la méthode biomoléculaire. Discipline émergente ou évolution de disciplines plus matures, même si j'emploie avec beaucoup de précaution le terme de discipline, tant son statut scientifique est encore hétérogène et en discussion, la biologie de synthèse est une idée neuve pour la communauté scientifique et le public. S'agissant de la communauté scientifique, le paradoxe est d'autant plus étonnant que l'idée même de biologie de synthèse a été forgée en 1912 par un savant français, Stéphane Leduc. On voit donc que la science s'inscrit dans une perspective historique. En outre, déjà dans les années 70, plusieurs travaux pouvaient être considérés comme relevant de la biologie de synthèse. Mais le fait est que, malgré un développement rapide et incontestable des recherches depuis les années 2000, la communauté des biologistes de synthèse serait actuellement limitée dans le monde à un millier de chercheurs, d'après les indications dont je dispose. Comme je viens de le constater lors d'un déplacement au Canada et aux Etats-Unis, le terme même de biologie de synthèse n'est pas utilisé partout, en particulier au Canada, où l'on préfère parler « d'ingénierie biologique ». En ce qui concerne le public, un sondage de septembre 2010 du Woodrow Wilson Institute de Washington montre que rares sont ceux qui connaissent, dans le grand public, la notion de biologie de synthèse.

Dans ce contexte, faut-il pour autant renoncer à faire oeuvre de pédagogie, en permettant au public de prendre connaissance des applications possibles de la biologie de synthèse, comme tentera de le faire la première table ronde ? Il est vrai, des scientifiques que j'ai rencontrés m'ont fait valoir que les déclarations surmédiatisées du chercheur américain Craig Venter par exemple, selon lesquelles il aurait créé la vie et même joué à Dieu – toujours un peu provocateur – ont pu susciter des craintes et desservir les chercheurs, et par là même, compromettre peut-être les recherches à venir. On peut également critiquer le comportement de scientifiques qui donnent une présentation démesurée et immédiate des applications de la biologie de synthèse, en vue de s'attirer les crédits. Mais compte tenu des réductions générales de crédits, on peut aussi avoir une certaine indulgence. Malgré tout, c'est préjudiciable, encore une fois, à la sérénité nécessaire au débat sur les enjeux économiques et sociétaux.

Si l'on présente la biologie de synthèse comme l'eldorado de la biologie du XXI^{ème} siècle, on prend en effet le risque de susciter des craintes, de la part des médias, des politiques, du public, ou de faire naître au contraire des espoirs immédiats qui pourront être déçus. Je ne citerai pas d'exemple. On en a eu avec certaines thérapies qui étaient promises, dans un avenir extrêmement proche, une vingtaine d'années, à guérir toutes sortes de cancers, et dont on a vu en réalité que l'application était beaucoup plus longue. Les effets d'annonce me paraissent tout à fait dommageables à l'instauration d'un débat ouvert, serein, et je dirais objectif et honnête.

Il apparaît donc opportun et raisonnable d'adopter une approche positive des potentialités offertes par la biologie de synthèse. D'ailleurs, l'attitude ouverte de l'opinion publique à l'égard des applications médicales des OGM démontre que les avancées auxquelles il sera possible de parvenir, grâce à la biologie de synthèse dans le traitement de maladies telles que le paludisme ou le cancer, peuvent bénéficier d'un a priori favorable. De même, la question de l'accès à l'énergie est cruciale, d'autant plus dans le contexte d'une actualité récente. Je ne vois pas pourquoi il ne faudrait pas soutenir les travaux visant à promouvoir une chimie plus verte, à travers la fabrication de biocarburants de la troisième génération. Nous avons eu l'occasion de faire un point sur l'état de l'art scientifique, notamment lors de la dernière intervention faite par le Pr Jay Keasling. Je crois que c'était tout à fait intéressant.

Au total, l'évolution de l'attitude d'une ONG comme l'ONG canadienne ETC Group, avec laquelle j'ai eu l'occasion de m'entretenir au Canada, me semble plutôt encourageante, puisque son directeur a confirmé avoir renoncé à son idée initiale de vouloir instaurer un moratoire sur les recherches en biologie de synthèse. Cette ouverture d'une ONG aussi emblématique dans le secteur, puisque je crois que c'est celle qui a le plus travaillé sur la biologie de synthèse, constitue-t-elle un pas suffisant pour parvenir à un débat apaisé et à l'acceptation sociale et sociétale des recherches ? C'est la question qu'abordera la deuxième table ronde, avec le modérateur et mon collègue de l'Office, Daniel Raoul. Sur ce point, j'estime essentiel de désamorcer les craintes que l'opinion publique peut éprouver à l'égard d'un domaine émergent, sur lequel elle n'est pas pour l'heure informée, et qui de plus, est susceptible d'évolutions non connues et difficilement anticipables à ce jour.

À cet égard, la communauté scientifique a un rôle important à jouer. De nombreux chercheurs m'ont affirmé que la biologie de synthèse ne présentait pas plus de risques, en l'état actuel, que le génie génétique ou la biologie systémique, et qu'il existait des moyens plus dangereux que les organismes synthétiques fabriqués en laboratoire, pour se livrer à des exactions ou à des utilisations malveillantes. Mais encore faudrait-il qu'ils le disent clairement à l'opinion publique. En effet, le débat engagé avec la société n'est pas vraiment mûr dans notre pays et en Europe en général. Et pour être pleinement responsable, la commande politique à ce jour n'a pas été formulée. De même, dans les Investissements d'avenir, la thématique de la biologie de synthèse n'est pas clairement identifiée dans les projets à soutenir, dans les projets présentés. Même si elle est bel et bien là, elle est présente de façon diffuse dans quelques projets. Je constate d'ailleurs avec satisfaction que les scientifiques que j'ai rencontrés sont tout à fait conscients et volontaires pour engager cette communication et ce dialogue, qu'on appelle souvent dialogue entre science et société. Je souhaite d'ailleurs que l'ensemble des projets scientifiques soutenus par les Investissements d'avenir, et plus largement par tous les organismes qui dépendent, soit du Ministère de l'industrie, soit du Ministère de l'Enseignement supérieur et de la Recherche, consacrent une partie de leurs dotations à la

communication scientifique et au dialogue avec la société en utilisant les outils existants. Je pense aux centres culturels, scientifiques, techniques, industriels par exemple, mais aussi à bien d'autres outils.

Quant à l'opinion publique, les informations que j'ai pu recueillir sur l'expérience britannique de dialogue avec la société civile, avec des formations préalables, cela me paraît très important, et des réunions publiques organisées sur l'ensemble du territoire, montrent la grande pertinence des questions posées par le public, sa maturité et son bon sens. Le bon sens et la maturité dont il fait preuve lorsqu'il est réellement impliqué et préparé à s'engager dans une démarche de connaissance partagée.

Mais pour que cet effort de pédagogie collective porte pleinement ses fruits, il me semble donc indispensable que trois conditions soient remplies :

1. **La nécessité de revoir l'enseignement des sciences** dans l'ensemble de notre système éducatif, afin qu'elle ne soit plus considérée comme un vecteur de sélection, mais bien comme un moyen d'épanouissement, de stimulation de la curiosité et de la créativité, contribuant ainsi à l'éveil de vocations scientifiques.

2. **Le rôle des médias** : à l'évidence, il est difficilement concevable, alors même que l'accent est mis sur le développement de l'économie de la connaissance, que les médias ne contribuent pas davantage à l'éducation scientifique du public. J'ai ainsi à plusieurs reprises déploré que, contrairement à la Grande-Bretagne, il y ait en France si peu d'émissions scientifiques de qualité à la télévision. Je n'oserais pas qualifier la seule émission qui ait lieu. Vous reconnaîtrez les deux frères. Je préfère ne pas en dire davantage. La plupart des documentaires scientifiques qui nous sont présentés ne sont pas, ou très rarement, réalisés en France. Dans ce cadre, au Royaume-Uni, la Royal Society propose des formations adaptées aux journalistes qui le souhaitent, afin de les informer sur l'état de l'art des recherches scientifiques et de leurs applications. On est bien dans une démarche coopérative et responsable.

3. **Adopter une nouvelle approche du principe de précaution**. Loin de moi l'idée de vouloir remettre en cause ce principe intégré dans notre Constitution, mais il m'apparaît nécessaire de revenir à son état d'esprit initial, en réaffirmant qu'il est un principe d'action, et pas un principe « de parapluie » ou un frein qui empêcherait les recherches. La notion de vigilance prudente et évolutive préconisée par la commission de bioéthique américaine me paraît être une position plus équilibrée, disons plus claire et moins sujette à interprétation. En effet, elle prend en compte la nécessité de ne pas entraver les recherches dans un domaine émergent, sans perdre de vue le devoir de procéder à un réexamen régulier de l'adéquation des réglementations. Le service de la science et de la technologie rattaché au Président Obama m'a déclaré qu'il avait engagé ce processus de réexamen, la suite du rapport qui lui avait été demandé par le pouvoir politique, par le Président Obama lui-même, par une lettre de mission. J'aimerais qu'en France on reprenne cette responsabilité. L'Office a tout son rôle à jouer dans cette

démarche. Ce processus de réexamen a été engagé à nouveau, et il me semble particulièrement adapté, de par son caractère évolutif, à un secteur aussi émergent et aussi évolutif que la biologie de synthèse. Quel pourrait être le comportement qu'il conviendrait de promouvoir, si la France, et au-delà l'Europe, veulent exploiter pleinement les atouts dont elles disposent, avec le soutien du public et de la société ? De ce point de vue, le principe de précaution, dans son état d'esprit initial, tel qu'il a été inscrit dans la Constitution, n'est pas en contradiction avec ces objectifs. Même si je ne sous-estime pas les difficultés d'une telle tâche, surtout en cette période de réduction budgétaire pour les laboratoires de recherche publique, cette conviction qui est la mienne s'appuie sur les propos de Jefferson affichés sur le mur d'entrée de l'Académie nationale américaine des sciences : « La liberté est le grand-parent de la science et de la vertu. Une nation sera grande dans l'une et l'autre, toujours en proportion de son attachement à la liberté. » L'autre citation prétend que « le droit de rechercher la vérité implique également que l'on ne doit pas dissimuler quoi que ce soit de ce que l'on a reconnu être vrai. » Tel pourrait être le comportement qu'il conviendrait de promouvoir. Ces deux phrases, ces deux convictions fortes, sont toujours d'actualité. Elles pourraient utilement inspirer et servir de guide à l'éthique dans laquelle nos recherches doivent être menées, l'éthique avec laquelle le pouvoir politique doit s'engager. On doit pouvoir réentendre les politiques sur les thèmes de la recherche et de ses applications industrielles, de la recherche et de ses enjeux sociétaux. Même si ces sujets ne sont pas très porteurs pour une carrière politique, j'en sais quelque chose, c'est quand même extrêmement porteur pour notre vie quotidienne, et extrêmement porteur également pour la création d'emplois. Les médias le soulignent suffisamment : l'emploi est la priorité première de 87% des Français. Nous avons aussi cette préoccupation à partager avec les chercheurs et les scientifiques. Et je pense que c'est assez général et que cela peut s'étendre aux Etats-Unis. Nos amis américains pourront en témoigner, avec un taux de chômage qui atteint et qui a même dépassé à un moment les 10%, ce qui est historique.

Les thèmes des deux tables rondes ont une relation directe avec ces préoccupations.

- La première, consacrée aux applications industrielles, permettra d'aborder notamment des questions dont je n'ai pas parlé, parce que je crois que cela va être largement abordé, liées à la propriété intellectuelle et à la propriété industrielle. Je pense que c'est un sujet réellement important, encore plus prégnant peut-être encore dans les sciences du vivant, puisqu'il faut promouvoir une démarche qui protège à la fois l'accès ouvert à la recherche et un développement industriel qui permette la création d'emplois, qui reconnaisse la créativité des applications, et qui permette également le développement de produits utiles pour l'énergie, l'environnement, la chimie verte et la santé.

- La deuxième, consacrée aux défis sociétaux, sera l'occasion de s'interroger sur l'opportunité et les conditions d'un débat public, et d'aborder

également les questions liées à la sécurité et à la sûreté.

Je passe la parole à Françoise Roure, qui représente aujourd'hui le Ministère de l’économie et de l’industrie. Je me réjouis de l’accueillir, parce qu’elle a beaucoup travaillé sur la biologie de synthèse. De plus, elle a une connaissance européenne, et même internationale de l’état de l’art dans le domaine. C’est elle qui animera cette première table ronde, avec de la conviction et de fortes compétences.

PREMIERE TABLE RONDE : LES ENJEUX INDUSTRIELS

MODERATEURS :
Mme FRANÇOISE ROURE, PRESIDENTE DU COMITE « TECHNOLOGIES ET SOCIETE » DU CONSEIL CONSULTATIF NATIONAL DE L'INDUSTRIE, DE L'ENERGIE ET DES TECHNOLOGIES, ET
M. JONATHAN BURBAUM, PROGRAM DIRECTOR, ADVANCED RESEARCH PROJECTS AGENCY - ENERGY U.S. DEPARTMENT OF ENERGY

Mme Françoise Roure. Je vous remercie. Nous sommes deux modérateurs M. Jonathan Burbaum, directeur de programme à *l'Advanced Research Projects Agency* au Département de l'énergie américain, et moi-même. Après une introduction aux enjeux industriels tels que nous les voyons depuis nos prismes, nous aurons une session composée de trois intervenants : une start-up et un grand groupe en ce qui concerne l'application de la biologie de synthèse au domaine énergétique, et un troisième intervenant abordera les aspects relatifs à l'apport de la biologie de synthèse dans le secteur de la chimie.

J'appartiens au Conseil général de l'industrie et des technologies qui est présidé par la ministre chargée des questions économiques, Mme Christine Lagarde. À ce titre-là, je suis en charge des questions relatives aux nanotechnologies et aux technologies émergentes. C'est probablement la raison pour laquelle j'ai eu le temps de m'investir sur ces sujets-là.

Je voudrais vous faire part de quelques propos préliminaires en matière d'enjeux industriels, car les aspects sociétaux conditionnent la traduction d'une avancée scientifique et technique dans l'innovation et le marché. L'affaire est entendue et la table ronde suivante sera dédiée à ces questions. Nous centrons donc la présente table ronde sur les enjeux industriels. Elle a pour objectif de cerner les opportunités et les éventuelles barrières (non tarifaires) à lever pour assurer le développement responsable et durable de solutions attendues par les consommateurs et les citoyens pour la qualité et la sécurité de leur vie quotidienne, et ce sur tous les continents.

Comme vous le savez, le développement durable tel que défini dans les instances internationales intergouvernementales repose sur trois piliers, un pilier économique, avec sa création d'emplois, un pilier social et un pilier environnemental. Et il y a un fort enjeu dans la réorientation des activités industrielles vers la création nette d'emplois dans les pays industrialisés de longue date. Ces aspects sont définis, en particulier par domaines d'application, dans le rapport de l'OCDE sur la bioéconomie à l'horizon prospectif de 2030, auquel je vous renvoie.

Les nanotechnologies, dont les technologies de l'ADN, apportent une dimension nouvelle et une échelle de taille et de temps d'observation aux sciences et techniques. Elles ouvrent la voie à des processus de production industriels qui incorporent des éléments biologiques mais pas seulement. La conjonction des lois de Moore et de Carlson et le perfectionnement de la robotique intelligente rendent économiquement accessibles des technologies pour la production industrielle en matière de biologie de synthèse. Il est donc intéressant de réunir un panel à ce stade.

Elles ouvrent aussi la voie aux innovations issues de la convergence dite « *Nano-Bio-Info-Cogno* », à l'échelle nanométrique, c'est-à-dire entre des technologies qui ont chacune un fort potentiel transformationnel et d'entraînement sur l'ensemble des filières industrielles et de l'économie. C'est un sujet qui a été traité par l'Académie française des technologies, en particulier en juin 2010. Serait-il éthique en ces temps de crises systémiques de se priver de solutions industrielles sobres en carbone et durables, qui permettent de desserrer les contraintes de stock limité de matières brutes et de surmonter les limites à la chimie du médicament ? Cette question est véritablement importante.

Mais au-delà de l'éthique, les investisseurs et les régulateurs demandent un cadre sûr pour accompagner les recherches et les innovations de la biologie de synthèse. À quelles conditions peut-on leur répondre que la biologie de synthèse est sûre ? Comment s'assurer que le cadre réglementaire sera approprié aux spécificités de la biologie de synthèse, afin qu'elle réalise tout son potentiel avec la confiance des populations ?

Le concept d'orthogonalité, je crois que vous l'avez travaillé en particulier dans la journée d'hier, fait partie de la réponse. C'est une opportunité, car ce concept est dans la culture des biologistes. Il fait écho à la culture du contrôle à laquelle faisait référence ce matin Nadrian Seeman de l'Université de New York (*Department of Chemistry*). Il y aura probablement lieu d'y revenir dans le débat.

Parmi les décalages à surveiller, les décalages potentiels qui pourraient effectivement s'accroître dans le temps, figure la question de la démocratisation de l'accès au savoir, pour l'enseignement auquel vous êtes sensible madame la députée, et pour les clusters de l'innovation. La question de la bio-informatique et des logiciels ouverts open source pour la représentation et l'organisation des connaissances font partie des enjeux aujourd'hui. Seront-ils payants ou ouverts ? Et avec quels effets ?

La démocratisation de l'accès aux savoirs fondamentaux conditionne en effet la démocratisation de l'innovation et la libération de la créativité, y compris pour éviter ou contenir des aspects non souhaités, comme la toxicologie ou l'écotoxicologie, issus de manière volontaire ou plutôt involontaire de produits industriels.

L’équilibre entre les aspects ouverts et ceux qui seront protégés par la propriété intellectuelle est ici crucial pour toutes les parties prenantes : sans les premiers (l’accès ouvert), il pourrait ne pas y avoir de seconds, ceux qui, avec valeur ajoutée, permettront la protection de la propriété intellectuelle et la commercialisation, à laquelle M. Jonathan Burbaum est aussi très attaché.

Les normes et les bases de données sur les propriétés fondamentales sont une clé, avec l’émergence de marché des savoirs sous forme de banques de données, qui – elles – seront protégées par la propriété intellectuelle en tant que de besoin.

Les aspects industriels sont actuellement discutés sous l’angle de la normalisation, dans une enceinte comme par exemple l’ISO (*International Organization for standardization* - Organisation internationale pour la normalisation). La définition ISO des nanomatériaux, nano-objets et objets nanostructurés inclut les éléments et systèmes biologiques à l’échelle nanométrique sur lesquels reposent les technologies de l’ADN. C’est quelque chose qui est relativement peu su, et pourtant cela donne lieu à des discussions sur les définitions et l’accord des industriels, à leur demande.

Les discussions sur la nano-énergie et sur la nanomédecine sont d’ores et déjà lancées dans cette instance ISO, sous l’angle des nanotechnologies, parce que les industriels y ont intérêt. Dans le même temps, les chercheurs de la biologie de synthèse sont invités à participer à des éléments qui sont en cours de développement dans cette instance. Je pense en particulier aux aspects relatifs à la nanomédecine, à la nanobiotechnologie et à la nano-énergie. Cependant, la participation des chercheurs aujourd'hui laisse à désirer. Heureusement, l’Union européenne a décidé de financer l’apport de chercheurs dans ces programmes de recherche scientifique et technique pour la normalisation. L’industrie en a absolument besoin pour sécuriser notamment les contrats B to B (*Business to Business*).

Je voudrais formuler trois propositions pour ouvrir le débat sur les enjeux industriels, qui ont été en particulier discutés dans le cadre transatlantique, mais pas seulement :

1. **Le découplage potentiel entre la conception des éléments de base pour la biologie de synthèse d’une part, et leur production**, ce qui pourrait conduire à un modèle économique décentralisé, voire très décentralisé, et dont l’efficacité en termes de coûts et de réduction des externalités négatives, pourrait s’avérer supérieure à terme à tous les autres modèles. Cela donne à réfléchir.

2. **L’utilisation libre de droits des connaissances fondamentales et des propriétés fondamentales.** Une coopération internationale précompétitive, par exemple pour une métabase de données référençant les propriétés à l’échelle nanométrique, qui s’inspire dans sa gouvernance de bases de données globales utilisées par les biologistes pour les protéines par exemple, est actuellement débattue dans des instances comme l’ISO et l’OCDE, avec un intérêt émergent

notamment de la National science foundation (NSF) côté américain, ou de l'Agence nationale de la recherche (ANR) côté français, comité sectoriel nano.

3. **Le partage libre de royalties de certains procédés de base dédiés à l'intégration des éléments bio ou non-bio à l'échelle nanométrique**, comme un vecteur d'accélération précompétitif essentiel pour accéder à la production à une large échelle, la rémunération de l'inventeur devant être garantie mais peut-être refondée à la marge. C'est l'un des points sur lesquels nous allons réfléchir.

L'énergie, l'environnement, la santé et l'évolution de l'industrie chimique sont certainement des domaines clés d'applications industrielles pour la biologie de synthèse. Les intervenants de la table ronde traiteront certaines de ces facettes et de ces perspectives d'avenir. L'un des enjeux de cette table ronde, telle que je le perçois, c'est d'élever, par la diversité des participants et par la publication des auditions, le niveau de compréhension des enjeux industriels de la biologie de synthèse, en vue de préparer les décideurs à mettre en place des cadres qui soient favorables aux applications issues de la biologie de synthèse, cadres qui incluront la responsabilité sociétale des organisations, en référence à la norme ISO 26 000 adoptée à l'automne dernier.

Ces travaux seront certainement utilisés, au-delà du cadre bilatéral de l'événement qui nous rassemble ici, en partenariat avec l'OPECST, par le Comité pour la politique scientifique et technique (CPST) de l'OCDE. La convergence bio-nano et nano-bio – Françoise Russo-Marie du Genopole Evry vous expliquerait de manière plus savante que moi la différence entre les deux – et la biologie de synthèse, est au coeur des débats du CPST depuis quelques années.

Je donne la parole à mon co-modérateur.

M. Jonathan Burbaum. De nombreux aspects qui ont été évoqués au sujet de la participation du Gouvernement sont les mêmes aux Etats-Unis. Je suis entré en fonction au sein de l'Administration il y a moins d'un an, mais je suis à la tête d'une agence : l'Agence des projets de recherche avancés pour l'énergie (ARPA-E Project). Cette agence a été créée en 2009. Son but est de reproduire l'agence DARPA (*Defense advanced research projects agency*), créée dans le domaine de la Défense il y a quelque cinquante ans. DARPA a joué un rôle significatif dans le développement de certaines technologies qu'on utilise aujourd'hui, telles que l'Internet, le GPS et d'autres technologies à usage militaire. Cela représente une nouvelle approche pour le ministère américain de l'énergie, qui consiste à financer la Recherche et le Développement, bien que ce ne soit pas une agence comme une autre. En quelques mots, je vais vous dire comment cela fonctionne et quelle est l'idée du Gouvernement américain.

L'idée est de saisir des découvertes au niveau des laboratoires et de les transformer en opportunités commerciales dans un but de création d'emplois, mais également pour servir la sécurité nationale, la sécurité économique, etc. Les types de projets financés ont quatre composantes.

- La principale chose à laquelle nous nous attachons, c'est **l'impact**, les conséquences. Est-ce que non seulement ces technologies fonctionneront, mais si ces technologies fonctionneront, est-ce qu'elle feront une différence ? C'est véritablement une différence fondamentale par rapport à d'autres projets financés. Ce qui nous préoccupe vraiment, c'est l'importance de l'impact et des conséquences au plan commercial.

- Nous sommes aussi à la recherche de **la rupture technologique.** On évalue quelle serait la percée technologique correspondante, la courbe d'apprentissage par rapport aux technologies existantes. Il faut que la technologie envisagée rende les technologies existantes obsolètes.

- On recherche aussi les meilleurs éléments, **les meilleurs profils** dans leurs catégories. Cela concerne à la fois les ingénieurs et les scientifiques. Il y a peut-être aussi des gens qui n'ont pas vraiment pensé à travailler dans la Recherche & Développement dans le domaine de l'énergie, mais en voyant quel est l'impact sur le monde d'aujourd'hui, ils vont s'y consacrer.

- Enfin, nous travaillons sur **la complémentarité.** Le but d'ARPA-E n'est pas de remplacer des sources existantes de financement, mais d'être un levier pour attirer d'autres formes de financement, en provenance par exemple du secteur privé. Il s'agit également de partager les frais, les coûts. Nous essayons d'avancer au rythme où va l'innovation, c'est-à-dire aussi vite que possible.

Le processus maintenant. Au départ, nous partons d'une vision en quelque sorte. Ensuite se tient un atelier, un séminaire. Puis il y a un appel à projets. On évalue alors les concepts proposés et enfin on élabore un contrat de recherche. Le tout en six ou huit mois. Il y a un certain nombre de projets sur lesquels je travaille. Pour certains, nous sommes au stade où l'on vient de lancer l'appel à projets. En ce qui concerne la biologie de synthèse, cela va avoir un impact dans les cinq ou dix prochaines années.

L'atelier que j'ai moi-même animé était intitulé : « Biotechnologies appliquées pour les carburants de transport ». On a exploré différents champs, afin d'examiner ce qu'il était possible de faire pour améliorer les biocarburants à l'avenir, et les chances correspondantes. Les trois axes forts portent sur :

1. **L'absorption :** les végétaux sont verts et non pas noirs. On ne récupère que la moitié de l'énergie disponible dans le végétal.

2. **Le métabolisme :** on peut sans doute améliorer l'absorption d'énergie par les plantes individuelles. Sur cet aspect, il y a actuellement, pour la plupart des biocarburants, une conversion. On utilise la biologie au deux bouts de la chaîne. Pourquoi ne pas l'utiliser tout du long ? Dans ce cas, la compétition pour l'alimentation disparaît.

3. **L'optimisation :** On veut également optimiser les organismes. Pouvons-nous utiliser par exemple une culture alimentaire ? Un certain nombre

d'outils sont disponibles depuis plusieurs centaines d'années. Pouvons-nous les utiliser pour avoir une nouvelle semence dédiée aux biocarburants, utile à la société ?

Le programme qui en est résulté se nomme PETRO, qui désigne l'ingénierie des végétaux pour remplacer le pétrole. Il y a eu une procédure budgétaire et le budget a été approuvé le 14 avril. Le 20 avril, nous avons annoncé un premier cycle de financement de 130 millions de dollars. L'appel à projets est lancé. La date de clôture des dossiers est fixée le 19 mai. Nous essayons d'avancer le plus vite possible. Pour plus d'informations, je vous invite à consulter le site Internet[1].

Mme Françoise Roure. Je vous remercie de cette introduction. Ces programmes ARPA-E constituent une innovation au sein du Gouvernement fédéral américain. Je donne la parole à Vincent Schächter.

M. Vincent Schächter, directeur R&D Energies Nouvelles du groupe Total. Je vais essayer de vous donner la perspective d'un groupe industriel sur les questions de biologie de synthèse, perspective qui est récente. Tout d'abord, il est important de replacer le cadre. Total a deux motivations principales pour s'intéresser aux énergies nouvelles :

- La première, c'est qu'en analysant assez simplement l'offre et la demande énergétiques, il est clair que **la demande croît plus vite que l'offre, tous types d'énergie confondus**. D'après les prédictions à l'horizon 2030 de l'Agence internationale de l'énergie (IEA), on sait que les besoins énergétiques de la planète ne seront pas satisfaits facilement avec la production, non pas d'hydrocarbures fossiles, mais de toutes les formes d'énergie dont on dispose aujourd'hui. Donc nous savons qu'il faudra beaucoup de créativité pour arriver à satisfaire la demande.

- La deuxième raison est d'ordre **environnemental**. Nous savons qu'un énorme effort va être nécessaire pour diminuer les émissions de gaz à effet de serre. Quel que soit le scénario, le scénario dit « *business as usual* » de l'IEA ou le scénario baptisé « 450 » (450 parties par million (ppm) de CO2), le renouvable et les biocarburants représentent une part significative de cet effort-là, l'efficacité énergétique en représentant la majorité. C'est pourquoi nous travaillons dans ces domaines.

Maintenant, regardons un peu plus en détail les voies que le groupe Total a choisies, celles qui nous semblent intéressantes. Il y en a deux du côté des énergies renouvelables : l'énergie solaire et la biomasse. Aujourd'hui, Total va se concentrer sur la biomasse. Mais dans les deux cas, il y a deux points communs dans notre analyse et dans notre approche :

[1] Programme PETRO (Plant engineered to replace oil) : https://arpa-e-foa.energy.gov/#bc334967-4db1-4458-9700-7371c75543cb

- Premier point commun : nous souhaitons devenir **un acteur intégré**, intégré au sens de la ressource, c'est-à-dire de la matière première jusqu'à la production. Dans le cas de l'énergie solaire, ce sont les panneaux solaires et la production d'électricité. Dans le cas de la biomasse, c'est la ressource de biomasse elle-même et la production de biocarburants ou de molécules pour la chimie.

- Second point commun : **l'importance de la technologie**. Il s'agit de deux domaines, où la technologie évolue extrêmement vite, et modifie en profondeur les chaînes de valeur. Nous souhaitons, dans ces domaines-là, comprendre les technologies qui vont affecter cette période de transition énergétique, et en maîtriser une partie, pour arriver à construire des solutions durables. Car il n'y aura pas de solution durable d'un point de vue environnemental et économique, sans des progrès technologiques très significatifs. Ceci est essentiel, et c'est la raison pour laquelle la biologie de synthèse a été notre point d'entrée principal dans la biomasse.

Quelles sont nos motivations principales pour les voies de valorisation de la biomasse ? Il y a deux domaines d'application, dont on parle souvent séparément, et dont je vais parler conjointement, parce que les technologies employées sont les mêmes : il s'agit des biocarburants et de la chimie. Les technologies sont les mêmes en partie. Est-ce que nous y croyons ?

- Nous croyons aux biocarburants à court et moyen terme, parce qu'existent la réglementation et le marché, et parce qu'il va falloir produire des biocarburants dans les dix, quinze, vingt prochaines années. À long terme, ce n'est pas que nous n'y croyons pas, c'est que nous ne savons pas. Bien entendu une substitution par la voiture électrique est possible, à condition toutefois que la science fasse des progrès réels en ce qui concerne le stockage d'énergie, et que l'électricité produite soit propre, ce qui est un autre sujet. Là-dessus, nous réservons notre jugement.

- Du côté de la chimie, la production des molécules pour les différentes applications de l'industrie chimique, en particulier les nôtres de manière renouvelable, passe par la biomasse et par sa transformation. Autrement dit, il n'existe pas de substitution possible comme dans le cas de l'énergie, où l'on peut substituer l'énergie liquide à autre chose. Donc nous croyons aux applications pour la chimie, pour une chimie renouvelable ou biosourcée. Il ne s'agit ni du même volume, ni du même timing, ni des mêmes prix bien évidemment. Ce sont des marchés très différents.

Dans ce domaine-là, il s'agit d'un jeu de substitution. Schématiquement pour un pétrolier, le travail en amont consiste à aller chercher la ressource, et à partir de celle-ci à produire les molécules ou les substances et en aval les substances d'intérêt. Le jeu de substitution doit permettre de produire des molécules d'entrée pour l'aval à partir de ressources de la biomasse. Parmi nos principaux marchés figurent la pétrochimie et le raffinage et le marketing.

La réglementation a permis le développement du marché des biocarburants. En ce qui concerne la chimie et la pétrochimie, il en va autrement. Il n'y a pas de réglementation, mais juste une préférence du consommateur pour des produits biosourcés. Cette préférence n’est pas économique. Le consommateur préfère, mais il n’est pas prêt à payer plus. C’est la situation d’aujourd'hui. Il est possible qu’elle change.

Enfin, je dirais que ce schéma-là respecte la structuration actuelle de l’industrie. Mais il est tout à fait possible et imaginable de produire des molécules qui ne sont pas des molécules d’input pour l’aval, mais des molécules qui sont directement utilisables ou de nouveaux intermédiaires à partir de la biologie de synthèse. Et cela change la chaîne de valeur. Le Pr Jay Keasling a donné beaucoup d’exemples ce matin. En voici un sous-ensemble qui nous intéresse. Dans le domaine du raffinage : biodiesel, lubrifiants, liquides spéciaux, additifs et combustibles spéciaux ; dans le domaine de la pétrochimie : éthylène, propylène, styrène, acide lactique, etc.

J’en viens maintenant à la recherche et à la technologie, dont j’ai dit qu’elle était essentielle pour arriver à construire ces nouvelles routes de bioproduction, bien qu’elles ne soient pas encore prêtes au plan industriel. Quels sont les domaines qui nous intéressent ? Parmi les différents types de ressources, ce sont les plantes céréalières, les plantes sucrières, la fraction lignocellulosique des plantes, les oléagineux, les micro-algues. Parmi les molécules pour les deux grands marchés que sont la pétrochimie, le raffinage et le marketing, on distingue notamment l’éthanol**,** les alcanes, les alcools lourds, etc. La première génération pour la production d’éthanol s’est faite à partir de plantes sucrières ou de céréales. De notre point de vue, la biologie de synthèse a considérablement ouvert le jeu en permettant de produire différentes molécules à partir de sucres, en particulier des molécules qui ne sont pas de l’éthanol, mais qui peuvent être des alcools lourds, ou des alcanes, ou des esters. Depuis moins de dix ans, cette évolution est considérable, grâce aux travaux de la biologie de synthèse, dont ceux de Jay Keasling entre autres.

Qu’est-ce que cela signifie pour nous ? La multiplicité des cibles pour un même cœur technologique, plus de flexibilité pour ce que l’on est capable de substituer ou de biosourcer. Très concrètement, le débat sur la première génération portait sur la possibilité de fabriquer de l’éthanol à partir du sucre. Or, ce processus est compliqué, du fait de la compétition avec l’alimentation à laquelle sont confrontées la plupart des sources du sucre, hormis la canne à sucre au Brésil. J’en parlerai. Pour le moment, la compétition n’est pas très forte. Elle le deviendra peut-être si les volumes augmentent. Si la déconstruction de la lignocellulose en sucre arrive à maturité industrielle, des sucres pourront être produits. Donc nous travaillons à la transformation de sucre en molécule d’intérêt pour les marchés qui en ont besoin aujourd'hui, mais également à la maturation de la déconstruction de la lignocellulose, les deux se reliant à peu près correctement.

S’il y avait une chose à retenir peut-être c’est qu’en Europe, il y a trop d’essence et pas assez de diesel. Si vous vous référez au biocarburant, non seulement l’éthanol n’est pas une excellente molécule de substitution pour l’essence, mais de plus, n’est pas si nécessaire, à la différence du biodiesel. Or le biodiesel est produit habituellement à partir de l’oléagineux, dont la capacité à croître est limitée. Il y a une grande tension sur les prix. Dans ce contexte, la biologie de synthèse a fait la liaison entre un type de ressource et une molécule, que celui-ci ne permettait pas de cibler auparavant, ce qui modifie la chaîne de valeur.

Nous travaillons avec des *start-up* et des laboratoires académiques. La plus visible de notre collaboration est celle que nous avons mise en place, il y a un peu moins d’un an, avec Amyris Technology. Jay Keasling en a parlé tout à l'heure. En termes d’outils génériques, de plate-forme de biologie de synthèse, c’est la *start-up* la plus avancée que nous ayons rencontrée. Total a construit un partenariat de long terme à large spectre avec Amyris non parce qu’elle travaille à l’heure actuelle sur telle ou telle molécule, mais parce qu’elle est capable à long terme de rendre réelle cette flexibilité dans les cibles moléculaires et parce que le domaine va continuer à évoluer. Encore une fois, c’est la multiplicité des cibles qui importe, et donc la flexibilité autant en amont qu’en aval.

Pour autant, Amyris ne suffit pas. D’autres technologies sont complémentaires. Dans la biologie de synthèse, non seulement il y a une notion de modularité dans la manière de traiter les modifications génétiques, mais il y a également beaucoup de technologies, et donc une modularité dans un autre sens. Pour arriver à construire une voie complète, un certain nombre de technologies sont nécessaires. Schématiquement, pour pouvoir construire cette voie complète, Amyris se situe au centre d’un réseau de collaboration, avec sa plate-forme de biologie de synthèse, son savoir-faire sur la fermentation et sur le scale-up des voies de bioproduction. Viennent s’y greffer le prétraitement et l’assimilation de la biomasse, en particulier lignocellulosique, des voies qu’Amyris ne maîtrise pas à l’heure actuelle, et qui pourraient être faites avec des tiers, des outils de biologie de synthèse, et bien entendu la chimie downstream. C’est tout cela qu’il faut arriver à combiner. C’est une aventure difficile, dans laquelle nous entrons avec des collègues, un réseau de collaboration, et donc un certain degré d’ouverture de notre fonctionnement en R&D, qui est nécessaire pour pouvoir travailler. J’ai été agréablement surpris de voir qu’au moins deux des Instituts faisant partie de notre réseau étaient représentés ce matin. Voilà la manière dont nous fonctionnons pour la R&D dans les biotechnologies blanches. La biologie de synthèse est au centre de cette affaire.

Comment évalue-t-on et comment s’assure-t-on qu’on ne fait pas fausse route, quand on essaie de construire des voies industrielles ?

- Tout d’abord, doivent être prises en considération la question des ressources et celle du passage à l’échelle industrielle. Sur la disponibilité de la biomasse, on distingue quatre grands types de ressources que l’on classe en termes

de temps et de coûts. Depuis 2005, existent les plantes non dédiées. Les trois autres appartiennent encore à l'avenir en termes d'exploitation industrielle. Et nous y travaillons (les résidus agricoles et les plantes dédiées à horizon 2015, les déchets industriels et domestiques à horizon 2025.) Pour y parvenir, le Brésil, à travers sa production de canne à sucre, est le seul lieu acceptable en termes environnemental, économique et de potentiel de croissance. Ce ne sera probablement pas toujours le cas, et nous espérons que la lignocellulose mûrira vite.

- L'acceptabilité environnementale est ici essentielle parce que la production des biocarburants est structurée par les mandats, par la réglementation, et en particulier par la réduction des gaz à effet de serre. La production des biocarburants avancés doit être opérationnelle en 2017 et 2020 respectivement en Europe et aux Etats-Unis. Il y aura toujours un important arbitrage entre les ressources rares que sont l'eau et la terre. On peut minimiser la compétition bien sûr, les solutions étant locales du fait des pratiques, des règles et des potentiels.

- Les coûts de production sont déterminants dans ce secteur. La science en laboratoire, c'est une chose. Mais la question qu'on se pose toujours, c'est de savoir à quel moment on arrivera à produire à un coût raisonnable et dans des volumes raisonnables qui correspondent au marché. Le marché des biocarburants représentant de très gros tonnages, la réponse à ces questions n'interviendra pas avant longtemps. Entre les travaux initiaux de Jay Keasling sur l'artémisinine et le moment où Amyris, qui est la continuation de ces travaux pour d'autres molécules, arrivera à l'équilibre sur des carburants, entre dix et quinze ans se seront écoulés. Pour autant, il s'agit d'un processus très rapide par rapport à ce qui prévalait avant la biologie de synthèse. Cela s'accélèrera probablement pour d'autres molécules que les biocarburants, parce que les biocarburants constituent les plus gros volumes et que leurs prix sont les plus bas. On arrivera bien avant cela à l'équilibre économique, avec des molécules qui correspondent à des marchés à petits volumes et à marge élevée bien sûr. Il faut le savoir et considérer l'industrie de cette manière-là.

Enfin, Françoise Roure m'a posé la question : que peut faire la puissance publique, que peut faire l'Europe pour aider la biologie de synthèse ? Ma réponse tient en cinq points :

1. La recherche fondamentale. C'est la clé de tout.

2. La masse critique d'équipement dans certains lieux. C'est nécessaire. C'est cela, par exemple, que nous sommes allés chercher chez Amyris. De même, collaborerons-nous en France avec ceux qui sauront se doter de ces équipements.

3. Des collaborations ouvertes. Dans un tel domaine, il est absolument nécessaire de faire travailler ensemble les différentes disciplines constitutives. On n'a pas le choix.

4. L’éducation. La bonne recherche, la recherche de rupture, celle dont parlait mon collègue Jonathan Burbaum, se développe dans certains environnements et pas dans d’autres. Il faut y travailler. Dans l’éducation, il s’agira de programmes interdisciplinaires.

5. De l’information, du débat public, mais aussi du travail de fond sur les questions d’éthique et de sécurité liées à la biologie de synthèse.

Mme Françoise Roure. Je vous remercie pour ce panorama que vous avez brossé du secteur énergétique. Une phase de transition s’amorce à l’heure actuelle. Je souhaiterais maintenant entendre l’approche de Marc Delcourt, qui est plutôt celle d’une *start-up* dans un domaine précis au sein de ce panorama. Et ensuite peut-être, prendrons-nous les premières questions sur le domaine énergétique, avant de passer au troisième intervenant.

M. Marc Delcourt, président-directeur-général de Global Bioénergies. Laissez-moi d’abord vous présenter notre société en quelques mots. Cette société est récente. Je l’ai cofondée en 2008 avec Philippe Marlière, un des pionniers de la biologie industrielle et de la biologie de synthèse. Cela fait vingt ans qu’il évolue dans ce domaine, où il est connu pour sa créativité. Moi-même, je suis entrepreneur depuis 2007. Avant de fonder *Global Bioenergies*, j’ai créé une autre société, *Biométhodes*, spécialisée dans la dégradation de la lignocellulose. Cela fait treize ans que j’exerce des activités dans le domaine de la biologie industrielle.

Aujourd'hui, l’isobutène, l’une des molécules qui est au coeur de la pétrochimie, est extraite du pétrole. Demain, on compte bien produire de façon massive cette molécule à partir de ressources renouvelables. Cette molécule, permet de produire des carburants, divers plastiques, des pneus aussi, certains matériaux comme le verre organique.

Que s’est-il passé dans le domaine des bioprocédés ces 10 000 dernières années ? Il y a 10 000 ans, le premier bioprocédé a été découvert pour produire de l’éthanol. A cet effet, il suffit de prendre un jus sucré, en écrasant n’importe quoi dans un peu d’eau, et vous attendez. De façon spontanée, des levures colonisent le jus sucré. Sur la plus grande partie de la planète, il s’agit du genre *Saccharomyces cerevisiae*, mais dans certains lieux, ce peut être d’autres micro-organismes. Il ne reste plus qu’à le distiller, c’est-à-dire à le chauffer à 80°C pour séparer l’alcool et l’eau. Jusqu'en 1900, les bioprocédés reposaient sur l’amélioration de ce procédé historique. Au XX^{ème} siècle, il y a eu quelques autres exemples de bioprocédés. On a sélectionné des micro-organismes naturels, certains de la famille des clostridium ou des pénicillium, pour fabriquer quelques produits en particulier. Les clostridium produisaient du butanol et de l’acétone, cette dernière molécule étant notamment utile pour fabriquer de la poudre à canon. A partir des pénicillium, on a produit des antibiotiques qui ont eu l’essor qu’on connaît. Au XX^{ème} siècle, les exemples se limitent à une dizaine de bioprocédés qui ont été vraiment développés jusqu'au

stade industriel. Pourquoi n’a-t-on pas développé plus de bioprocédés ? En fait, il n'y a pas beaucoup de micro-organismes qui, spontanément, produisent un seul composé dans des quantités très importantes, suffisantes et compatibles avec l’exploitation industrielle. Les micro-organismes produisent de nombreux composés d’intérêt industriel, mais en faible quantité. On a estimé que si on pouvait modifier les voies métaboliques et faire en sorte qu’ils produisent un composé principalement, alors on pourrait fabriquer biologiquement toute une série de composés d’intérêt industriel à partir de ressources renouvelables. C’est ce qui est en train de se passer. La vague des bioprocédés est en voie d’industrialisation. On améliore les voies métaboliques existantes d’un micro-organisme qui produit une petite quantité d’un produit, pour qu’il en produise beaucoup, et dans des quantités compatibles avec l’industrialisation.

Il reste une limite importante : les grandes molécules de la pétrochimie que sont les oléfines légères. C’est, par exemple, l’éthylène qu’on convertit en polyéthylène et dont on fait, entre autres, le plastique d’emballage. Ce marché représente 150 milliards de dollars. C’est vraiment le premier produit de la pétrochimie, à côté des carburants. Les oléfines légères, c’est aussi le propylène, dont on fait le plastique dur, notamment le plastique des voitures. L’éthylène comporte deux carbones, le propylène en a trois, l’isobutène en a quatre. Jusqu'à présent, peu d’efforts ont été accomplis pour produire ces trois composés par voie biologique. Pourquoi ? Parce qu’il n'y a pas de point de départ. L’ingénierie enzymatique et l’ingénierie métabolique permettaient d’améliorer l’existant, mais pas de construire des objets biologiques de toutes pièces. Cela est regrettable, parce que les plus grandes opportunités, les plus gros marchés, les molécules qui sont vraiment au coeur de la pétrochimie, personne ne s’est vraiment attaché à les produire biologiquement. C’est ce défi-là que Philippe Marlière et moi avions voulu relever. Le premier exemple qu’on a voulu traiter est celui de l’isobutène, pour diverses raisons. Aujourd'hui nous sommes parvenus à créer de toutes pièces une voie métabolique, qui, lorsqu’elle est implantée dans des micro-organismes, permet la conversion du sucre en isobutène. Cet isobutène que l’on peut ensuite utiliser à diverses fins.

Ainsi, sert-il à produire de l'iso-octane, une molécule connue du grand public, car c’est la référence de l’indice d’octane. Quand on achète du carburant, du super 95, on achète un mélange de molécules qui ont 95% des propriétés (idéales) de l’iso-octane. L’iso-octane pur, qui est un dimère d’isobutène, serait du « super 100 ». À partir de l’isobutène, on peut fabriquer aussi des produits qu’on met dans le diesel et dans le carburant d’aviation (kérosène), et dans le domaine des matériaux, du PET (plastique des bouteilles), du verre organique, ou du caoutchouc butyle (chambre à air).

Nous nous attachons à ce que les nouveaux procédés biologiques débouchent sur des produits *drop-in*, c'est-à-dire les mêmes produits que ceux qui sont issus de la pétrochimie aujourd'hui, pour pouvoir assurer la continuité des filières, ne pas avoir à reconstruire les circuits de distribution et de stockage. L'isobutène est une molécule *drop-in* qui, existant aujourd'hui, peut être industrialisée. C'est cette industrie que l'on compte perpétuer.

Rien n'existait il y a trois ans sur les bioprocédés isobutène. Philippe Marlière a dessiné une voie métabolique qui était basée sur le détournement d'enzymes naturelles. On modifie une enzyme qui fait quelque chose dans la nature pour lui faire catalyser une autre réaction chimique, d'intérêt pour nous. Ce quelque chose est un maillon d'une voie métabolique qui permet la conversion en plusieurs étapes de sucre en isobutène. Les intermédiaires métaboliques de cette chaîne n'existent pas dans la nature. Ils sont uniquement présents chez Global Bioénergies, situé à Evry. Cette voie métabolique artificielle, c'est l'un des exemples d'une façon de faire de la biologie de synthèse, un nouveau domaine d'activité reposant sur la fabrication de nouveaux objets biologiques.

Que nous reste-t-il à faire ? Aujourd'hui le procédé fonctionne en laboratoire et à faible niveau. On travaille à l'industrialisation de ce procédé, c'est-à-dire à l'amélioration de son rendement et à l'augmentation de son volume. L'idée est de sortir du laboratoire, de faire une usine pilote, puis de créer des usines de taille vraiment industrielle. En outre, il nous faut adapter ce procédé à d'autres molécules de la famille des oléfines légères, telles que l'éthylène, le propylène et quelques autres. On y travaille intensément.

L'idée est aussi de pouvoir convertir les ressources agricoles, c'est-à-dire le vrai sucre (de canne ou de betterave), l'amidon de céréales (maïs, blé, seigle, riz), l'amidon de la pomme de terre. L'amidon, c'est l'essentiel de la production agricole mondiale. Demain, on utilisera aussi les matériaux lignocellulosiques, c'est-à-dire les déchets agricoles, les déchets forestiers, et puis aussi des plantes dédiées. De nouvelles plantes seront amenées à être au centre de cette agriculture à vocation énergétique qui est en train de se mettre en place.

Schématiquement, voici le procédé. Le sucre est converti par les micro-organismes en isobutène, qui est un gaz. C'est d'ailleurs pour cela que les bactéries n'en produisent pas naturellement, parce que si elles volatilisaient leur carbone, elles « maigriraient », ce qui est « contre-sélectionné » par l'évolution. L'isobutène qui se volatilise présente l'intérêt d'éviter de faire des efforts pour purifier le produit. Par exemple, si vous prenez l'éthanol, il faut le purifier. Et l'éthanol est également toxique pour les levures. Au bout d'un certain moment, l'éthanol finit par tuer l'organisme de production, et cela a un coût industriel. C'est ce qui explique que le vin de Sauternes soit à 13 degrés. En réalité, il a suffisamment de sucre pour faire un vin à 30 degrés si tout était converti en termes d'alcool. Mais la part du sucre qui correspond à 13 degrés d'alcool est la seule qui soit convertible, parce qu'ensuite, l'éthanol tue les levures.

En définitive, cette volatilisation spontanée permet de prévenir ce problème de toxicité au niveau industriel et d'éviter des coûts de « *downstream processing* », de purification trop élevés. Une fois qu'on a obtenu l'isobutène, tous les procédés sont déjà en place pour le transformer :

- en iso-octane, le meilleur carburant pour les voitures ;
- en composé, qu'on peut l'intégrer dans le kérosène ou dans le diesel ;
- dans toute une famille de plastiques, de textiles, de verre organique et de pneus.

Toutes ces technologies existent déjà. Nous souhaitons que notre procédé en fasse partie.

Mme Françoise Roure. Je crois également que tous les procédés que vous développez sont de nature à diminuer les émissions de CO^2.

M. Marc Delcourt. Je vais vous parler brièvement du bilan CO^2, l'aspect environnemental. Aujourd'hui on extrait du pétrole, on le met dans nos voitures ou on en fait du plastique, la combustion étant l'étape finale de la production (les plastiques finissent dans une déchèterie au bout de quelques années, le carburant est brûlé dans le moteur très rapidement). Ce schéma est linéaire : On va du sous-sol vers l'atmosphère. On extrait des hydrocarbures, qu'on va ensuite volatiliser sous forme de CO^2 dans l'atmosphère**.** Et cela produit environ 3,2 kg de CO^2 par kg de pétrole extrait.

Regardons maintenant un bioprocédé. La fermentation émet aussi du CO^2 : pour chaque molécule d'éthanol produite, on produit aussi une molécule de CO^2. *A priori*, ce pourrait être dommageable pour l'environnement. En fait, il faut voir les bioprocédés de façon plus globale, comme un cycle. Le CO^2 qui est produit est capté par les plantes qui, *via* la photosynthèse, en font des polymères végétaux (carbohydrates). Ces carbohydrates sont utilisés ensuite via le bioprocédé pour faire les matériaux qui nous intéressent, lesquels vont finir par être brûlés. C'est donc un cycle, et si ce cycle était parfait, il n'y aurait plus du tout d'émissions de CO^2. On aurait donc une économie totale de gaz à effet de serre. Malheureusement, rien n'est jamais parfait, et ce cycle comporte des frottements. En effet, il faut un tracteur pour aller récolter les betteraves, des engrais… Mais on peut quand même mesurer les économies par rapport à la quantité de CO^2 émise par l'utilisation du pétrole. Selon les cas, l'économie de gaz à effet de serre est de 0%, 10%, 20%, 50%, voire 80% dans les meilleurs cas, notamment lorsque les bioprocédés utilisent de la canne à sucre au Brésil, en comparaison de l'utilisation de la même quantité énergétique de pétrole exprimée en mégajoule.

Mme Françoise Roure. M. Philippe Soucaille, vous exercez une fonction scientifique et une fonction dans une entreprise, et dans le même temps, vos clients finaux sont très sensibles au fait que ce que vous inventez et ce que vous produisez leur permet d'économiser beaucoup d'énergie dans leurs processus de production.

M. Philippe Soucaille, président-directeur-général de Metabolic Explorer. Je vais vous parler d'applications de l'ingénierie métabolique et de la biologie de synthèse. Les deux sont très proches maintenant quand on parle d'ingénierie métabolique moderne aboutissant à la production de produits chimiques de commodité. Metabolic Explorer ne s'intéresse pas aux biocarburants, parce qu'à très court terme en tout cas, on n'y croit pas. On veut produire des produits qui soient économiquement rentables. C'est pour cela qu'on s'est intéressé aux produits chimiques de commodité, et à des produits chimiques existants. On veut partir directement de matières premières renouvelables et aller vers le produit fini. On ne veut pas produire un intermédiaire qui serait ensuite utilisé pour faire un produit fini. Cela signifie que la plupart de nos produits, comme vous le verrez, sont des substituts de produits qui utilisent du propylène comme matière première, ce qui impose d'aller directement de la matière première renouvelable au produit.

S'agissant de Metabolic Explorer, elle a été créée en 1999 et est une *start-up* entrée en bourse en 2007, bien avant ce qui a été le cas aux Etats-Unis concernant l'ingénierie métabolique pour la production de bioénergie ou de produits chimiques. Metabolic Explorer était relativement en avance, et avait développé pas mal d'outils de bio-informatique, dont je vous parlerai, qui ont permis de bien concevoir les micro-organismes. Ce qui manquait, c'étaient toutes les plates-formes de biologie moléculaire et d'analyse qui ont été développées à partir de 2002. Aujourd'hui, Metabolic Explorer compte 120 personnes et ne s'intéresse pas seulement au développement des souches, comme je vous le montrerai, mais aussi à l'industrialisation.

- En termes d'industrialisation, nous avons un pré-pilote qui nous sert à tout développement du *process book* de fermentation, et un pilote d'industrialisation qui permet de produire, à partir de la matière première, le produit fini en intégrant fermentation, purification et les spécifications du marché. Sur place, il est possible de produire les produits et de fournir les clients.

- En termes de propriété intellectuelle, plus de 300 brevets ont été déposés par Metabolic. C'est une société *high-tech* qui a mis fortement l'accent sur le dépôt de brevets.

Qu'est-ce qu'on entend par ingénierie métabolique ou par biologie de synthèse ? Et quels sont les outils dont on a besoin ? Les dirigeants de Total n'ont pas visité Metabolic, et donc ils ne connaissent pas notre plate-forme. Car il y a aussi des plates-formes chez Metabolic Explorer.

Des plates-formes de bio-informatique nous permettent de modéliser, avant de commencer la moindre expérimentation, le rendement maximum que l'on est en

droit d'atteindre pour un produit, à partir d'une matière première donnée. Il est essentiel, lorsque des projets de recherche lourds sont menés, de s'assurer du rendement maximum, des titres et des productivités qui pourront être obtenus. Sans ces trois critères-là, qui sont importants pour l'industrialisation, on ne peut pas envisager d'aller dépenser le moindre euro dans ce type de développement. Très tôt, ces outils-là ont été développés, pendant les trois premières années d'incubation de la société. Ce sont des outils appartenant à Metabolic Explorer et ils sont vraiment très performants. Je vous en reparlerai ultérieurement. Une fois que les rendements pratiques sont fixés, il y a lieu de déterminer les conditions dans lesquelles sera effectuée l'ingénierie de votre souche. C'est ce que permettent aussi ces outils de bio-informatique.

Il est évident qu'il faut ensuite construire la souche et, pour cela, sont nécessaires un certain nombre d'outils de biologie moléculaire que Metabolic Explorer a développés. Certains d'entre eux ont été brevetés. Ils permettent de produire, avec des débits importants, des souches recombinables, qui ont donc les propriétés voulues. Lorsqu'on veut faire de la biologie et produire de nouveaux produits, il est évident que de nouvelles activités enzymatiques sont nécessaires, car il faut être capable de faire évoluer des enzymes. On a mis en place une plate-forme d'évolution in vivo d'enzymes qui a été utilisée de nombreuses fois dans les brevets et dans les produits que l'on a développés.

Ceci étant fait, une fois qu'on a construit une première génération de souches, on ne peut pas envisager d'aller plus loin sans comprendre ce qui se passe à l'intérieur du micro-organisme. C'est à cette fin que l'une des plates-formes développées soit par la RMN[1], soit par GC-MS[2], il est possible d'avoir accès à tous les flux intracellulaires. D'autre part, nos moyens nous permettent de mesurer les niveaux de toutes les protéines à l'intérieur de la cellule, s'agissant tout au moins de toutes celles qui sont impliquées dans le métabolisme central de la bactérie. On sait immédiatement où l'on se situe quand on fait des constructions génétiques en termes d'expression des différentes protéines. Et on a une association flux *in vivo* – concentration de la protéine *in vitro* – et éventuellement l'activité *in vitro* de la protéine.

Un lien direct nous permet de modéliser et de revenir à notre plate-forme de bio-informatique afin d'améliorer les souches en question. Ce cycle-là, et ces plates-formes qui ont été mises en place permettent de raccourcir énormément les temps de développement des produits.

Comme je vous l'ai dit, Metabolic Explorer compte 120 personnes et développe cinq projets en parallèle. Ce serait totalement inenvisageable avec un nombre de personnes aussi réduit si nous n'avions pas des outils très performants.

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[1] RMN : Résonance magnétique nucléaire.

[2] GC-MS : Chromatographie en phase gazeuse-spectométrie de masse : combinaison de deux techniques pour former une seule méthode d'analyse des mélanges de produits chimiques.

En résumé,

- **la plate-forme de bio-informatique** nous permet d'identifier la meilleure route pour obtenir un produit ;
- **la plate-forme de biologie moléculaire** nous permet d'obtenir d'autres souches le plus rapidement possible ;
- **la plate-forme d'analyse et de fermentation** nous permet de vraiment analyser ce qui a lieu à l'intérieur de la cellule, quels peuvent être les problèmes éventuels au sein de cette cellule, avant d'améliorer les choses.

L'idée, c'est d'avoir rapidement des bactéries qui soient efficaces et des procédés de production qu'on choisit en fonction de critères économiques. Ces procédés doivent permettre de bénéficier d'une économie d'au moins 30% par rapport au projet compétitif qui est celui de la chimie. Comme l'a souligné Vincent Schächter, il n'y a pas de premium pour un produit bio. Il y a simplement une demande, c'est vrai, des clients pour un produit biosourcé. Ils ne sont pas prêts à payer plus. Donc vous ne pourrez remplacer des procédés chimiques que si vos coûts de production, en intégrant les amortissements de votre CAPEX (*Capital Expenditure* - dépenses en immobilisations), sont plus faibles. S'ils ne sont pas plus faibles, votre procédé ne sera jamais rentable.

Quels produits sont développés ? Les cinq produits que nous développons ne sont pas au même stade d'avancement.

Deux produits sont développés en partenariat avec Roquette, un amidonnier français. Il s'agit de :

- L-Méthionine,
- acide glycolique.

Ces deux produits sont industrialisés. Le *scale-up*, la purification et l'homologation sont effectués par la société Roquette. On s'est contenté de faire un travail sur la souche industrielle de production et le procédé de fermentation. On s'intéresse à des marchés de chimie de commodité. Le marché de la L-Méthionine représente 740 kilotonnes (Kt) par voie chimique pour un volume de 2,35 milliards €. Celui de l'acide glycolique représente 800 kt pour un volume de 1,6 milliards €. L'objectif souhaité n'est pas de substituer la totalité du marché de la chimie par ces molécules-là, mais de prendre une part du marché en ayant une économie bien meilleure. Si vous arrivez à produire moins cher, si le « parapluie » du produit de la chimie est plus élevé, cela vous permet de faire des marges de spécialité sur votre produit, alors que vous produisez un produit de commodité. C'est tout l'intérêt pour un chimiste nouveau de s'intéresser à ce type de bioproduction, à condition qu'elle soit bien plus rentable qu'un procédé chimique.

Postérieurement à notre introduction en bourse, nous avons développé trois produits en propre dans la société, en voulant aller du développement de la souche jusqu'à l'industrialisation. Il s'agit de :

- **1,3-propanediol** (700 kt, 1,75 milliards €) : c'est le produit le plus abouti. On a fini toutes les étapes de *process book* à l'échelle pilote et nous sommes en train de construire une usine de production de 1,3-propanediol. J'ai été le dernier responsable du projet 1,3-propanediol aux Etats-Unis chez Genencor International Inc. Le projet 1,3-propanediol développé chez Metabolic Explorer se différencie par la matière première et les enzymes utilisées. On a développé un procédé à base de glycérine pour la production de 1,3 propanediol.

- **butanol** (3 300 kt, 3,35 milliards €) : ce projet est à base de clostridium. On va créer une souche qui ne produit que du butanol. Ce projet est donc très avancé aussi. Il est au stade final de développement.

- **1,2-propanediol** (1 840 kt, 2,05 milliards €) : on produit directement du 1,2-propanediol base saccharose.

La plupart de ces projets vont être terminés d'ici un à deux ans. Il est évident qu'il y a un certain nombre d'autres projets en cours.

Juste un point sur le 1,3-propanediol. On part d'une matière première qui est de la glycérine brute. Ce procédé de 1,3-propanediol a été développé en partenariat avec l'Institut national des sciences appliquées (INSA) et l'Institut national de recherche en informatique et automatique (INRIA). On a breveté un travail qui avait été fait dans mon laboratoire académique à l'époque sur une nouvelle enzyme, un nouveau micro-organisme pour la production de 1,3-propanediol. Metabolic Explorer a amélioré ce procédé-là en éliminant des sous-produits de cette fermentation, de manière à rendre ce procédé industriel réalisable, en particulier au niveau de la purification. Tout cela s'est souvent fait en partenariat. Cela nous semble essentiel pour une petite société d'aller au plus vite vers le marché. Par contre, on internalise tout le développement du *process book* au sein de la société. Vous avez les fermenteurs et derrière, le processus de purification du 1,3-propanediol. Tout cela se situe à Clermont-Ferrand où se trouve la R&D de Metabolic Explorer. Et nous produisons donc plusieurs centaines de kilos de 1,3-propanediol pour nos clients potentiels. Ils ont validé le produit pour les applications. La première unité devra être opérationnelle en 2012. La première pierre devrait être posée très rapidement. Dans cette unité, on produira 50 000 tonnes appartenant à Metabolic Explorer, avec une première échelle qui sera à 8 000 tonnes.

Débat

Mme Françoise Roure. Merci pour ce troisième exposé. C'est l'industrialisation de la biologie de synthèse en route, telle que vous avez pu la regarder. J'aurais une question sur le raccourcissement des temps de développement des produits et l'intérêt pour un industriel des problématiques de normalisation. En quoi les consensus et les aspects précompétitifs peuvent être importants ? La parole est à la salle.

M. Patrice Binder, fonctionnaire de sécurité et de défense à l'INSERM. J'aurais voulu que les trois orateurs nous en disent un peu plus sur les questions de confinement de vos constructions, notamment des souches bactériennes que vous utilisez. J'imagine que c'est une question que vous prenez en compte dès le début dans l'établissement de vos *process*.

M. Thomas Heams, enseignant en génomique fonctionnelle à AgroParisTech et chercheur à l'INRA. Je viens d'une discipline qui est la génétique quantitative. Depuis un siècle, cette discipline, qui est un peu moins à la mode, insiste sur le fait qu'une grande partie des caractères complexes des organismes sont le produit, non pas de petites chaînes métaboliques, mais d'un grand nombre de réseaux de gènes qui interviennent avec de petits effets cumulatifs. On a modernisé progressivement cette théorie. La contrepartie, c'est qu'un grand nombre de gènes ont un impact sur beaucoup de caractères, de manière infinitésimale parfois, mais significative. Ma question est assez générale. Je la pose aux industriels, sans diabolisation aucune évidemment, mais elle consiste à vous interroger sur vos démarches légitimes de valorisation de vos voies de synthèse. Elles vont embarquer un certain nombre de gènes et les inclure dans un travail d'innovation que vous aurez réalisé. Vous intéressez-vous à la question de savoir s'il n'y a pas une privatisation de l'effet de certains gènes, ou de leur utilisation en groupe, au détriment de fonctions beaucoup plus larges ?

Mme Françoise Roure. Vos réponses sur le confinement.

M. Philippe Soucaille. Tous les micro-organismes que l'on peut construire sont confinés dans des biofermenteurs. Ce sont des micro-organismes à qui on a enlevé toute une série de voies métaboliques qui leur permettent de s'adapter au milieu naturel. Ces micro-organismes sont donc complètement incapables de s'adapter au milieu naturel. En second lieu, un bioprocédé permet de travailler avec un fermenteur, en milieu confiné, et de récupérer les micro-organismes à la fin. Dans tous nos procédés, le micro-organisme est brûlé à la fin du processus. Il ne s'échappe pas de l'usine, ce qui permet de prévenir tout problème de manipulation et de fuite. Les micro-organismes étant complètement inadaptés au milieu naturel, ils meurent quasiment immédiatement dans le milieu naturel.

Mme Françoise Roure. Et sur la valorisation ?

M. Philippe Soucaille. Je peux laisser d'autres intervenir.

M. Marc Delcourt. Le plus souvent, les brevets déposés ne revendiquent pas le gène lui-même, l'enzyme elle-même, mais son utilisation dans un certain cadre. Donc on ne prive en aucun cas qui que ce soit qui voudrait faire autre chose à partir du gène concerné.

S'agissant du monopole temporaire de vingt ans, qui est un temps très court, pour permettre l'éclosion de ces innovations, des débats ont eu lieu dans le domaine médical, où une protéine du sang était industrialisée telle quelle. Là, la question pouvait se poser, puisque c'était vraiment un produit naturel, juste une question de course et non pas tellement de construction technologique. Dans notre cas, il y a une construction technologique extrêmement aboutie, une innovation qui entre vraiment dans les canaux de la brevetabilité, et très clairement. Ce qui fait que cette question sur la brevetabilité et la légitimité de ces questions de propriété intellectuelle me semblent assez peu adaptées à ce domaine-là.

M. Vincent Schächter. Sur la première question, celle de l'impact environnemental, dans notre cas, il s'agit de levures. Comme l'a dit Philippe Soucaille tout à l'heure, on recourt à des fermenteurs en milieu confiné. Les mesures nécessaires sont prises pour empêcher la dissémination des organismes. Au cas où ces organismes s'échapperaient, effectivement, ils auront du mal à survivre en milieu naturel. En outre, la manière dont ils sont modifiés ne comporte aucun effet néfaste. Et enfin, nous allons évidemment tester l'impact environnemental activement pour toutes les nouvelles souches, conformément à la réglementation en vigueur. Les levures que nous utilisons sont des micro-organismes génétiquement modifiés dits de type 1. Dans le jargon, en anglais on dit GRAS (« *Generally Recognized As Safe* »). Et au Brésil, premier pays où, probablement, on industrialisera, l'agence compétente a accordé une autorisation en un temps record pour ces organismes génétiquement modifiés.

Sur la question de la brevetabilité, vous évoquez en fait des problèmes différents. L'un, de nature scientifique, tient à ce que beaucoup de traits phénotypiques sont multigéniques et qu'en conséquence, il est difficile de désimbriquer les causes et les effets. De fait, cette question est réglée dans le cas qui nous intéresse selon les modalités exposées par mon collègue. Pour que ce soit brevetable, on lie bien l'élément génétique à son usage, sans quoi les critères de brevetabilité ne seront pas remplis. D'autre part, on ne brevette ni des gènes ni des ensembles de gènes en tant que tels. Ce n'est pas une union, c'est une intersection. En ce qui concerne une voie métabolique particulière, ce n'est pas chacun des gènes de la voie métabolique qui est breveté, mais l'intégralité du dispositif. Au fur et à mesure que l'état de l'art avance, les critères sont de plus en plus fermes, même si parfois des brevets sont accordés alors qu'ils devraient être refusés.

Mme Françoise Roure. Sur la brevetabilité du vivant, il y a des débats de spécialistes et de non-spécialistes qui sont l'un et l'autre autorisés, mais il faudrait y consacrer pratiquement une audition entière. Encore une question.

M. Jacques Haïech, professeur à l'Ecole supérieure de biotechnologie de Strasbourg et vice-président du conseil scientifique de l'Alliance pour la recherche et l'innovation des industries de santé (ARIIS). Sur la propriété intellectuelle, mon commentaire est un peu naïf. J'ai l'impression que dans le domaine de la propriété intellectuelle, la biologie était fondée pour l'instant sur le régime un produit - un brevet, avec une gestion des portefeuilles de brevets assez simple par rapport à ce qui se passe en électronique, où pour construire un produit, il faut un ensemble de brevets dont on va demander un certain nombre de licences non exclusives et négocier le type de licence non exclusive. Avec la biologie de synthèse, j'ai l'impression qu'on est en train de passer d'une culture de brevet unique de type biologie à une culture de brevet de type électronique. Qu'en pensez-vous ? Voyez-vous déjà cette évolution dans la gestion de la propriété industrielle actuellement ?

M. Marc Delcourt. Je trouve que ce parallèle est extrêmement juste. Un bioprocédé, on peut presque voir cela comme un ordinateur. D'une part, il y a le hardware, c'est toute la cuve, le système physique. D'autre part, il y a le software, le logiciel, qui est en fait le micro-organisme. Un micro-organisme ressemble, au niveau intellectuel, à un software, puisque c'est quelque chose qu'on a mis énormément de temps à construire, qui contient une bonne partie de la propriété intellectuelle, et qui est très facilement répliquable. Il n'a pas de coûts de réplication. Donc on peut faire ce parallèle. Il y a des brevets qui sont susceptibles d'être déposés, sur le logiciel, c'est-à-dire le micro-organisme. Effectivement, il y en a un assez grand nombre sur la voie métabolique, l'arrière-plan métabolique, que certains appellent le châssis métabolique. En outre, il y a aussi des brevets sur le hardware, c'est-à-dire sur le procédé lui-même, avec des étapes de purification qui peuvent être spécifiques et brevetables notamment.

En revanche, cette situation est-elle nouvelle ? Pas vraiment. Dans le secteur médical, il y a aussi pour chaque produit un ensemble de brevets qui viennent de son principe actif lui-même, de son utilisation, de la façon de le produire, de sa formulation. Donc il y avait déjà dans la biologie médicale un environnement assez complexe, qui est peut-être moins complexe que celui de l'électronique, mais qui ne correspond pas au régime simple dont vous parlez : un produit, un brevet.

M. Vincent Schächter. Je pense aussi que la situation se complexifie. Je le constate avec mes collègues qui ont l'habitude des brevets ou de la propriété intellectuelle, dans l'industrie chimique par exemple, ou du côté des carburants. Ils ont du mal à comprendre qu'on ne puisse pas librement opérer (« *freedom to operate* »), ce qui donne des résultats simples, dans le cas de propriété intellectuelle en biologie de synthèse. En résumé, une partie de l'approche modulaire du vivant par la biologie de synthèse se reflète dans la propriété intellectuelle, et franchement ce n'est pas simple pour les juristes spécialisés en propriété intellectuelle.

M. Philippe Soucaille. Je voudrais juste rajouter un point là-dessus, qui complexifie énormément les choses. Il faut savoir qu'un grand nombre de ces voies métaboliques qu'on peut produire utilise des intermédiaires qui sont communs, la production de l'intermédiaire étant très souvent protégée. On peut donc protéger le micro-organisme pour fabriquer tel et tel produit, mais la production sera très souvent dépendante de l'intermédiaire commun, ce qui donnera lieu à toute une série de négociations. Plus un industriel parvient à s'implanter rapidement sur un marché, plus il a de chances de déposer des brevets en amont. Plus il arrive tardivement, plus il sera confronté à de nombreuses négociations. Ce sont des négociations d'entreprises, bien entendu.

Mme Françoise Roure. M. Burbaum ne souhaitant pas reprendre la parole, j'ajoute un dernier élément qui nous vient des Etats-Unis. Je citerais Drew Endy, directeur de BIOFAB (International open facility advancing biotechnology), qui dit, au fond, que s'il fallait qu'il brevette 15 000 bio-parts par an, il y perdrait à la fois son âme, son équilibre économique et sa capacité à innover. Donc il y a probablement un équilibre à trouver, avec des critères qui soient pertinents entre ce qui sera du domaine protégé, et ce qui sera de l'*open source*, précisément pour accélérer la commercialisation de produits issus d'une innovation responsable. Mais ces critères sont encore à expliciter, et je crois que la table ronde qui suit sera également pertinente pour nous aider à le faire.

Mme Geneviève Fioraso. Je remercie Françoise Roure et tous les interlocuteurs.

DEUXIEME TABLE RONDE : LES DEFIS SOCIETAUX

MODERATEUR :
M. DANIEL RAOUL, SENATEUR, VICE-PRESIDENT DE L'OPECST

M. Daniel Raoul, Sénateur, Vice-président de l'Opecst. Je remercie Mme Geneviève Fioraso de m'avoir invité en tant que vice-président de l'Office pour suppléer MM. Claude Birraux et Jean-Yves Le Déaut, retenus à l'étranger dans une rencontre concernant le nucléaire. Je voudrais saluer aussi la présence d'un député, M. Philippe Tourtelier, également membre de l'Office.

Geneviève Fioraso vous a expliqué le rôle de l'Office. On est en train de mesurer encore tout le champ qui nous reste à explorer autour du thème Science et Société, qui est devant nous, que ce soit pour des disciplines existantes ou pour des disciplines émergentes, ce que j'ai pu constater à l'occasion de deux rapports. Je sais qu'il existe quelques organisations qui s'en préoccupent, dont la vôtre, Mme Françoise Roure. Vos propos et votre Institution nous intéressent fortement. **Mais c'est sans doute en collaboration avec l'Office qu'il faudrait conforter les liens**. En tous les cas, les élus que nous sommes auraient besoin sans doute de vos apports dans ce domaine-là. Quelles que soient les disciplines d'origine des uns et des autres, il y a des domaines dans lesquels nous sommes un peu candides, quelquefois d'ailleurs. Je le dis sciemment, à propos des débats que Geneviève Fioraso a pu connaître, avec Minatec, etc, et dans lesquels nous sommes quelquefois désarmés. C'est bien pour cela que dans les deux rapports que j'ai pu établir pour l'Office, sur la téléphonie mobile et la santé, sur les nanotechnologies, et le progrès médical, **j'ai vu combien la culture scientifique était insuffisante, y compris chez les journalistes. Je ne sais pas s'il ne faudrait pas inventer un centre de formation continue scientifique et technique pour les médias**. **Mais je le dis aussi pour nos collègues élus**, c'est l'Office qui doit servir d'interface normalement. Mais pour ce qui concerne nos concitoyens, il faudrait aussi une interface relativement solide. En écoutant les exposés précédents, je sais que même le physicien que je suis est quelquefois embarrassé par les termes qui ont été employés.

Ce matin, nous avions à auditionner le futur président du Conseil des biotechnologies, qui aurait dû être lui aussi un lieu de médiation entre les scientifiques et les représentants des associations, etc, autrement dit la société civile. Je constate, au bout de deux ans de fonctionnement, que ce système idéal ne fonctionne pas. Il y a bien le Comité scientifique, avec ses experts, et puis il y a le Comité économique, éthique et social, dans lequel chacun garde sa posture. C'est-à-dire que les choses n'évoluent pas et qu'il y a un véritable blocage. Il faudrait, là

aussi, une interface. On l'a évoqué avec M. Jean-François Dhainaut ce matin. Ancien président de l'Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES), il est sollicité pour prendre la présidence de ce Haut conseil. Nous en avons discuté assez longuement. Nous sommes face à un enjeu véritable de société.

Alors je sais, Mme Françoise Roure, que vous n'appréciez pas le terme « acceptabilité ». **Mais il s'agit quand même bien de faire comprendre à nos concitoyens quels sont les enjeux, les avantages et les risques**. Je n'évacue pas les risques non plus. Il y a donc bien le fait d'accepter le risque par rapport au progrès, malgré ce que j'ai entendu. Le terme « acceptabilité » pourrait être ambigu. Comme l'a montré l'exemple des nanotechnologies, c'est un domaine un peu spécifique dans lequel, pour une fois, les applications ont été en avance par rapport à la théorie. Les nanosciences en sont encore à leurs balbutiements, alors que les applications, que ce soit du *top-down* ou du *bottom-up*, existent déjà. Vous le vivez au quotidien dans les applications touchant à la micro-électronique ou aux cosmétiques hélas, avec les dioxydes de titane. Mais c'est un autre débat.

En tous les cas, le mot qui a été employé par Geneviève Fioraso, rappelant la commission présidentielle de bioéthique, me paraît tout à fait en phase **avec notre démarche, « une vigilance prudente »**. J'y vois une notion satisfaisante, mais en même temps je rajouterais « transparence ». En France, on paie le prix d'une certaine opacité. Je ne veux pas citer certaines institutions, ni parler des nuages qui s'arrêtent aux frontières, ni de l'amiante. Hélas, l'Académie des sciences n'a pas pleinement perçu les enjeux. **Il y a un écart et une suspicion dorénavant entre les "sachants" comme on dit, et les habitants. Cela ne pourra disparaître qu'à l'aide d'une transparence complète**. Mais pour que la transparence soit efficace - je vous rejoins là Mme Françoise Roure - il faut sans doute qu'il y ait de la pédagogie et **qu'on arrive à diffuser, grâce sans doute aux médias, mais aussi dans tout notre système scolaire, une culture scientifique et technique**. Je suis frappé par le fait qu'à l'heure actuelle il y ait une désaffection complète des étudiants vis-à-vis des études scientifiques, alors que nos écoles d'ingénieur ont du mal dorénavant, malgré tout ce qu'on dit, à recruter des candidats. Ce fameux bac S a été dévoyé complètement de sa vocation. Il sert surtout à entrer dans les écoles de commerce, éventuellement à Sciences Po, mais regardez le pourcentage restant des étudiants qui poursuivent des études scientifiques et technologiques. Regardez la difficulté à laquelle sont confrontés actuellement les IUT, alors qu'ils étaient une « filière de sélection ». Eux aussi ont du mal à recruter leurs étudiants. Il y a eu, culturellement, globalement, une désaffection sinon une suspicion vis-à-vis de tout ce qui est scientifique et technique.

Force est de constater que dans ce domaine-là, il y a quand même quelques associations qui peuvent nous aider. Je parlais des médias, évidemment, à condition peut-être qu'on les aide aussi à se former. Je ne sais pas si c'est la vocation de votre

Institution, Mme Françoise Roure, mais en tous les cas, il y a **des associations telles que VivAgora**. Je suis sûr qu'elle est présente. Je sais aussi le travail que vous avez fait à Grenoble. Mais c'est au niveau national que ce genre de médiation devrait exister. C'est pourquoi, dans les deux rapports que j'avais établis, j'avais voulu associer des philosophes et des sociologues. Il est vrai que la culture scientifique peut être trop spécialisée, ce qui pourrait empêcher les scientifiques de bien exposer le contenu de leurs recherches. Ils emploient un jargon qui n'est pas du tout adapté, ce qui permet à certains groupes, dont c'est le fonds de commerce, de dénoncer les dangers, quelquefois virtuels. Je vous conseille de relire Macbeth, acte 3. La traduction est la mienne, mais c'est à peu près ceci *: « les gens ont plus peur de dangers virtuels que des risques réels. »* Je crois que cela n'a jamais été autant d'actualité par rapport au progrès.

La biologie de synthèse est inconnue du grand public pour le moment. Donc il ne réagit pas encore à ce sujet. Mais dans les nanotechnologies, en matière de téléphonie mobile et d'OGM, terme que je n'apprécie pas du tout, on mélange tout : le problème socio-économique et, sans doute aussi, la dimension scientifique. Mais le problème socio-économique soulevé par certaines firmes américaines pour ne pas les citer, est réel, y compris dans les pays émergents, avec ces semences. Dans le domaine des organismes génétiquement modifiés, les opposants feignent de méconnaître que les OGM sont à l'origine de multiples progrès : les vaccins, la lutte contre la rage, le pain que l'on mange, l'insuline dont on a besoin. Donc le slogan « Non aux OGM » est une supercherie intellectuelle. Ou alors les gens ne mangent plus, ne boivent plus, ne se vaccinent plus ! Il y a un vrai débat sur les PGM, et je l'accepte pleinement. Oui, en ce qui concerne les plantes génétiquement modifiées, les cultures en plein champ, il faut examiner ce qui se passe. Pour ce faire, je regrette quand même l'expérience de Colmar, où toutes les associations étaient présentes, associées, dans un comité de suivi. Or, cette expérience, visant à lutter contre le court-noué de la vigne, a été sabotée. Pourtant, j'avais, essayé de défendre en tous cas, une commission locale d'information et de suivi, comme cela existe pour certains équipements de type Seveso, et évidemment pour les centrales nucléaires, qui sont d'actualité. Mais sur des expérimentations en grandeur réelle, plein champ, pour démontrer éventuellement les risques, le problème, c'est de procéder à une expérimentation transparente, et avec une « vigilance prudente ».

Voilà les quelques propos que je voulais tenir en introduction. Mais je suis persuadé qu'il y a de plus grands spécialistes concernant ce problème de science et de société. Je donne la parole à M. Jean-Michel Besnier.

M. Jean-Michel Besnier, professeur à l'Université de Paris IV - Sorbonne. Je me réjouis d'adosser mon propos à votre introduction, puisque je vais reprendre un certain nombre de vos thèmes. Pour ce qui me concerne, je ne suis pas un expert en biologie de synthèse, je suis tout simplement un observateur de l'accueil des technologies dans les sociétés modernes. Je le fais avec une culture de philosophe. Et je suis d'accord avec vous, **on ne parle pas encore dans le**

grand public de la biologie de synthèse, mais c'est précisément la raison pour laquelle il faut anticiper le débat qui aura lieu inévitablement dans un avenir proche.

Je partirai d'un constat que je vais formuler de la manière suivante : **l'innocuité démontrée d'une innovation n'est pas toujours le gage de son acceptation par le public**. Je crois que c'est un constat qu'on a pu vérifier évidemment avec les OGM, les PGM ou les ondes électromagnétiques, les nanotechnologies. Je pense qu'il faudrait essayer d'éviter de commettre les mêmes erreurs avec la biologie de synthèse, en étant bien convaincu que ce n'est pas parce qu'on rassurera techniquement le public qu'on coupera court à tout débat. **Car il me paraît important de prendre en compte les représentations, les risques virtuels, les risques imaginés, fantasmés**. Il faut, je crois, prendre en compte les extrapolations que génèrent d'une façon générale les innovations technologiques. C'est ce que ne font pas les experts lorsqu'ils s'expriment en tant qu'experts. Ils croient couper court à la discussion en exhibant des faits, des évaluations, et ils sont souvent les premiers étonnés de constater que cela ne suffit pas à lever les objections.

Je crois, pour le dire encore autrement, que l'échec des débats publics récents, que ce soit celui sur les nanotechnologies, et antérieurement celui sur les OGM, a montré la nécessité de distinguer entre la question technique de l'évaluation des risques et des inconvénients, et la question éthique du bien-vivre collectif et des idéaux sociaux. En effet, **si la biologie de synthèse se révélait sûre, elle n'en poserait pas moins la question du bouleversement mental et sociétal qu'elle risque d'impliquer au cas où elle réaliserait les annonces tapageuses que l'on diffuse assez volontiers dans l'espace public**. J'y insiste, parce qu'il me semble que le politique, les élus, sont précisément à la charnière des questions techniques et des questions sociétales. **Ils n'ont pas d'abord affaire à des consommateurs soucieux de leur sécurité et de leur bien-être, mais à des citoyens désireux de bien commun**. De ce point de vue, l'élu, le politique, doit compter avec l'imaginaire généré par ces technologies, en dépit même des satisfactions qu'on pourrait donner au consommateur. C'est ce qu'a pu expérimenter, je crois, votre collègue Alain Gest à propos des ondes électromagnétiques : le résultat de son travail a pu mettre en évidence justement cette dissociation nécessaire entre les questions techniques, qui appellent évaluation des risques et des avantages, et la question éthique du bien-vivre collectif.

La biologie de synthèse, Mme Geneviève Fioraso le disait tout à l'heure, *« c'est une discipline, sans en être tout à fait une »*… **On a du mal à qualifier cette biologie de synthèse**. Appelons-là une discipline pour l'instant. Je crois que c'est une discipline à haut potentiel de fantasmatisation. Le philosophe trouve matière à penser avec la biologie de synthèse, parce qu'il est en pleine métaphysique. Et pour une fois, ce n'est pas de son fait. Ce sont les acteurs mêmes de la biologie de synthèse qui alimentent cette fantasmatisation. Ce sont eux qui

annoncent, qui ont annoncé, à un moment ou un autre, qu'ils allaient créer de la vie sans ADN. Et ce sont eux qui définissent la biologie de synthèse dans les termes suivants, selon la définition proposée par le consortium européen Synbiology : *« La biologie de synthèse, c'est l'ingénierie de composants et systèmes biologiques qui n'existent pas dans la nature, et la réingénierie d'éléments biologiques existants. Elle porte sur la conception intentionnelle de systèmes biologiques artificiels, plutôt que sur la compréhension analytique de la biologie naturelle. »* Cette définition mériterait un large commentaire, parce qu'il y a en elle énormément d'éléments implicites. La chose la plus évidente, c'est donc cette ambition de créer, on s'exprime bien en termes de création, ce qui est éminemment théologique, la création venant se substituer à la compréhension. À une approche scientifique qui visait à nous faire comprendre le monde, on substitue une approche qui vise à intervenir, à transformer le monde. D'ailleurs, c'est pourquoi on parle de plus en plus de technosciences aujourd'hui. Cette idée de produire des créatures vivantes qui n'existent pas dans la nature, c'est une ambition qui est proprement métaphysique, et qui va mettre en avant un certain nombre d'événements mentaux qui vont finir par pénètrer l'esprit du public, et conditionner son attitude à l'égard de ces réalisations-là.

Par exemple, l'idée d'hybrider l'artificiel et le naturel, c'est un bouleversement que les philosophes qualifieraient d'ontologique. C'est la conception même de la réalité qu'on est en train de bouleverser. Ce sont le mixte et l'impur qui prennent le dessus. Il y a dans l'ambition de la biologie de synthèse quelque chose de démiurgique, ce pourquoi, d'ailleurs, les premiers à commenter les réalisations de la biologie de synthèse dans le champ des sciences humaines et sociales comparent volontiers la façon dont on décrit l'acteur de la biologie de synthèse aux procédés mis en œuvre par l'alchimiste. Pourquoi ? Il y aurait quantité de raisons, mais essentiellement parce que la biologie de synthèse met en évidence le continuum entre l'inerte et le vivant, ce qui est proprement bouleversant dans les cadres cartésiens qui sont les nôtres, et qu'on est en train de bousculer.

La biologie de synthèse, c'est aussi une discipline qui révèle, je dirais, la vraie nature de la science. On nous a traditionnellement bercé dans l'idée qu'il pourrait y avoir une science pure, une science hypothético-déductive, une science sachant, en tout cas, contrôler ses moyens et ses effets. Et là, avec la biologie de synthèse, on a affaire à la manifestation d'une science qui pactiserait avec le bricolage, avec le tâtonnement. On parle de « biologistes de garage » pour parler des acteurs de la biologie de synthèse, on évoque les « biohakers », etc. On est donc dans une posture épistémologique, pardonnez-moi le jargon ici, qui est clairement anti-positiviste, c'est-à-dire qui va à l'encontre de l'esprit dans lequel la Troisième République nous a fait grandir dans la science. Et cet anti-positivisme, il est perçu comme un facteur d'insécurité, un motif d'insécurisation. C'est la raison pour laquelle la science délivrée du positivisme est de moins en moins associée à l'idée d'un progrès linéaire. Elle est au contraire plus volontiers pensée en termes de rupture, d'émergence. Elle est supposée pouvoir faire émerger l'inédit, surprendre

ses acteurs. Si l'on ajoute à cela l'engouement pour les sciences de la complexité qui mettent en avant le caractère imprédictible des systèmes, on a là tout un contexte qui va justifier vraisemblablement la vulnérabilité du public lorsque les annonces ou les réalisations de la biologie de synthèse lui seront présentées médiatiquement.

La biologie de synthèse, je dirais aussi que c'est, à sa façon, le symptôme de l'ambivalence qui est la nôtre par rapport aux idéaux modernes. Les idéaux modernes, ce sont ceux qui se sont trouvés exprimés au sortir de la Renaissance, avec le développement de la science, des techniques, associées à l'idée du progrès. L'ambivalence qui est la nôtre à l'égard de la modernité, on pourrait l'exprimer en termes de paradoxe. Nous continuons de vouloir l'émancipation grâce à la science, nous continuons de penser la science comme un facteur d'émancipation par rapport au déterminisme naturel, par rapport à la condition qui est la nôtre, et en même temps, nous redoutons de plus en plus les transgressions générées par les techniques. En toute logique, nous devrions être adeptes de toutes les transgressions du monde, puisqu'elles servent l'objectif d'émancipation. Et pourtant, nous en sommes incapables. C'est la raison pour laquelle on voit le retour des « luddites », comme on les appelle, dans le paysage public. Et c'est la raison pour laquelle on s'inquiète de savoir comment on pourrait bien se réconcilier avec l'idée de progrès.

La biologie de synthèse présente également le visage d'une certaine esthétisation. Les manipulations sur le vivant sont aujourd'hui de plus en plus le prétexte à esthétique. Il se développe un « bioart ». J'ai rencontré des bioartistes qui soutiennent que les réalisations qu'ils produisent en hybridant l'électronique et le vivant seraient destinées à désenchanter le monde de la biologie de synthèse. À leur manière, ces artistes pensent pouvoir faire œuvre pédagogique, en montrant qu'il n'y a pas de miraculeux dans tout ça, puisque tout un chacun peut le faire, à commencer par l'artiste. Mais cette esthétisation a un revers. Elle conforte une certaine célébration du *bottom-up*, de l'émergenciel. On cède volontiers à une espèce de « mystique de l'immaîtrise », pensée comme la dernière chance, là où la maîtrise a connu une impasse. Ce sont évidemment là des discours de philosophes, d'essayistes, qui s'attachent à dire que les idéaux de maîtrise associés au cartésianisme se sont révélés comme une impasse. Nous avons échoué dans l'émancipation grâce aux sciences et aux techniques. Et aujourd'hui, nos sciences et nos techniques nous donneraient seulement les moyens d'influer sur les conditions initiales des systèmes, de sorte à faire émerger quelque chose qui ne pourra pas être pire que ce que nous avons généré délibérément. Je fais écho à tous les fantasmes qui entourent les NBIC (Nano-Bio-Info-Cogno), à tous ces mouvements - qu'on les appelle transhumanistes ou comme on voudra -, à tous les arguments qui militent en faveur de l'avènement d'une singularité. Tous ces mouvements technophiles attachés aux réalisations high-tech partagent la conviction qu'on tient les moyens de faire émerger quelque chose de profondément inédit, qui pourrait constituer une relance, évidemment après la rupture et dans la non-linéarité, susceptible de constituer comme une planche de salut. Et la biologie de synthèse s'inscrit déjà

dans ce paysage propice à l'émergence de l'inédit, offert au point de vue de ceux qui vont la fantasmer et la communiquer.

Par ailleurs, il y a aussi un contexte disons sociopolitique favorable à l'apparition ou à l'installation de la biologie de synthèse. En effet, la biologie de synthèse apparaît facilement comme l'emblème de l'innovation que l'on érige aujourd'hui en principe de développement dans le contexte des sociétés modernes, où la compétition, la compétitivité, nous sont présentées comme fatales et inéluctables.

Je vais conclure sur cette idée de l'innovation pour l'innovation, sans finalité autre qu'elle-même. Je fais écho à ce que j'évoquais tout à l'heure en parlant des « biologistes de garage ». C'est cette idée que l'innovation, mise en avant comme elle l'est aujourd'hui, risque d'écraser toute réflexion éthique sur les finalités. De ce point de vue, pour faire écho à Mme Geneviève Fioraso qui en appelait à une attitude positive à l'égard de la biologie de synthèse, je crois que la seule attitude positive que nous puissions espérer, outre le fait que la biologie de synthèse sera présentée comme une solution au paludisme, au cancer, à la pollution, etc., cette attitude positive ne pourra être adoptée que parce que la biologie de synthèse apparaîtra comme un projet associé à la philosophie d'une humanité réconciliée avec elle-même et non pas désireuse d'échapper à ses limites, dans une fuite en avant, qu'on l'appelle innovation ou autrement.

M. Daniel Raoul. Ce que vous avez évoqué, ce n'est pas tout à fait une nouveauté par rapport aux dérives possibles. Savez-vous quelle sera la différence entre un homme réparé et un homme augmenté ? Je disais à Mme Jouanno : vous connaîtrez un jour une championne d'arts martiaux qui aura sans doute, au-delà du dopage chimique, un dopage technologique possible avec des nano-implants. Je ne vais pas me pencher outre mesure sur ce sujet.

M. Brice Laurent, Ingénieur des Mines, doctorant au Centre de sociologie de l'innovation à l'École des Mines. Je termine actuellement une thèse consacrée aux nanotechnologies, en particulier aux questions politiques que soulève ce domaine. Ma question, c'est de savoir comment on traite des nanotechnologies en démocratie. Je ne suis pas spécialiste de la biologie de synthèse, mais je pense néanmoins que le cas des nanotechnologies est extrêmement intéressant pour soulever quelques enjeux pour le traitement démocratique de la biologie de synthèse.

Il y a de nombreuses similarités et de nombreux liens entre les nanotechnologies et la biologie de synthèse. On en a déjà un peu parlé avec l'intervention de Mme Françoise Roure. **La biologie de synthèse suit le développement des nanotechnologies. Comme les nanotechnologies, elle amène à construire de nouveaux objets, des objets qui entrent mal dans les classifications des régulations nationales ou européennes**. Et comme les nanotechnologies, elle fait l'objet d'une politique scientifique très large, qui touche

à de nombreux domaines, et qui, à ce titre, peut poser des questions extrêmement différentes, pouvant concerner potentiellement toute la société.

Pour réfléchir à la question du débat public autour de la biologie de synthèse, je voudrais essayer de tirer deux enseignements à partir de l'exemple des nanotechnologies. Mon intervention va s'inscrire directement dans la continuité de l'intervention précédente. Et puis j'aurai quelques points de différence, je pense que ce sera intéressant pour la discussion.

Le premier point a trait à la nature même de la biologie de synthèse, qui consiste en la création de nouveaux objets, de nouveaux êtres, comme je disais, qui ne figurent pas, qui entrent mal dans les catégories des réglementations ou dans les catégories scientifiques. Pour les nanotechnologies, on crée des substances chimiques que la régulation a du mal à attraper, puisque tout simplement on ne sait pas **différencier, dans la réglementation existante, deux substances qui ne diffèrent seulement que par la taille, quand bien même ces substances auraient des propriétés différentes. Dans le cas de la biologie de synthèse, on arrive à peu près au même problème, en créant des objets qui sont à la fois artificiels et vivants**, qui ont des propriétés nouvelles, peut-être des risques. Doit-on les réguler comme des substances chimiques ou comme des objets biologiques ? C'est une question qu'on peut se poser.

Dans les nanotechnologies comme dans la biologie de synthèse, l'enjeu, un enjeu politique central, a trait au mode de gestion de ces nouveaux objets. Le mode de gestion, c'est non seulement définir des dispositifs qui peuvent les prendre en charge, mais c'est aussi caractériser ces nouveaux objets, si l'on souhaite imposer plus de contraintes sur ces nouveaux objets. C'est-à-dire : comment veut-on faire la différence entre un objet qui serait nano et un objet qui ne le serait pas ? Un objet qui serait de la biologie de synthèse et un objet qui n'en serait pas ?

Dans le cas des nanotechnologies, on a pu voir une série d'expérimentations très intéressantes, qui sont, d'une certaine façon, des expérimentations démocratiques, des façons de faire fonctionner la démocratie, et qui ont trait précisément à la fabrique de ces objets. On en voit l'exemple dans des organismes de normalisation. **En France, à l'AFNOR par exemple, un projet en cours vise à développer une norme nanoresponsable**. Elle donnerait des outils, pour un industriel, visant à produire des nanomatériaux de façon à ce que cet industriel inclue, dans ses pratiques de production mêmes, les attentes, les inquiétudes, de tout un tas d'acteurs sociaux. On est dans une approche que les Anglo-Saxons appellent « *Safe by design* », c'est-à-dire qu'on construit l'objet de telle sorte qu'il prenne en charge les problèmes publics, les attentes de la société.

Ici, on est dans une approche qui est assez différente de ce que M. Jean-Michel Besnier évoquait tout à l'heure sur le fait qu'on pouvait tout à fait séparer la question éthique de la question technique. Je voudrais prendre le contrepoint. **La construction des objets est une question qui est tout à fait technique. Il faut**

choisir des critères physico-chimiques, il faut définir des substances. En même temps, c'est une question éminemment politique. Si on choisit un critère physico-chimique plutôt qu'un autre, cela veut dire qu'un certain nombre de substances sont exclues de l'ensemble des nanomatériaux ou des substances qu'on veut considérer. Évidemment, c'est un enjeu énorme, à la fois pour les industriels et pour des acteurs de la société civile qui s'intéresseraient aux risques liés à ces nouvelles substances.

Si l'on considère qu'un problème démocratique central a trait à la caractérisation à la fois technique et politique de nouvelles substances, **cela veut dire aussi qu'il faut s'autoriser l'expérimentation de dispositifs qui permettent de discuter collectivement de problèmes qui sont à la fois techniques et politiques. L'exemple de la norme de l'AFNOR démontre que cette chose-là est possible**. Mais si cette chose-là est possible, il faut bien voir que traiter cette question, résoudre ce problème, ne peut se faire en se disant qu'il n'y a qu'une seule façon de faire du débat public ou de faire de la démocratie participative, il n'y a qu'une procédure valable partout qu'on pourrait répliquer sur un problème après un autre. Au contraire, je pense que, dès lors qu'on a pris au sérieux la question politique de la création de nouvelles substances, il faut se dire qu'on va expérimenter des dispositifs qui vont justement permettre le traitement politique de ce point. Sur ce point, on pourra suivre ce que disait Mme Geneviève Fioraso, à savoir **comprendre le principe de précaution comme un principe actif qui construit des substances collectivement, de sorte que l'innovation technique et la démocratie puissent fonctionner**.

Qu'est-ce que cela signifie pour la fabrique de ces expérimentations démocratiques de ces nouveaux dispositifs ? Cela implique qu'on ne peut pas solidifier trop vite, en tous les cas, **on ne peut pas solidifier *a priori* à la fois la technologie et le public**. Avoir une vision monolithique de la technique, et donc de l'ensemble des objets de la biologie de synthèse, conduit à s'interdire précisément d'examiner le détail des caractéristiques techniques à prendre en compte pour la gestion publique des objets. De façon symétrique, avoir une vision monolithique du public, qui serait par exemple un grand public à qui on va expliquer des avancées techniques qu'il finira par comprendre, interdirait de réfléchir aux façons de traiter collectivement de la fabrique de nouveaux êtres. Au contraire, il faut se dire que ce sont de nouveaux groupes concernés, de nouveaux acteurs sociaux, qui doivent être impliquées à mesure qu'ils sont justement concernés par les problèmes.

Cette perspective étant exposée assez brièvement, il faut bien voir que je ne suis pas en train de dire qu'on tient là la façon consensuelle, collective, de produire l'avenir du développement technologique. C'est le deuxième enseignement que je voulais tirer de l'exemple des nanotechnologies. On peut effectivement **tenter de faire des expérimentations démocratiques, sachant qu'elles sont intrinsèquement sujettes à controverse. Elles ne seront jamais sans heurts**. La chose se passe à deux niveaux, il me semble.

Premier niveau. À partir du moment où l'on se dit qu'on va discuter collectivement de la fabrication de nouvelles substances, de la façon de les gérer, de caractéristiques techniques à prendre en compte, forcément il y a des oppositions qui vont jouer. Ce n'est pas du tout un problème. **En démocratie, je pense que c'est même plutôt sain que des pouvoirs publics par exemple, qui doivent contrôler des industriels, n'aient pas exactement les mêmes intérêts que ces mêmes industriels**. Au contraire, il faut trouver des enceintes, des dispositifs, où ces intérêts puissent se discuter, se confronter, et éventuellement se stabiliser. Sur cette question des controverses, on peut donc faire des expérimentations démocratiques. Elles doivent mettre au jour des oppositions entre des intérêts divergents.

Deuxième niveau. C'est un autre aspect de ce problème d'opposition, de controverse. Les critiques sont parfois extrêmement virulentes et parfois difficilement gérables. Le cas des nanotechnologies est significatif à cet égard. La plupart des gens présents ici ont à l'esprit le débat national qui s'est déroulé l'an dernier, où toutes les réunions publiques étaient interrompues par un groupe d'activistes anti-nanotechnologies. Du coup, la question est la suivante : que fait-on avec ces critiques-là ?

Il y a plusieurs choses à voir. D'abord comprendre quels sont les ressorts du refus, pourquoi il y a ces critiques, et d'où elles viennent. Je pense que c'est le point principal à bien saisir, et là encore, c'est peut-être une différence avec l'intervenant précédent, qui faisait référence aux fantasmes, aux grands problèmes philosophiques posés par l'innovation technique. Pour ma part, j'insisterai plutôt sur des façons de poser des problèmes qui sont différentes. Si l'on prend l'exemple des activistes les plus virulents dans le cas des nanotechnologies, leur façon de se poser le problème, c'est de se dire : *« nous, allons nous mettre à distance du programme des nanotechnologies, et nous mettrons en évidence ce que nous imaginons être des intérêts cachés, des intérêts économiques, des intérêts financiers, des liens coupables entre sciences humaines et développement technique par exemple »*. C'est une façon de poser le problème qui en fait un problème de critique sociale, ce qui n'est pas du tout compatible avec ce que je vous proposais juste avant, c'est-à-dire de faire une construction collective des nouveaux objets. Donc il faut bien comprendre que ce n'est pas du tout une histoire de compréhension plus ou moins bonne de la technologie, mais des façons distinctes de poser les problèmes publics.

Le cas des nanotechnologies nous donne un exemple assez radical et très frappant. On peut réfléchir à beaucoup d'autres choses. On a parlé des OGM. Là aussi, on voit très bien, et toutes les études de perception du public l'ont montré, que **le refus des OGM de la part de l'opinion publique européenne était moins dû à une mauvaise compréhension des risques et des bénéfices qu'à une façon différente de poser le problème des OGM qui est la suivante : *« les OGM posent un problème d'organisation du système agroalimentaire. Qui détient la***

propriété industrielle ? Qui décide de ce qu'on met sur les marchés, de ce qui est contrôlé ? Donc il y a un problème de légitimité démocratique, de construction du système technico-politique ».

Pour résumer le deuxième enseignement que je voulais tirer des nanotechnologies, il faut se dire que la fabrication démocratique de la technique met en jeu nécessairement différentes façons de se poser les problèmes. **En démocratie, c'est plutôt sain qu'il n'y ait pas qu'une seule façon de se poser les problèmes publics. On peut imaginer d'être attentif à ces différentes problématisations, tout en sachant que c'est complètement illusoire de se dire qu'on aura une espèce de consensus général où toutes ces définitions des problèmes pourraient venir ensemble**. La problématisation critique en est un très bon exemple, en se mettant à distance du programme pour en faire une critique sociale. **C'est le meilleur exemple de la difficulté à regrouper de façon consensuelle l'ensemble de ces positions**.

Pour conclure, je vais revenir sur le problème des relations avec la société, sur le problème du débat public, en insistant vraiment sur ce point : quel est le problème que nous voulons traiter ? Je dis « nous » avec beaucoup de guillemets, que ce soit les décideurs ou nous-mêmes en tant que société. **Est-on en train de se dire que le développement de la biologie de synthèse est acquis et qu'il s'agit simplement de s'assurer que chacun est persuadé de sa valeur ? Dans tous les cas, il y aura là, forcément, des façons concurrentes de poser le problème qui vont arriver, qu'on pourra gérer de façon plus ou moins satisfaisante. Le problème peut aussi être : choisit-on de définir collectivement une politique scientifique et des objets techniques ?** Ce qui est beaucoup plus ambitieux, ce qui requiert une certaine innovation procédurale en termes d'expérimentation démocratique, ce qui impose de ne pas considérer comme figées les institutions qui, à la fois, font fonctionner la démocratie et construisent les systèmes techniques, et s'autorisent justement des expérimentations démocratiques.

M. Daniel Raoul. Ces deux interventions étaient complémentaires, même s'il pouvait y avoir de petites différences dans les approches. Je pense que chacun est imprégné de sa culture propre dans l'analyse de ce problème. Vous êtes dans un centre d'innovation scientifique, l'École des Mines, et vous, votre spécialité, c'est la philosophie. On voit bien l'approche des deux cultures. Il nous reste à entendre quelqu'un, j'allais dire, qui met les mains dans le cambouis, mais ce n'est pas le terme que je devrais employer au CEA. Cela a d'ailleurs été l'une de mes premières surprises, lorsque je suis arrivé à l'Office, c'est là que j'ai découvert que le CEA était l'un des acteurs majeurs des sciences du vivant. Alors que pour nous, le CEA est connoté énergie nucléaire...

M. Alexei Grinbaum, philosophe au Laboratoire des recherches sur les sciences de la matière, Commissariat à l'énergie atomique et aux énergies alternatives (CEA). Mais aussi de l'électronique.

M. Daniel Raoul. Oui, mais cela ne m'a pas échappé. Mais les sciences du vivant, cela me paraissait un peu exotique par rapport à la mission originelle qui lui avait été donnée par le général de Gaulle. Enfin, vous êtes donc philosophe en même temps, mais vous allez sans doute nous faire une intervention qui sera elle aussi imprégnée de la culture de l'organisme auquel vous appartenez.

M. Alexei Grinbaum. Merci monsieur le président. C'est un grand organisme qui comprend 15 000 chercheurs, comme vous le savez, sur plusieurs centres en France. Si je parle aujourd'hui, ce n'est pas en tant que physicien, mais en tant que philosophe. Je fais partie d'un laboratoire du CEA de philosophie des sciences[1]. Depuis bientôt quatre ans, c'est une première pour le CEA, qui est ainsi devenu un moyen de réflexion sur les relations entre la science et la société.

M. Daniel Raoul. Ce sont ceux qu'on entend sur certaines radios, le Pr Etienne Klein…

M. Alexei Grinbaum. Oui, M. Vincent Bontems, M. Etienne Klein… Je vais commencer par ma définition de ce qu'est l'éthique des sciences et des technologies. C'est la différence entre deux conditions de l'homme, avec et sans cet objet que vous voyez entre les mains d'Adam et Eve sur cette représentation de peinture flamande (où l'on a remplacé le fruit défendu par un iPod). La question de l'éthique, c'est : quelle est cette nouvelle condition que nous créons pour l'homme dans le monde, en amenant dans ce monde différents objets technologiques ? Cette question se pose depuis 2000 ans, même plus. Aujourd'hui, cette question se pose pour la biologie de synthèse. Cette question ne se pose pas non plus pour la première fois. Concernant la biologie de synthèse, je vous signale par exemple l'existence en Europe de quelques rapports extrêmement intéressants, celui du Groupe européen d'éthique (EGE) par exemple, sur les questions éthiques de la biologie de synthèse[2], ainsi que plusieurs ouvrages et articles scientifiques traitant de ce sujet. C'est donc un sujet de discussion qui aujourd'hui apparaît en France, mais qui est déjà connu à l'échelle européenne par exemple.

Voici plusieurs questions qui ne sont pas nouvelles et dont je ne parlerai pas, tout en soulignant leur extrême importance pour le cas de la biologie de synthèse. Ces questions ont été posées par rapport aux autres générations de nouvelles technologies, non seulement les nanotechnologies, mais également les technologies de l'information, et même le nucléaire, même la radioactivité dans les années 20, et puis vous pouvez remonter jusqu'à la navigation en mer chez les Grecs et les Romains, qui a été une nouvelle technologie. Ce sont des questions juridiques, liées à la brevetabilité dont nous avons parlé. **Ce sont des questions de**

[1] CEA-LARSIM (Laboratoire des recherches sur les sciences de la matière)

[2] « Ethical Aspects of Synthetic Biology - Proceedings of the round-table debate », European group on ethics in science and new technologies to the European commission Brussels, 19 mai 2009. Pour télécharger le rapport : http://ec.europa.eu/bepa/european-group-ethics/publications/proceedings-ege-roundtables/index_fr.htm

justice distributive : qui en profite ? Et comment fait-on pour assurer la justice au niveau international, la justice intergénérationnelle, et puis la justice sociale tout court ? Ce sont les questions de biosécurité qui sont extrêmement importantes, c'est-à-dire le confinement, probablement l'orthogonalité et d'autres notions que nous avons déjà évoquées. Les questions de sûreté, ce sont des questions de risques mesurables, de la protection des travailleurs, des consommateurs, etc. Et finalement, la grande question qui, pour nous, est particulièrement intéressante, parce que dans le contexte français le principe de précaution est inscrit dans la Constitution, **c'est la question de gouvernance, ou de gestion de l'incertitude, la prise de décision devant un avenir incertain. Toutes ces questions sont extrêmement importantes et pourtant elles ne sont pas nouvelles. La biologie de synthèse pose un contexte nouveau mais réactive, réanime, ces questions déjà anciennes**.

Ce dont je vais vous parler est un peu similaire au cas des nanotechnologies. Très rapidement, on connaît non seulement les deux citations de Richard Feynman qui ont été évoquées pour la biologie de synthèse, et puis pour les nanotechnologies, *« there's plenty of room at the bottom »* (*« il y a beaucoup d'espace en-bas de nous »*), est une autre citation fondamentale pour l'image des nanotechnologies. Il y a des similarités dans les problèmes de définition, de normalisation, il y a un discours de convergence commun aux deux disciplines, les histoires de *top-down* et *bottom-up* sont communes aux deux domaines. Il y a plusieurs similarités structurelles entre la biologie de synthèse et le cas des nanotechnologies. Et puis je vais essayer de tirer quelques enseignements de ces documents extrêmement intéressants sur les questions éthiques des nanotechnologies, en particulier le rapport européen DEEPEN[1], et des documents que vous pouvez trouver dans les publications par exemple de mon laboratoire ou dans la revue internationale NanoEthics. Elles parlent de l'importance, pour comprendre la perception par la société des nouvelles technologies, de comprendre les récits, les histoires que les gens se racontent et que les scientifiques aussi racontent aux citoyens, à propos de l'innovation technologique. Je vais souligner cet aspect sur les relations entre science et société. Pour moi, il est fondamental de comprendre avant d'agir.

Pourquoi les récits ? Les citations de Platon et de spécialistes de la philosophie grecque, même si elles n'ont rien à voir avec la technique d'aujourd'hui, posent exactement le même problème que pose Hans Jonas dans son ouvrage fondamental « Le principe responsabilité », écrit il y a trente ans (1979). L'esprit se polarise, on parle même d'une religion d'urgence. En l'état qui est le nôtre, les gens sont gouvernés, dit Platon, non pas par la connaissance, mais par la passion, par le plaisir, par la souffrance, par l'amour, et souvent par la peur. Et si

[1] « Reconfiguring Responsibility : Deepening Debate on Nanotechnology », DEEPEN project (Deepening Ethical Engagement and Participation in Emerging Nanotechnologies), sept. 2009. Pour télécharger le rapport final : http://www.geography.dur.ac.uk/Projects/Default.aspx?alias=www.geography.dur.ac.uk/projects/deepen

Hans Jonas nous pose exactement les mêmes défis pour les technologies du XX^{ème} siècle, ce n'est pas un hasard, c'est parce que la société perçoit les nouvelles technologies, les innovations, en termes de grands récits. Quels sont-ils ces grands récits ? On peut en faire plusieurs listes. Ce sont les histoires que vous connaissez : Prométhée, Golem, Frankenstein, La boîte de Pandore, qui est très pertinente, Dédale, etc., qu'on lie aux questions d'éthique et des sciences et techniques aujourd'hui.

Un exemple : le Livre de Tobie. Une histoire extrêmement intéressante, dont je vais essayer de tirer quelques leçons. Dans le Livre de Tobie, on raconte que Tobie, qui est parti en voyage, descend un jour dans un fleuve. *« Comme il descendait sur la rive pour se laver les pieds, voici qu'un énorme poisson s'élança pour le dévorer. Effrayé, Tobie poussa un grand cri, en disant: " Seigneur, il se jette sur moi ! " L'ange lui dit : " Prends-le par les ouïes et tire-le à toi. " Ce qu'ayant fait, il le tira sur la terre sèche, et le poisson se débattit à ses pieds. L'ange lui dit : " Vide ce poisson, et conserves-en le coeur, le fiel et le foie, car ils sont employés comme d'utiles remèdes. »* ***(Tobie, ch. 6)*** Comme on dirait aujourd'hui, il utilise ce poisson à des fins de nouvelles technologies médicales. Alors que se passe-t-il ? Comment est-ce possible que Tobie, finalement, de cet état de peur et presque de perte de contrôle, ait pu savoir en un seul instant ce qu'il fallait faire ? Ce n'est pas seulement le problème de la nouveauté. **Évidemment, on a peur de ce qui est nouveau**. C'est une des leçons à tirer de ce récit. Ce sont les récits de nouveauté qui font le plus peur. **Mais c'est également une question d'éducation**. Je veux revenir en force sur ce sujet qui a déjà été mentionné plusieurs fois. **Ce qu'il faut faire, c'est éviter qu'il y ait une réaction spontanée, une réaction momentanée, irréfléchie, de la part du public**. J'en ai parlé dans quelques publications[1]. Pour éviter cette réaction spontanée, qui est une réaction de peur, et **pour exiger que le citoyen se donne un temps de réflexion, il faut de l'éducation, peut-être pas nécessairement de la vulgarisation scientifique, mais en tout cas, l'explication de ce qu'est la méthode scientifique, et ce, dès le jeune âge**.

Je veux souligner que parmi les Ministères commanditaires du débat public sur les nanotechnologies, le Ministère de l'Éducation nationale a été absent, contrairement à ce qu'on voit par exemple aux Etats-Unis, où la *National nanotechnology initiative* (NNI) consacre un énorme financement aux questions d'éducation. Vous voyez ce qu'il en est résulté en France, comme cela a été rappelé. À ce titre, je vous propose de comparer la mise en page du site web du débat français sur les nanotechnologies[2], conçu dans la bonne tradition philosophique cartésienne, où il y a quand même beaucoup de mots. Sur le site web du débat national néerlandais sur les nanotechnologies[3], on voit par exemple ce

[1] « Barrières cognitives dans la perception des nanotechnologies », Alexei Grinbaum, in Revue Réalités industrielles, mai 2007, pp. 47-53
[2] www.debatpublic-nano.org
[3] http://www.nanopodium.nl

professeur, très sérieux. Et si on compare avec le site web du débat national anglais sur les nanotechnologies[1], vous voyez bien qu'il peut exister plusieurs approches différentes par rapport au débat national sur les nouvelles technologies. L'approche choisie en France, qui a conduit à un échec très malheureux, n'est pas la seule approche existante.

Pour conclure, je dirai que ce qui concerne la biologie de synthèse en particulier, ce sont les récits liés à la création du vivant, à la création de la vie. Est-ce que c'est de la création, ou juste la recomposition, le réassemblage de quelque chose qui existe déjà ? Paul Valéry disait : Ce qui a un but n'est pas vivant, c'est artificiel.[2] Parle-t-on encore de la vie ? Cette notion même va-t-elle évoluer dans le langage commun ? Je n'aurai pas le temps de vous raconter un très beau mythe de Golem sur lequel j'ai pu écrire également, car il pose toutes ces questions. Mais c'est à travers les récits qui ne touchent pas aux technologies d'aujourd'hui, mais qui font partie de la culture, qu'on arrivera à parler avec les citoyens.

Finalement, un autre récit touche au problème du désir, de la perfection. C'est très intéressant quand on perfectionne quelque chose presque de façon illimitée. Est-ce qu'on brouille la frontière entre le désir, le sacré et le mal ou est-ce que la perfection est liée toujours au mystérieux ? Ce sont des questions de philosophie très profondes. Et ces questions, comme vous pouvez le lire dans cette citation du rapport DEEPEN sur l'éthique des nanotechnologies[3], ces questions font partie de la représentation que le citoyen se fait du scientifique. Le récit sur le désir illimité fait partie intégrante de l'idée que chacun se fait de cet homme derrière les murs de son immeuble scientifique. Est-ce qu'il désire perfectionner, un peu comme un démiurge ? Est-ce qu'il est possible de juger son activité à travers ces récits millénaires ? Je peux citer La boîte de Pandore ou Cicéron : *« En effet, la nature en aucun genre ne produit rien de parfait : elle semble craindre d'épuiser ses perfections en les prodiguant à un seul individu, et fait toujours acheter ses faveurs par quelque disgrâce. »* (Cicéron, *De inventiones*, II, 1).

C'est en se demandant quelles sont ces représentations fondamentales, ces récits qui circulent dans la culture, sur la science, sur la technique, que nous arriverons à un autre climat de débat que celui que nous avons vécu avec les OGM et les nanotechnologies. Et je tiens à souligner toute l'importance de cet enseignement éthique en France. **Si l'on considère par exemple le programme d'une des formations à la biologie de synthèse, la biologie de systèmes, tel que proposé en France, vous verrez que, dans ce cas précis, il n'y a pas un mot d'éthique. Nous devons donner aux futurs ingénieurs et aux futurs**

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[1] http://www.nanoandme.org

[2] « Tout ce qui parvient à apparaître sous la forme d'un but net et fini devient artificiel… Si la vie avait un but, elle ne serait plus la vie. » *Paul Valéry*

[3] *« the 'be careful what you wish for' narrative builds on the age-old notion that getting exactly what you want may not ultimately be good for you, and may, inadvertently, lead to unforeseen disaster and catastrophe. This narrative was especially potent in structuring public resistance to the seductive and apparently boundless promises provided by nanotechnologies. »* DEEPEN report, op. cit., pp. 18-19.

scientifiques des moyens de réflexion et des moyens de penser ces questions par eux-mêmes. Si on les laisse communiquer spontanément leur avis, encore une fois nous arriverons au même échec qu'avec le cas des OGM ou des nanotechnologies. Cette formation n'est pas unique. En toute formation en France, il y a bien quelques débuts de formation à la réflexion éthique, mais je pense que pour l'éducation, aussi bien que pour l'enseignement supérieur, ces questions sont d'actualité.

M. Daniel Raoul. Merci à tous les trois. Je pense que cela doit susciter quelques questions.

Débat

Mme Dorothée Benoît Browaeys, Déléguée générale de VivAgora. J'ai beaucoup apprécié la richesse des propositions qui viennent d'être évoquées. J'en ajouterai une du point de vue de l'importance au plan de la démocratie de ces sujets liés à la biologie de synthèse. C'est une question centrale à mon avis. Pourquoi a-t-on besoin de cette biologie-là ? Et là je me place en tant que biologiste, c'est ma formation. C'est-à-dire qu'il y a beaucoup de possibilités avec le vivant, il y a beaucoup de possibilités de travaux sur le vivant, d'usages des organismes vivants, et de considérations qui sont impliquées dans les différentes démarches de la biologie. Il y a une différence entre la valorisation des systèmes, la valorisation de l'histoire naturelle et la valorisation de l'information. Il est très clair ici que nous faisons des choix, en allant dans un investissement que d'ailleurs j'aimerais préciser du point de vue des efforts que la France met aujourd'hui dans la biologie de synthèse. Il n'y a pas de transparence dans ce domaine, alors que c'est une recommandation du rapport de la commission Obama. Ce serait donc intéressant d'avoir ces données. Ces investissements-là ne seront pas neutres du point de vue des valeurs qui sont données à un certain nombre de questions. On peut faire une biologie qui valorise le temps, c'est-à-dire le travail de l'évolution, la considération du temps. On peut faire une biologie qui valorise les interactions entre les organismes, et donc qui s'intéresse au milieu, à la biosphère. Et on peut faire une biologie, c'est celle-ci, qui s'intéresse au programme. Et donc, la question que je pose, et que posera forcément la société, c'est : pourquoi choisit-on cette biologie-là ?

On a eu en France beaucoup de réflexions sur la gestion du vivant, avec Michel Foucault, avec le biopouvoir, et on voit très clairement, avec les travaux de Rajan, qui a publié Le Biocapital[1], qu'il y a une certaine convergence à laquelle il faut réfléchir entre la valorisation des briques élémentaires et l'industrialisation,

[1] « Biocapital : the Constitution of Postgenomic Life », Kaushik Sunder Rajan, Duke University Press, 2006.

parce que c'est par ce biais-là que l'économie va pouvoir travailler. Et donc on a une convergence entre cette science-là et notre contexte économique. Et c'est là que je voudrais juste poser la question du moment démocratique sur lequel nous discutons ici. Dans le cadre de la dynamique des nanotechnologies, beaucoup ont évoqué le débat national, mais il y a eu un autre processus qui a fait l'objet de onze réunions tout à fait importantes, **c'est le NanoForum**. Ce NanoForum est typiquement un processus qui a dans ses gènes, ou dans son état d'esprit, l'idée d'une vigilance coopérative. Et nous ne pouvons pas nous en sortir aujourd'hui sur des questions aussi complexes avec la radicalité des questions qui ont été évoquées par Jean-Michel Besnier. Nous n'allons pas pouvoir impunément dire : voilà notre rapport au vivant, on considère les organismes vivants comme des boîtes à gènes. On ne pourra pas développer ce point-là sans poser cette question de la considération du vivant. Et ce que j'aurais voulu proposer à la discussion, c'est : dans quelle mesure, sur les différents aspects qui ont été développés, on métabolise dans la réflexion des questionnements sur l'utilité de ces projets, sur les choix qui sont faits en matière de rapport au vivant, sur les risques acceptables ou pas acceptables, sur les effets collatéraux. Tout cela, pour la société civile, va nécessiter véritablement un processus permanent. Et j'aimerais savoir si l'idée d'un processus permanent de dialogue ne serait pas véritablement une solution sérieuse.

M. Daniel Raoul. Je pense qu'à la base de votre interrogation, il y a la question de la raison d'être de cette technologie et les problèmes annexes qu'elle pose. La balle est dans le camp des partenaires de la table ronde précédente, pour apporter une réponse.

M. Vincent Schächter. Le sujet est certainement trop vaste pour l'épuiser ici. Plusieurs remarques sur votre intervention. La première, **c'est que le dialogue est important, et donc il faut réfléchir à la manière de l'organiser**. C'est certain. La deuxième, c'est qu'effectivement il y a des choix implicites de représentation qui sont faits à chaque avancée scientifique. En revanche, ils ne sont pas plus clairs que la définition de la biologie de synthèse, qui elle-même l'est assez peu. Autrement dit, et là je me place plus en observateur et ex-chercheur dans le secteur public qu'en industriel, je ne vois pas que la biologie de synthèse en elle-même, soit un ensemble cohérent. Je ne vois pas que le fait de faire avancer des recherches en biologie de synthèse en France ou à l'étranger représente un choix collectif sur la manière de faire de la biologie. Des avancées ont eu lieu en génomique qui ont fait débat dans les années 90. Ces avancées ont évidemment changé la manière de faire de la biologie 20 ans après. Pour autant, on continue à faire de la biochimie ; toutes les branches de la biologie continuent d'exister, mais informées par des outils nouveaux et des concepts nouveaux. Cela risque d'arriver pour la biologie de synthèse. Encore une fois, ce n'est pas du tout anodin qu'on ait du mal à dessiner une boîte dans les sciences du vivant à l'heure actuelle, grâce à laquelle la biologie de synthèse serait définie. Il est possible que les choses évoluent différemment, car beaucoup d'outils, qui sont en cours de développement, seront ensuite réutilisés dans beaucoup de branches des sciences du vivant, pour des finalités différentes,

mélangées avec d'autres outils. Certaines de ces finalités seront probablement très impliquées dans l'économie, d'autres pas du tout. Au contraire, vous aurez de la biologie de synthèse qui sera très exploratoire pour mieux comprendre le vivant, dépourvue de l'aspect utilitaire. Donc je pense qu'il faut y faire attention. La question de la définition est importante. Finalement, je répondrai que le débat est important, mais qu'en revanche, il faut l'appréhender dans toute sa complexité, ce sur quoi nous nous rejoignons.

M. Daniel Raoul. Sur l'autre partie de la question de Dorothée Benoît Browaeys, je vais solliciter M. François Képès, qui serait peut-être mieux à même de répondre sur la question de moyens, y compris dans le Grand emprunt. Quels sont les moyens prévus ?

M. François Képès, Directeur de recherche au CNRS à l'Institut de biologie systémique et synthétique et Directeur du programme d'Epigénomique de Genopole d'Evry. Je vais faire une intervention extrêmement brève et vraiment centrée sur cet aspect, même s'il y a bien d'autres choses qu'il serait intéressant de discuter. Au niveau des financements publics en France, c'est pour l'instant extrêmement limité. Cela vient de changer très récemment, et seulement avec les Investissements d'avenir, avec des sommes qui sont peut-être de l'ordre de quelques dizaines de millions d'euros. Il existait néanmoins un financement européen durant le 6ème programme-cadre qui a atteint un total de 25 millions d'euros, pour l'ensemble de l'Europe, et qui était effectivement un guichet spécifiquement dédié à la biologie de synthèse. Open Science Foundation a également ouvert un guichet très brièvement pour un seul appel d'offre. Si l'on excepte cela, on se rend compte qu'au niveau national il n'y a pas de guichet intitulé biologie de synthèse qui permette un financement. Aujourd'hui, ces financements publics sont faibles et contrairement au niveau européen, ils ne sont pas identifiés, au niveau national, comme biologie de synthèse.

M. Ariel Lindner, Professeur à l'Université de Paris V-Descartes, chercheur INSERM. À part mon travail de recherche à l'INSERM, je dirige aussi un master. Nous avons beaucoup entendu parler de comment il fallait éduquer la population, comment aborder le public, comment former les journalistes, notamment à travers des programmes de formation. En revanche, on a moins parlé de comment il fallait éduquer les scientifiques et comment ils devaient aborder les questions éthiques. Et comment les scientifiques, forts de ce savoir, peuvent l'appliquer quand ils enseignent ? Je pense que c'est une question très importante, et si quelqu'un pouvait me donner son opinion là-dessus, ce serait très enrichissant.

Je veux partager avec vous, en une phrase, ce que nous essayons de faire, parce que pour nous, c'était la méthode la plus efficace de procéder, même si ce n'est pas forcément le meilleur système. Ce que nous avons vu, c'est que lorsque

vous enseignez l'éthique, et que vous mettez des cas d'études sur la table, les uns et les autres peuvent les analyser et donner leur opinion. Mais quand on commence à leur parler de ce sur quoi ils travaillent vraiment, qu'il s'agisse de docteurs en médecine ou même d'étudiants dans une petite équipe, ils se défendent très fortement. Il leur est très difficile de dire autre chose que : « ce que nous faisons n'a rien à voir avec ces questions. » Alors, ce qu'on essaie de faire maintenant, c'est de constituer des panels d'experts qui viennent voir les étudiants au début de leur projet, et qui suivent le projet dans la durée afin de leur donner la possibilité d'exprimer leurs sentiments, leurs pensées, leurs craintes, de recevoir des retours d'information de la part d'autres personnes à propos de leur projet. C'est un projet pilote qui va débuter l'année prochaine et l'on a déjà quelques exemples de l'année passée. Ma question : avez-vous un meilleur système ? Et que pensez-vous de notre initiative ? Peut-elle être également appliquée à des scientifiques aguerris ?

M. Alexei Grinbaum. Ce que vous avez dit est tout à fait important. Je vais rajouter un élément. La question ne se pose pas seulement pour la biologie de synthèse, elle se pose pour l'ensemble des nouvelles technologies au niveau de la formation que nous donnons aujourd'hui aux scientifiques et aux ingénieurs. Les nouveaux objets qu'ils conçoivent sortent sur la place publique, et **la tour d'ivoire n'existe plus. Et nous devons donner aux scientifiques, pas seulement aux jeunes, des moyens de comprendre cette nouvelle situation où la tour d'ivoire n'existe plus, où ils sont exposés au dialogue, et souvent à la pression sociale.**

C'est une des questions que la Commission européenne s'est posée. Juste pour compléter votre information par rapport à ce que vous faites à Paris, la Commission européenne nous a demandé, à nous et à d'autres partenaires, de rédiger ce document qui est une sorte de boîte à outils dédiée aux scientifiques. Il s'intitule « *Toolkit for ethical reflection and communication* »[1]. C'est un texte de 70 pages qui permet au scientifique qui n'a pas été formé d'entrer dans la réflexion éthique. Et la généralisation de cette démarche, à la fois pour les programmes de formation et d'enseignement, mais également dans les laboratoires, pour les gens qui travaillent aujourd'hui en biologie et dans d'autres domaines, c'est quelque chose de tout à fait important.

M. Jean-Michel Besnier. Effectivement, l'éducation des scientifiques est une question cruciale. Elle devrait assurément passer aussi par une sensibilisation à l'éthique. Or on s'aperçoit que c'est extrêmement difficile. J'appartiens au Comité d'éthique du CNRS (COMETS), et je mesure à quel point on est quelquefois dans une situation perverse, liée au fait que la constitution des comités d'éthique dans les organismes de recherche a eu comme conséquence que bon nombre de chercheurs se sont imaginés qu'on pouvait professionnaliser l'éthique. On pouvait donc confier l'éthique à des experts. Et de plus en plus de chercheurs disent haut et fort que pour

[1] « *Toolkit for ethical reflection and communication* », ObservatoryNano-CEA-LARSIM, juin 2010. Pour le télécharger : http://www.observatorynano.eu/project/catalogue/4ET/

les questions éthiques, il y a des spécialistes, ce qui sous-entend qu'ils sont dédouanés de la prise en charge des questions afférentes à leur activité. Questions sur la finalité de ce qu'ils font, questions sur les risques par exemple, questions sur les effets d'annonce auxquels ils sont contraints souvent de céder, du fait même de la pression qui s'exerce sur eux. Ils en disent souvent plus qu'ils n'en peuvent, parce qu'il leur faut toujours aller plus loin. Toutes ces perversions-là sont difficiles à aborder. Et puis concernant l'éducation scientifique, je suis de ceux qui militent depuis longtemps pour que, dans les cursus scientifiques, à l'université et dans les grandes écoles, on introduise au moins l'histoire des sciences. L'histoire des sciences permet de mettre en perspective, de décentrer le point de vue. L'aptitude à la décentration est une des conditions pour qu'il y ait une sensibilité à l'éthique. Cela permet aussi de relativiser ce que l'on sait, et de poser, par exemple, la question que formulait tout à l'heure Dorothée Benoît Browaeys, à savoir : pourquoi est-ce qu'on fait cette biologie-là plutôt qu'une autre ? Il faut au moins savoir qu'on pourrait en faire une autre, qu'on a fait jadis et ailleurs d'autres biologies. De ce point de vue, l'initiation ou la fréquentation de l'histoire des sciences et des techniques dans les cursus scientifiques sont à mon avis capitaux.

M. Joël de Rosnay, Conseiller de la Présidente de la Cité des Sciences et de l'Industrie, membre du Conseil scientifique de l'OPECST. Je voudrais revenir sur cette question de l'éducation pluridisciplinaire, notamment pour la biologie de synthèse. Comme cela a été sûrement dit, ce n'est pas une discipline, c'est un carrefour pluridisciplinaire. Et donc je pense, avec d'autres, que l'on doit utiliser la méthode d'alternance pour former les jeunes à ces disciplines et à leurs applications. Nous venons d'ouvrir ce matin à Universcience le Forum de l'alternance, c'est-à-dire un forum qui est destiné à des jeunes apprenants pour savoir comment effectuer des stages en entreprise tout en poursuivant ses études, dans un aller-retour entre l'entreprise et les études. Je pense qu'il devrait y avoir une sorte d'alternance dans la formation en biologie de synthèse à trois : une alternance de formation dans les laboratoires, une alternance de formation théorique et une alternance de formation dans les entreprises que vous représentez. La formation théorique sur la biologie de synthèse nécessiterait une accumulation linéaire de disciplines sans interdépendance réelle entre elles. Il n'y a que la construction de projets, la création de projets, la capacité à résoudre des problèmes sur place pour revenir sur le plan théorique et approfondir. C'est pourquoi je pense aussi, qu'en plus de cette formation en alternance dans ces trois lieux, des concours comme le concours international de biologie synthétique du MIT iGEM (« *International Genetically Engineered Machine* »), sont des lieux de rencontre et de convergence des jeunes sur leurs idées. Hier, un autre colloque se tenait ici, auquel participait François Képès, sur les avancées et les percées en biologie de synthèse. Il y avait un groupe d'étudiants du Centre de recherches interdisciplinaires (CRI) de François Taddéi, que je salue. Il a réussi en France à créer des conditions réelles de formation pluridisciplinaire. Ces étudiants étaient tous en train de faire du *brainstorming*, de réfléchir au type de sujet qu'ils allaient

proposer au prochain concours iGEM. Je trouve que cette formation est indissociable de la notion de créativité, d'innovation et de stage d'alternance. On essaie de le faire à Universcience, notamment dans ce que l'on appelle l'éducation informelle, à travers toute une série de débats, de colloques, de rencontres, de groupes de travail, qui utilisent Internet, les réseaux sociaux et la pédagogie qu'on peut trouver aujourd'hui sur le Net. Donc c'est plus complexe que la formation traditionnelle.

Mme Geneviève Fioraso. Pour information, il se trouve que dans le cadre du rapport sur la biologie de synthèse que je dois rédiger pour le compte de l'OPECST, on a rencontré le créateur de iGEM. Les équipes françaises y participent, certaines ont même été lauréates, je pense à l'INSA de Lyon, à des équipes parisiennes. Elles sont donc bien intégrées dans cette dynamique. Actuellement est étudiée la possibilité de créer un iGEM-Europe, qui pourrait être localisé en France. Si on pouvait ensemble pousser cette idée, ce serait une bonne initiative, parce que c'est extrêmement stimulant pour les étudiants. Il y a un aspect créatif et ludique, ouvert à tous et un côté rassemblement d'idées qui paraît tout à fait intéressant. On est déjà bien inscrit dans cette dynamique. Si on pouvait ensemble la faire fructifier, je pense que ce serait très bien.

Depuis deux ans, l'éthique a été introduite. Je le dis pour Dorothée Benoît Browaeys, parce que ça marche aussi avec des récompenses, il y a ce côté un peu ludique pour les étudiants, à qui cela demande beaucoup de travail. Ils renoncent à leurs vacances d'été pour s'y consacrer. Ils ont des séances de formation. Depuis deux ans, la remise d'un prix pour l'éthique encourage justement, dès le début des recherches, et avant de se lancer dans des bioconstructions, la prise en compte de la finalité de la recherche et l'établissement d'une charte éthique. Il y a là aussi une démarche intéressante.

M. Ariel Lindner. On a gagné ce prix. L'équipe de Paris a gagné ce prix.

M. Jacques Joyard, directeur de recherche au CNRS, Laboratoire de physiologie cellulaire végétale, Université Joseph Fourier, Grenoble. Par rapport à la discussion qui a eu lieu entre vous deux, sans qu'y ait eu de discussion, sur le fait qu'il faille dissocier l'aspect technique d'un aspect un peu fantasmé, il me semble que la question ne devrait pas se poser. Quand on discute avec un certain nombre de personnes qui sont intervenues dans les débats sur les OGM, sur les nanotechnologies, etc, où les arguments qu'ils avancent sont avant tout des arguments fantasmés, leur revendication essentielle, c'est une question de transparence et une question technique, c'est-à-dire une question de connaissance d'expert. Donc il ne me semble pas qu'on puisse distinguer et dissocier complètement la prise en compte de l'aspect fantasmé des choses de l'aspect

technique. À mon avis, ce n'est pas possible. Dans la discussion que vous avez concrètement avec les gens, leur revendication essentielle, c'est d'avoir une sorte d'information technique, une sorte de réalité, et cela pose, à ce moment-là, la question de la qualité des experts, la reconnaissance des experts. À mon avis, c'est là que se situe le débat. On ne peut pas avoir de discussion s'il n'y a pas de reconnaissance de la qualité des autres.

M. Jean-Michel Besnier. C'est là que je ne suis pas tout à fait d'accord avec vous. Le débat sur les nanotechnologies l'a prouvé. Il y avait les gens qui venaient pour débattre et les gens qui venaient pour s'informer. Ces derniers attendaient effectivement des experts des informations. Ils situaient donc le débat au niveau technique. Les gens qui venaient pour débattre se croyaient dépositaires d'un savoir à propos des nanotechnologies, et ils venaient échanger des conceptions du monde. N'ayons pas peur du mot. Ils posaient la question : pourquoi veut-on ce monde-là ? Ils ne posaient pas la question de savoir si les chaussettes avec nanoparticules étaient nocives ou pas. Ils posaient la question : pourquoi voulez-vous qu'on fasse ce monde-là ? Donnez-nous des arguments pour nous expliquer que la prospérité de la société doit passer par « la maîtrise de l'invisible », puisqu'ils s'exprimaient volontiers en ces termes. Et ce sont ces gens-là qu'on n'a pas entendus, et qui se sont fait entendre malheureusement de la manière qu'on sait. C'est pour cela que je ne distingue pas l'approche technique du problème de l'approche fantasmée comme vous le disiez, mais de l'approche éthique. L'éthique pose la question de savoir quel type de société on veut collectivement. Ce n'est pas pareil que de se demander si c'est bon ou mauvais.

M. Jacques Joyard. Je ne suis pas tout à fait convaincu que leur question, c'était de vouloir savoir quel type de société on veut. Je ne pense pas que c'était cela la discussion. J'ai beaucoup discuté avec eux et je peux vous assurer que ce n'était pas cela leur interrogation.

M. Daniel Raoul. Non, je ne suis pas persuadé non plus. C'est donner beaucoup trop de valeur éthique à leur comportement.

M. Brice Laurent. Je pense que c'est important, quand on parle des gens, de se demander qui sont les gens. Dans la caractérisation technique des substances, dans les façons de faire l'analyse des risques, de construire de la réglementation chimique, **il y a un problème politique central, qui pose énormément de questions sur l'organisation collective. Quelles contraintes institue-t-on ?** À quels industriels ? Pour défendre quels intérêts ? Je suis aussi convaincu que ce n'est pas un problème qui intéresse tout le monde. Certains groupes peuvent être concernés par le problème, qui peuvent avoir envie de travailler dessus, de s'y investir, de défendre un point de vue particulier, et donc il faut trouver des

dispositifs qui permettent d'avoir cette discussion finalement assez pointue, mais qu'il n'y a aucune raison de réserver à une liste de gens qui serait définie a priori. Dans les gens en général, il y a aussi le grand public, qui ne connaît pas forcément le sujet, et qui peut poser le problème de façon complètement différente des gens à qui il lui parle. C'est un peu ce que disait Jean-Michel Besnier. Pour ma part, j'estime qu'il y a une bonne façon de discuter avec les gens. Encore une fois, cela dépend du problème auquel on veut répondre.

M. Vincent Schächter. S'agissant de la question de la représentation des gens et de leur origine, le regard sociologique sur la biologie de synthèse est intéressant. Ce débat sur les experts d'un côté et la société de l'autre, existe aussi au sein de la communauté scientifique. La biologie de synthèse s'est créée par des rencontres assez intéressantes entre des communautés qui ne se parlaient pas, d'ailleurs catalysées par des opérations comme iGEM. Une partie de la biologie de synthèse, celle de Randy Rettberg, de Drew Endy, etc., c'est une sorte de prise de pouvoir de la biologie par des ingénieurs. Cela a été vécu ainsi de l'intérieur et par le public. Les bandes dessinées de Drew Endy dans « Nature et Science » véhiculaient un discours lié à Internet, à l'open source, techno-libertaire d'ouverture. Je pense que c'est très important qu'on ait des initiatives comme iGEM et qu'on les soutienne, là je vous rejoins. Ce sont une sorte de laboratoire du débat de société, mais un laboratoire positif, avec des gens qui évidemment ont une motivation d'apprendre et de construire ensemble.

M. Thomas Heams, enseignant à AgroParisTech et chercheur à l'Institut national de la recherche agronomique (INRA). Un tout petit contrepoint en tant qu'enseignant, précisément pour rebondir sur ce point avec lequel je suis entièrement d'accord, sur ce thème du discours sur la biologie. Pour reprendre votre terme de « discours », de « *storytelling* » sur cette biologie qui serait forcément collaborative, forcément 2.0, forcément Wiki… Enfin, on l'entend beaucoup, et cela a beaucoup contribué à la popularité et à la pédagogie de cette approche multidisciplinaire. En outre, on a vu les succès des équipes françaises à iGEM, ce dont tout le monde se félicite vraiment, en tout cas c'est mon cas.

Cependant, je tiens à rappeler qu'il ne faut pas oublier l'enseignement disciplinaire, comme le montre une expérience vécue. De plus en plus d'étudiants me font part de leur souhait de devenir un biologiste de synthèse. Je leur conseille d'abord de commencer par être un bon biologiste, ou un bon informaticien, ou un bon modalisateur. Cela est très important.

Pour être un bon biologiste actuellement, il faut voir ces données massives qui sont en train de provenir de la biologie expérimentale, lesquelles relativisent le discours très important, qui a assimilé des organismes à des programmes d'ordinateur durant cinquante ans. La métaphore de la cellule-ordinateur, dont on se distancie tous plus ou moins rapidement, mais sur les brisées desquelles on continue de vivre, est quand même largement contredite par des dizaines d'articles par an sur l'expression aléatoire des gènes et sur le chaos qui règne à l'intérieur des

cellules. Il faut aussi y faire attention, dès lors qu'on a des visées pédagogiques sur l'enseignement d'une biologie de synthèse, à laquelle je suis très attaché par ailleurs.

M. Jacques Haiech, professeur à l'Ecole supérieure de biotechnologie de Strasbourg. Je pose une question de manière différente de la première table ronde. J'ai participé à la deuxième équipe française à iGEM, pas simplement dans l'idée de participer au concours, mais dans l'idée d'accompagner iGEM dans la construction d'une option pédagogique au niveau des enseignants de l'Ecole supérieure de biotechnologie de Strasbourg. A cet égard, je crois que **iGEM permet de réinventer ou de retrouver une pédagogie-projet qu'on avait essayée d'impulser au niveau du collège, et même avant, avec la main à la pâte, et qui n'a pas été un véritable succès**. Ce n'est pas une pédagogie qui se substitue à quelque chose mais qui se trouve réinventée. Elle relève de l'alternance, s'inscrit dans un projet pluridisciplinaire et dans lequel les étudiants sont acteurs. Si on peut accompagner ce type de concours par la mise en place de cursus qui utilisent cette pédagogie, je pense que ce serait extrêmement bien. Cela ne veut pas dire qu'on retire à la pédagogie son rôle de socle ou sa dimension disciplinaire permettant d'avoir un langage de base.

J'en viens à ma deuxième remarque par rapport à une question qui a été posée dans cette table ronde. Il me semble que dans un processus démocratique, le minimum, c'est que les gens qui sont autour d'une table aient un champ sémantique commun, c'est-à-dire que quand ils utilisent un mot, ils l'utilisent avec le même sens, avant d'en avoir une interprétation mentale ou une interprétation qui aille au-delà de l'interprétation sémantique. J'aurais une double réponse à la question de l'absence de définition de la biologie de synthèse. Au niveau académique, quand émerge une nouveauté, au regard de l'histoire des sciences, on ne souhaite pas être enfermé dans un champ qui pourrait brider la créativité. Donc il y a tout intérêt en fait à avoir les définitions les plus floues. Par contre, au niveau d'un débat démocratique, on a intérêt à avoir, comme l'Académie des sciences, au moins un certain nombre de mots avec des définitions assez précises pour pouvoir discuter. Sinon, si chaque personne qui discute utilise les mêmes mots avec des significations différentes, le débat démocratique aura peu de chance d'arriver au premier niveau.

Je souhaiterais savoir quelles seraient les méthodes pour instituer un vrai processus démocratique, qui utiliserait, au moins au départ, un certain nombre de définitions, quitte à avoir plusieurs débats démocratiques avec des définitions différentes. Mais au départ, si l'on veut avoir un premier débat, ou à un moment donné un débat de forum citoyen, il faut qu'on puisse définir le champ dans lequel on va commencer à discuter.

M. Daniel Raoul. J'étais en train d'établir un parallèle. Où commencent les nanotechnologies ? Quelle est la définition exacte ? À part la taille des matériaux en jeu, je ne sais pas ce qu'en est la définition réelle.

M. Joël de Rosnay. Je trouve vraiment intéressantes les deux dernières interventions. La première nous disait qu'il faut former d'abord de bons biologistes avant de penser à des enseignements soit alternés, soit sur le tas, soit par co-éducation mutuelle entre les étudiants, voire une co-éducation intergénérationnelle entre les plus anciens et les jeunes. C'est effectivement intéressant de former de bons biologistes, mais il faut regarder comment. C'est-à-dire que pour former un bon biologiste, il faut une formation disciplinaire, une formation assez linéaire, et en général assez longue. Or, le domaine de la biologie de synthèse et tout ce qu'il y a autour dans le monde avancent à une telle vitesse, les échanges sur Internet et sur les réseaux sont tellement rapides, que je pense, en étant assez d'accord avec vous sur le fait qu'une formation disciplinaire est essentielle, qu'elle doit être associée, complétée par des formations du type de celles dont nous avons parlé : créativité, innovation, gestion de projet, proposition de projet, co-éducation des étudiants entre eux, co-éducation des professeurs avec les étudiants, dans une éducation de type informel, comme celle que je décrivais pour Universcience tout à l'heure.

La deuxième intervention était aussi assez intéressante, mais je crois qu'elle relève — un peu comme la vôtre, excusez-moi de le dire ; ce n'est pas une critique, mais c'est une remarque — d'un classicisme de type professoral. J'ai entendu qu'il fallait définir la biologie de synthèse avant de commencer à savoir quel type d'enseignement on devait faire. Mais on ne sait même pas quelle est la définition de la vie ! On en discute tout le temps entre nous. Il ne faut pas s'enfermer dans une définition qui ne fera que créer des débats et des discussions interminables sur la définition des nanotechnologies, ou celle de la biologie de synthèse. On a une approche pluridisciplinaire, qui conduit à des objectifs, et ces objectifs peuvent conduire à la fois à former les gens et à des applications précises, celles que les industriels sont capables de mettre en oeuvre pour la société. Avec les risques que cela implique, et par conséquent les précautions qu'il faut prendre.

M. Brice Laurent. Juste sur la question de la définition. Ce qui est intéressant, à la fois dans les nanotechnologies ou dans la biologie de synthèse, **c'est que définir, c'est le cœur de l'enjeu politique et de l'enjeu démocratique. Discuter de quelle définition on choisit, c'est précisément cela un enjeu collectif**. Et c'est exactement ce qui est en train de se passer en ce moment, dans différentes enceintes, notamment à la Commission européenne, où l'on réfléchit à la définition des nanomatériaux. Si l'on choisit tel ou tel critère, si l'on définit d'une certaine façon, cela veut dire que tout un champ de l'industrie chimique nano sort d'une régulation potentielle. Donc sur un problème comme celui-là, on voit bien qu'on ne peut pas dire : on définit d'abord, on discute après. Ce serait plutôt : on s'accorde sur une façon de poser le problème.

M. Joël de Rosnay. Je suis d'accord avec vous pour une définition heuristique, mais pas une définition optimale.

M. Ariel Lindner. Peut-être juste un mot pour reconsidérer le débat sur le fait de savoir s'il faut enseigner de manière disciplinaire ou interdisciplinaire. Je

pense que cela a aussi à voir avec la technologie. L'image que nous avons du professeur, remontant au XVIII^{ème} siècle, ce professeur qui portait le savoir sur ses épaules et le donnait par cuillerées aux étudiants, est révolue depuis longtemps. L'information existe, le savoir aussi. Ce que j'appelle la science, c'est tout ce que l'on sait déjà. Et la recherche, c'est cette entité vaste, où nous avons encore des choses à apprendre. En donnant aux étudiants des outils qui leur permettent d'apprendre plutôt que de leur enseigner le savoir en tant que tel, ils vont pouvoir passer par une voie disciplinaire ou une voie interdisciplinaire, et trouver pour eux-mêmes des informations pertinentes pour quelque projet qu'ils seront susceptibles de mener à bien. C'est ainsi que les scientifiques travaillent. Nous assumons des projets, nous apprenons avec l'expérience que nous tirons, et si les étudiants travaillent de cette façon-là, ils deviendront de bons chercheurs. C'est notre but.

Mme Geneviève Fioraso. Je vous remercie. Vos interventions, vos questions, vos réponses, vont beaucoup m'aider pour le rapport que je dois rédiger pour l'Office d'ici à la fin de cette année. Je voudrais quand même réhabiliter les membres de mon Comité scientifique, en particulier Thomas Heams, qui n'est pas un académique classique, contrairement aux apparences peut-être, et que je n'imagine pas au XIX^{ème} siècle. Il contribue très positivement, ainsi que l'ensemble des membres du Comité scientifique qui s'est constitué pour la tenue de ces deux tables rondes. Je remercie Françoise Roure et mon ami Daniel Raoul qui ont accepté de présider ces tables rondes à haut risque, car c'est un sujet qui n'est pas facile. C'est une discipline, une technologie, ou disons domaine, ce sera plus neutre, un domaine pluridisciplinaire émergent qui pose beaucoup de questions. Il n'a pas encore émergé en France au niveau du grand public ou des médias. Donc c'est le bon moment, je crois, d'anticiper cette question. Et je trouve courageux de votre part d'être venu, ainsi que de la part de l'ensemble des intervenants, qu'ils viennent du secteur public, du secteur privé, ou des associations. Ce sont tous des citoyens ! Nous sommes tous des citoyens, nous devons tous nous poser des questions sur notre avenir, nous engageons tous l'avenir de nos enfants et petits-enfants. Je pense que tous nos débats doivent s'inscrire dans le sens de cet intérêt général. Je voudrais également remercier Ronan Stephan, qui représente Mme Valérie Pécresse ce soir, et qui va conclure nos travaux.

ALLOCUTION DE CLOTURE

M. RONAN STEPHAN, DIRECTEUR GENERAL POUR LA RECHERCHE ET L'INNOVATION (DGRI) AU MINISTERE DE L'ENSEIGNEMENT SUPERIEUR ET DE LA RECHERCHE

M. Ronan Stephan. Mesdames, Messieurs les parlementaires, Mesdames, Messieurs, c'est un véritable honneur sur un sujet aussi important, aussi émergent, et qui risque de conduire à tant d'évolutions, que de clôturer cette journée d'audition publique. Je rappellerai quelque chose que vous savez pertinemment par ailleurs. La biologie de synthèse vise en partie à concevoir des systèmes biologiques artificiels, en couplant la modélisation et la simulation mathématique et les méthodes biomoléculaires. Je pense déjà, à ce titre, en m'arrêtant sur ce premier propos, et peut-être pour faire écho à la dernière intervention, que nous avons certainement un devoir de faire émerger dans notre pays des formations adaptées qui mêlent, beaucoup plus qu'elles ne le font aujourd'hui, biologie et technologies de l'information. Technologies de l'information au sens large, allant des mathématiques appliquées aux réseaux et aux sciences de l'information. L'enjeu est absolument colossal. Nombre de laboratoires qui travaillent dans ce domaine souffrent aujourd'hui d'un certain déficit dans leurs capacités de recrutement de personnes véritablement bien formées en la matière.

La biologie de synthèse émerge du progrès énorme des connaissances en matière de biologie moléculaire, mais aussi de facteurs technologiques, comme la diminution des coûts de séquençage, et enfin de ces synergies tellement souhaitables avec les nanotechnologies et les sciences mathématiques au sens large. Nous avons la conviction que la biologie de synthèse est plus une évolution, très significative il est vrai, qu'une véritable révolution. Elle recouvre aujourd'hui deux approches qui peuvent être considérées comme distinctes.

- Une première approche qui s'intéresse à **la synthèse de génomes minimaux**, c'est-à-dire de génomes comportant des nombres minimaux d'éléments génétiques suffisants pour construire un organisme cellulaire, autonome, et d'un nouveau type. Et cette synthèse de génomes minimaux permet la création de cellules hautes, dotées de fonctions simples, prédéterminées, et d'autant mieux déterminées que modélisation et simulation en amont auront pu jouer tout leur rôle. Un certain nombre de ces fonctions répondent à des enjeux sociétaux, la capacité à dégrader des substances toxiques par exemple, tels les métaux lourds ou les pesticides.

- Deuxième approche, c'est **la construction de dispositifs ou de systèmes artificiels**, biochimiques ou biomécaniques, ayant un comportement tout

à fait spécifié, typé, et là aussi déterminé, comme des micro-dispositifs biologiques fondés sur l'assemblage moléculaire de gènes, de protéines, qui peuvent agir dans le corps humain pour détecter, réparer, corriger des pathologies à un stade précoce. On parlera effectivement de réparation ou de régénération des tissus. Beaucoup de recherches sont conduites en la matière.

Pour aller plus loin en matière d'applications, on est certainement très loin d'avoir pu en faire le tour aujourd'hui. Néanmoins, les applications qui sont aujourd'hui visibles sont nombreuses. Elles concernent bien sûr la santé, je l'évoquais à l'instant en préambule, les médicaments personnalisés, et donc la médecine personnalisée en termes de services ; les biomarqueurs ; l'énergie, avec les biocarburants ; l'environnement, avec des bioprocédés peu polluants, des bioraffineries, la bioremédiation. Pour résumer, on recense aujourd'hui cinq grands types d'applications possibles :

- ces nouvelles techniques moins polluantes de bioproduction ;
- ces outils diagnostics améliorés,
- des médicaments et des vaccins nouveaux : les biocapteurs, les biosenseurs ;
- des outils innovants de bioremédiation ;
- des outils complémentaires dans la boîte à outils, au service des matériaux intelligents, et donc des matériaux fonctionnels d'un nouveau type, ou bien des biomatériaux.

Le potentiel scientifique et économique vu aujourd'hui pour la biologie de synthèse a permis ou a fait passer cet objet, cette problématique ou cette thématique, dans les grandes priorités de la stratégie nationale de recherche et d'innovation, stratégie qui a été élaborée durant l'année 2009 et qui, aujourd'hui, est en train d'être mise en oeuvre, en particulier au travers des Investissements d'avenir. La biologie de synthèse ouvre les portes à un potentiel d'innovation extrêmement large, et comme je le disais, nous sommes loin d'avoir fait le tour et mesuré l'ensemble des spectres d'applications. Elle doit permettre aux biotechnologies au sens large de réaliser un saut quantitatif, mais aussi qualitatif, important, et elle devrait faire partie – je ne suis pas spécialiste de biologie, je suis physicien – et donc je dis qu'elle devrait faire partie des évolutions majeures apportées à la biologie dans ce XXI^{ème} siècle.

Incidemment, et ce n'est pas la moindre de ses qualités, ou de ses qualités perspectives, la biologie de synthèse a un impact économique, ou un potentiel économique, qui est extrêmement fort. Le marché abordable, ou adressé par la biologie de synthèse, était estimé à 500 millions de dollars en 2006. D'ici cinq ans,

il pourrait être porté à 3 voire 5 milliards de dollars[1]. À titre d'exemple, un pays comme l'Inde investit aujourd'hui sur cinq années 1,6 million de dollars pour sa recherche en biologie de synthèse, ce qui est un effort tout à fait significatif.

En France, comme je le disais, la stratégie nationale de recherche et d'innovation a retenu comme l'une de ses priorités thématiques la biologie de synthèse. Les éléments documentaires qui ont été produits en marge de cet exercice d'élaboration stratégique ont impliqué plus de 600 personnalités issues de la recherche académique, des entreprises, les petites, émergentes, les start-up, comme les grandes entreprises et le monde associatif, c'est-à-dire l'ensemble des porteurs d'enjeux et des acteurs de ce domaine. L'exercice a permis de définir un certain nombre de grands principes, qui, cette fois, sont beaucoup plus généraux, beaucoup plus matriciels que la biologie de synthèse elle-même.

- En particulier, il y a un principe très fort, qui ne sera pas remis en cause, c'est que **la recherche fondamentale doit être soutenue à son meilleur niveau**, parce qu'elle est indispensable à toute société qui veut devenir, qui veut passer au stade de société de la connaissance.

- Deuxième constat, deuxième recommandation, deuxième principe : **la recherche ouverte à la société, et en particulier ouverte à l'économie**, **est le gage de la croissance**, et dans la croissance il y a de l'emploi, de la valeur créée, ce qui est la ligne directrice des Investissements d'avenir, qu'on appelle par ailleurs le Grand emprunt.

- Enfin, **l'importance, dès l'amont, de la prise en compte des risques et de la maîtrise de ces risques, ainsi que du renforcement de la sécurité**. Je reviendrai plus tard au cas particulier du sujet d'aujourd'hui.

Autre point essentiel : **le rôle majeur que jouent les sciences humaines et sociales**, non pas comme supplément d'âme, mais véritablement comme discipline participant de ces projets interdisciplinaires et pluridisciplinaires dans l'ensemble des réponses que nous apportons, ou cherchons à apporter, à ces grands défis technologiques, ces grands défis scientifiques, qui sont les nôtres aujourd'hui. Et c'est vrai que si l'on parle de SHS (Sciences humaines et sociales), on est obligé de parler ensuite, comme pour synthétiser l'ensemble, de pluridisciplinarité, de transdisciplinarité, de fracture des silos disciplinaires, lesquelles fractures sont souvent des augures d'approches innovantes et tout à fait adaptées.

Trois axes prioritaire de recherche ont été définis : l'un autour de la santé, du bien-être, de l'alimentation et des biotechnologies ; un autre autour

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[1] « *D'autres estimations sont plus optimistes. En particulier la firme indépendante Lux Research estime qu'avant 2015, un cinquième de l'industrie chimique américaine (estimée actuellement à 1800 milliards de $) pourrait dépendre de la biologie de synthèse.* » Source : « Biologie de Synthèse : développement, potentiel et défis », par François Képès, Directeur, Programme d'Épigénomique, Annales des Mines REALITES INDUSTRIELLES, fév. 2010, www.issb.genopole.fr/~kepes/Media/Kepes%20-%20RI%202010.pdf

de l’urgence environnementale et des écotechnologies ; et un enfin autour de l’information, de la communication et des nanotechnologies. Vous remarquez bien évidemment que le sujet qui vous a rassemblé ces derniers jours s’inscrit dans ces trois grandes priorités thématiques de recherche.

Le problème de l’acceptabilité sociale est absolument essentiel, dès lors qu'il s’agit de développer, de diffuser les apports, les difficultés d’une nouvelle technologie ou d’une nouvelle matrice technologique émergente. Au cas particulier de la biologie de synthèse, nous devons donc aujourd'hui soutenir son développement, que l’on considère comme insuffisant à ce jour dans notre pays, mais aussi l’accompagner en parallèle, et ce dès l’amont, tant au plan scientifique et technologique, qu’au plan sociétal. Comme tout nouveau grand champ disciplinaire, particulièrement parce que ce champ disciplinaire touche de plein fouet le vivant, la biologie de synthèse pose un certain nombre de questions d’ordre éthique ou sociétal. Nous ne sommes pas, je pense, démunis face à ces questions. En témoigne la diversité des interlocuteurs qui participent à cette journée. La biologie de synthèse s’intéresse tout au moins pour partie à la reproduction d’un certain nombre des propriétés de la cellule. Il s’agit là, en partie, de chimie innovante, très innovante, domaine pour lequel nous n’avons pas réellement aujourd'hui de problèmes de sécurité, de problématique forte de sécurité, dans la mesure où les normes en vigueur dans la chimie, dans l’industrie chimique, peuvent tout à fait s’appliquer à la chimie de synthèse. Quant à la synthèse des génomes, nous sommes dans le domaine du génie génétique, et là on rejoint un certain nombre de questions qui ont été posées par les organismes génétiquement modifiés, pour lesquels un certain nombre de législations et de réglementations en cours s’appliquent aujourd'hui.

Néanmoins, la biologie de synthèse suscite un certain nombre d’inquiétudes en matière de bio-sécurité et de sûreté. Je me rappelle une discussion très intéressante que j’avais eue avec mon ami Jean-Michel Besnier, il y a quelques mois sur le sujet. La biosûreté concerne la possibilité de détourner la biologie de synthèse à des fins qui pourraient être malveillantes, en créant des organismes pathogènes, ou des produits chimiques qui auraient des propriétés nocives. La Direction générale de l’armement (DGA) a réalisé une base de données des acteurs de la biologie de synthèse, a identifié un certain nombre d’options en matière de biosûreté. De la même manière, l’Agence nationale de sécurité sanitaire, de l’alimentation, de l’environnement et du travail (ANSES), va mettre en place une veille scientifique prospective sur la biologie de synthèse.

Si je reviens en quelques mots à la question de la bio-sécurité, les procédures qui existent pour les OGM, que ce soit pour prévenir les infections accidentelles ou pour confiner les organismes en laboratoire ou dans des installations de production classées, sont pour la majeure partie applicables au développement actuel de la biologie de synthèse, qui vise à en améliorer les méthodes de production ou de bioproduction. Néanmoins, les méthodes d’évaluation des OGM, qui sont fondées sur la comparaison entre l’organisme modifié d’une part, et l’organisme naturel

dont il dérive d'autre part, ne sont pas forcément transposables au cas de la biologie de synthèse, parce qu'il n'y a pas nécessairement d'organisme naturel avec lequel on puisse considérer un certain mimétisme, qui pourrait donc servir de référence. Il y a là une petite difficulté qu'il convient d'avoir en tête. Il peut s'agir aussi de nouveaux circuits, artificiels cette fois, de régulation, et non d'organismes. Et c'est pourquoi nous considérons assez largement que le développement de la biologie de synthèse doit être accompagné, et bien accompagné par les pouvoirs publics.

Dans ce contexte, le groupe européen d'éthique, des sciences et de nouvelles technologies, placé auprès de la Commission européenne, a formulé un certain nombre de recommandations à la fin de l'année 2009, qui couvrent ces différents aspects, et qui visent à ce qu'un cadre de gouvernance communautaire soit défini et mis en place au niveau européen.

En conclusion sur ce point, même si nous ne sommes pas complètement démunis sur le sujet, il n'en reste pas moins que les pouvoirs publics se doivent d'accompagner cette évolution de la biologie, afin de ne pas tomber dans l'écueil que nous avons pu rencontrer dans le cadre des OGM, ou plus récemment, des nanotechnologies. Nous avons donc le devoir d'anticiper cette évolution par la formation du public, la diffusion vers le plus grand nombre, et aussi la formation des scientifiques, et si nécessaire, d'assurer un encadrement approprié à un développement positif et vertueux dans ce domaine. Je pense là aussi que la mise en place de plus de formation, des réflexions conduites et rassemblant le plus grand nombre de parties prenantes sur la définition de ce que pourraient être ces cursus, entre la biologie d'une part, et les technologies de l'information d'autre part, seraient extrêmement vertueuses pour aller plus loin justement dans la diffusion, et aussi pour donner plus de leviers, plus d'atouts compétitifs aux acteurs économiques qui ne manqueront pas de se développer autour de ces enjeux que la biologie de synthèse permet d'aborder.

Quelques recommandations pour assurer le développement de la biologie de synthèse en France. Je vous ai parlé de la stratégie nationale de recherche et d'innovation. Cette stratégie n'est pas quelque chose d'immuable, l'alpha et l'oméga de ce que doit être la science, la recherche, etc., dans ce pays, mais beaucoup plus une espèce de point de départ, sans cesse alimenté par un certain nombre de groupes de travail. En particulier au début de l'année 2010, un groupe de travail a été constitué, animé par François Képès (Genopole d'Evry), qui a produit en mars 2010 un rapport intitulé *: « Biologie de Synthèse : développements, potentiel et défis »*[1]. Ce groupe de travail, placé sous l'égide de la Direction que j'ai l'honneur de conduire, a proposé plusieurs actions et recommandations.

[1] Id. op. cit.

1. **Organiser un dialogue avec la société** pour la prise en compte et le recensement des préoccupations sociétales dans le processus de programmation scientifique sur ce sujet. Pour s'assurer de l'efficacité d'un tel débat public, la Direction générale de la recherche et de l'innovation entend confier une étude à l'Institut francilien recherche innovation société (IFRIS). Les résultats sont attendus pour l'été 2011. Ils portent sur les bonnes modalités d'un débat public sur ce thème, débat qui a été réalisé avec plutôt un bon succès en Grande-Bretagne et dans un certain nombre d'autres pays européens. Les questions auxquelles il faut répondre sont les suivantes : quelles sont les clés du succès de ce dialogue entre science et société ? Quelles sont les pratiques, parmi celles retenues, qui sont transposables chez nous ? L'objectif de cette étude est de disposer de bases, d'analyses, nous permettant d'organiser un débat qui associerait public et chercheurs. Cette phase d'organisation pourrait résulter en une journée d'étude dont les modalités seraient à définir dans un délai relativement proche.

2. **Favoriser l'émergence de quelques centres d'excellence multidisciplinaires, qui allient recherche et formation**. Ces centres devraient naturellement travailler en réseau. La biologie de synthèse a été retenue comme un des thèmes particulièrement pertinents dans les projets d'Investissements d'avenir. Dans les années qui viennent, nous devrions observer l'émergence de compétences organisées dans ce domaine. On peut citer l'exemple de Toulouse, le projet SYNTHACS, lauréat de l'appel à projets « biotechnologie et bioressources » dans le cadre du plan Investissements d'avenir. Il vise à produire un additif pour l'alimentation animale à partir d'une biomasse renouvelable, offrant ainsi une alternative au carbone fossile, et donc à la pétrochimie. Ce nouveau procédé biologique est beaucoup moins polluant. Il permettra en outre la synthèse d'autres produits dérivés. Ce projet associe l'Institut national de recherche agronomique (INSA) de Toulouse, la plate-forme TWB (« Toulouse White Biotechnology »), qui a été également lauréate de l'appel à projets "Démonstrateurs préindustriels en biotechnologie" des Investissements d'avenir le 4 mars dernier, et puis une société Adisseo sur les sites de Toulouse et d'Evry, ainsi que l'Institut de biologie systémique et synthétique (iSSB). Ils constituent autant de centres d'excellence que nous pourrions renforcer.

3. **Mobiliser, en synergie avec ses acteurs institutionnels, publics et industriels, des infrastructures, des plates-formes technologiques, qui pourraient émerger, complémentaires de ce qui existe aujourd'hui**. Parce que la dimension très technologique des développements en matière de biologie de synthèse implique un vrai partenariat avec l'entreprise, non pas un partenariat de type presse-bouton ou de prestations de service, mais un partenariat dès l'amont, dès l'établissement des stratégies, des trajectoires. L'Etat pour sa part devra réfléchir aux mécanismes de soutien qui sont les plus adaptés à ce type de coopération.

4. **Mettre en place une programmation européenne.** Là aussi, décloisonnement vis-à-vis de la sphère économique et décloisonnement vis-à-vis de

nos partenaires européens, de manière à ce que la biologie de synthèse puisse atteindre une taille critique au plan européen, et que cette taille critique, en particulier à l'aune de la préparation du 8ème programme-cadre, puisse être prise en compte et permette de l'inscrire dans les préoccupations de ce nouveau programme.

5. Dernier point, mais qui n'est pas mineur, surtout quand on a parlé d'implications des industriels et de problématiques sociétales, c'est **une participation active des acteurs compétents aux travaux réglementaires et normatifs à l'échelle européenne et internationale**, afin qu'ils puissent déboucher sur des cadres réellement incitatifs, qui prennent en compte à leur juste valeur les risques potentiels qu'on a évoqués, et d'autre part, les demandes tout à fait légitimes du public.

En termes d'outils et d'acteurs, la programmation et la coordination de ces différentes actions mettront en scène des acteurs comme les alliances en particulier, l'Alliance pour les sciences de la vie et de la santé (Aviesan), l'Alliance nationale de recherche pour l'environnement (AllEnvi), les universités bien sûr, celle d'Evry à l'évidence, où un master 2 a été accrédité fin 2008 en matière de biologie systémique et synthétique. Ce master 2 a une véritable ouverture européenne. L'ANR bien évidemment, ainsi que l'ensemble des ministères techniques concernés et des représentants de la société, de ses porteurs d'enjeux.

Il faut aussi que les projets de recherche, qui comportent une évaluation du rapport entre les bénéfices et les risques au niveau de la société, trouvent leur place dans cette programmation de recherche, sinon nous n'aurions fait qu'une partie du chemin. À ce titre, il a été demandé à l'ensemble des projets « Biotechnologies et Bioressources » des Investissements d'avenir d'intégrer dans leurs projets un groupe de travail ou une composante qui traite de l'acceptabilité sociale. Je peux témoigner, pour avoir lu beaucoup de ces projets, que cela a été chose faite. Les porteurs de projets, les groupes de ces projets se sont inscrits et ont répondu favorablement à cette demande.

Pour conclure, je dirais que les pouvoirs publics vont accompagner cette nouvelle évolution de la biologie afin de ne pas tomber dans les écueils relatifs des OGM et des nanotechnologies. Nous avons un véritable devoir d'anticiper cette évolution, par la formation, et en particulier la formation du public et des scientifiques, et si nécessaire, d'assurer un encadrement approprié en amont du développement de ce domaine, et non pas répondant à une situation de crise. Nous devons bien sûr répondre aux inquiétudes qui pourraient être suscitées, en formant d'une part, et en informant le public en toute transparence d'autre part, mais aussi en veillant à ce qu'il soit associé à la réflexion, et en accompagnant le développement de la biologie de synthèse de tous les dispositifs les meilleurs. Ils doivent permettre d'exprimer son potentiel d'innovation pour de la création de valeur, pour du service de qualité, et du service auquel les individus peuvent aspirer.

Voilà ce qu'au nom de Valérie Pécresse je voulais vous dire aujourd'hui, en vous félicitant véritablement de cette initiative, et aussi pour la qualité de ces journées de discussions, en particulier de cette journée. Il me reste à vous remercier pour l'attention que vous m'avez portée.

Mme Geneviève Fioraso. Je vous remercie beaucoup de la part du président de l'OPECST Claude Birraux, que nous tentons de représenter tous les deux, Daniel Raoul et moi-même. Ces propos encourageants s'inscrivent dans le droit fil de nos préoccupations. Je remercie également l'ensemble des participants.

Stratégie nationale de recherche et d'innovation

« Biologie de synthèse :
développements, potentialités et défis »
(mars 2011)

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MINISTÈRE
DE L'ENSEIGNEMENT SUPÉRIEUR
ET DE LA RECHERCHE

SNRI
STRATÉGIE NATIONALE DE RECHERCHE ET D'INNOVATION

BIOLOGIE DE SYNTHÈSE :

DÉVELOPPEMENTS, POTENTIALITÉS ET DÉFIS

Mars 2011

Groupe de travail
« Biologie de Synthèse »

Sommaire

SYNTHÈSE

Notre société est confrontée à des exigences nouvelles en matière de médicaments innovants, de production industrielle plus respectueuse de l'environnement, d'alternatives énergétiques, de nouveaux matériaux.

En raison de son fort potentiel économique dans de vastes domaines applicatifs (santé, environnement, énergie et matériaux), la biologie de synthèse (BS) a été identifiée comme une priorité de la stratégie nationale de recherche et d'innovation. À ce titre, la BS s'inscrit bien dans le programme "Investissements d'avenir" du gouvernement, en tant que technologie émergente d'ingénierie biologique. L'enjeu actuel est de déterminer les actions à conduire afin de développer les compétences et de créer les infrastructures requises pour un développement en phase avec les besoins économiques et les attentes éthiques et sociétales du pays.

La BS se définit par la conception intentionnelle de systèmes biologiques artificiels, en couplant modélisation mathématique et méthodes biomoléculaires. Son émergence s'appuie sur la puissance analytique de la biologie moléculaire (-omiques) et sur les modèles prédictifs et explicatifs qui en intègrent les résultats (biologie systémique), ainsi que sur la chute drastique des coûts du calcul scientifique et de la lecture et écriture de l'ADN.

Ce rapport propose :

- Une analyse de l'évolution récente de la BS :

L'émergence de la BS est fondée sur la progression rapide des connaissances fondamentales en biologie et chimie du vivant et surtout sur les convergences entre nanotechnologies, sciences de la vie et de l'information. Couplées à de nouvelles technologies de fabrication et de robotisation, elles permettent d'envisager une évolution rapide des potentialités offertes par la BS (médicaments, biosenseurs, systèmes de production propres…).

- Les applications potentielles et enjeux sociétaux :

Le potentiel économique de la BS est considérable et pourrait permettre de réaliser un saut substantiel pour les biotechnologies dans notre pays. A court terme, les applications les plus intéressantes se situent dans l'élaboration de procédés de bio-production peu polluants dans de nombreux domaines, des innovations dans les outils et méthodes de diagnostic, de nouvelles thérapeutiques, et des matériaux innovants. Le développement de la BS soulève un certain nombre de questions en matière d'éthique, de sécurité, ou de propriété intellectuelle. C'est à ce stade, en amont de la recherche, que ces questions doivent être affrontées, car elles sont décisives pour les orientations à poursuivre.

- Un état des lieux de cette technologie en France :

Il existe en France un gisement de compétences à mobiliser, permettant de viser une position mondiale de second ou troisième. Les principales barrières se situent au niveau de l'éclatement des équipes et moyens, et de l'absence de structuration du domaine, notamment en lien avec les industries concernées.

- Cinq recommandations pour soutenir l'émergence et la montée en puissance de la BS en France :

1. Promouvoir un véritable dialogue entre science et société, impliquer la société dans les choix de programmation. Les expériences passées en matière de nouvelles technologies démontrent l'importance d'organiser un dialogue en amont avec tous les acteurs concernés, et surtout, de l'intégrer dans le processus de programmation.
2. Favoriser l'émergence de centres d'excellence multidisciplinaires, alliant recherche et formation. Ceci nécessitera la poursuite de l'effort prospectif actuel, l'incitation à créer, et la mise en réseau des centres d'excellence, le développement d'une formation initiale

appropriée, et la création d'un forum national de la BS afin de faciliter les échanges de bonnes pratiques.

3. Mobiliser en synergie les acteurs institutionnels, publics et industriels. Au niveau national, l'émergence de 2 à 4 plateformes technologiques complémentaires parait souhaitable. L'aspect multidisciplinaire de la BS et de ses applications nécessite une coordination globale des différents acteurs impliqués qui doit s'insérer dans une dimension au moins européenne, voire internationale. La dimension très technologique de la BS implique aussi un partenariat avec l'industrie dans la stratégie amont et des mécanismes de soutien les impliquant directement.
4. Mettre en place une programmation permettant à la BS d'atteindre une taille critique qu'elle ne possède pas encore en Europe. Ceci passe par le développement des centres d'excellence et de projets prenant en compte les aspects sociétaux. Au niveau européen, la France devrait proposer d'identifier la BS comme un domaine à part entière dans la programmation du prochain PCRD.
5. Harmoniser les politiques et maîtriser les risques à l'échelle européenne et internationale. Le développement économique de la BS est étroitement lié à son futur cadre réglementaire et normatif, qui pourra être soit incitatif soit restrictif. Il est essentiel que la France soit fortement présente à l'échelon européen et international pour proposer un cadre incitatif qui prenne en compte à leur juste valeur les risques potentiels et les demandes légitimes du public.

Afin de permettre un développement coordonné du potentiel présenté par la BS, ce document propose enfin une série d'objectifs à réaliser à échéance de 2, 5 et 15 ans : phases de montée en puissance, de consolidation, et de généralisation. Différents leviers d'actions sont envisagés afin de permettre la réalisation de ces objectifs.

I - INTRODUCTION

Nombreux sont les citoyens qui appellent de leurs vœux une chimie et des méthodes de production industrielle plus soucieuses de l'environnement, ou une médecine plus douce et plus personnalisée [1].

Parmi les approches susceptibles de répondre à une partie de ces vœux, la biologie de synthèse (BS) occupe une place de choix. En effet la BS offre dans plusieurs secteurs des solutions innovantes et respectueuses de l'environnement. En raison de son fort potentiel économique dans de vastes domaines applicatifs (santé, environnement, énergie et matériaux), la biologie de synthèse (BS) a été identifiée comme une priorité de la stratégie nationale de recherche et d'innovation. L'enjeu actuel est de déterminer les actions à conduire afin de développer les compétences et de créer les infrastructures requises pour un développement en phase avec les besoins économiques et les attentes éthiques et sociétales du pays. Citons des médicaments, vaccins et diagnostics améliorés ; des techniques novatrices en médecine régénératrice ; de nouveaux outils pour réhabiliter les sols pollués ou traiter l'eau ; des carburants et matières plastiques avec une empreinte carbone réduite. Les analystes estiment que la BS sera durant le 21ème siècle un pourvoyeur d'emplois majeur ; elle engendrera une nouvelle génération de produits, d'industries et de marchés, tout comme le fit la chimie de synthèse un siècle plus tôt, et pour des raisons essentiellement similaires. Comme toute approche innovante, la BS induira aussi de nouveaux débats et défis, qui devront être assumés en toute transparence, et si possible anticipés.

[1] Voir par exemple le rapport du WWF en 2009 à http://wwf.panda.org/?174201/Biotechnology-could-cut-C02-sharply-help-build-green-economy

II - DÉFINITION DE LA BIOLOGIE DE SYNTHÈSE

La biologie de synthèse (BS) a été définie par le consortium européen "Synbiology" comme « l'ingénierie de composants et systèmes biologiques qui n'existent pas dans la nature (par exemple, l'outil de diagnostic Versant™ de Siemens qui permet annuellement le suivi de 400.000 patients atteints de viroses multiples) et la ré-ingénierie d'éléments biologiques existants (p.ex., la production de l'artemisinine, un puissant traitement anti-malaria concernant 500 millions de patients). Elle porte sur la conception intentionnelle de systèmes biologiques artificiels, plutôt que sur la compréhension (analytique) de la biologie naturelle ». Il est bien entendu que la biotechnologie classique est hors du champ de la BS. Si l'accent mis sur l'ingénierie la positionne d'emblée sur le versant appliqué de la recherche et la destine à l'industrialisation, la BS en occupe aussi le versant fondamental.

La BS opère typiquement en trois phases successives :

1. la **conception** rationnelle d'un nouveau composant, dispositif ou système biologique, faisant appel à la modélisation mathématique et à la simulation informatique ; cette approche qui s'appuie sur les données disponibles (génomique, protéomique…) permet d'explorer par avance les propriétés de l'objet qui sera construit ; le recours à cette méthodologie et la complexité des objets conçus sont les éléments qui distinguent la BS du génie génétique ;
2. la **construction** de l'objet ainsi conçu ; selon les cas, elle fera appel au génie génétique, à la chimie de synthèse, à la microfluidique, ou encore à une combinaison de ces approches ;
3. la **caractérisation** de l'objet ainsi construit au moyen de toute méthode adaptée, et l'évaluation de ses impacts sur la santé, l'environnement et la société.

Malgré son émergence récente, deux démarches sensiblement différentes relèvent de la BS :

1. **la construction de systèmes métaboliques minimaux, de dispositifs ou de systèmes artificiels biochimiques ou biomécaniques ayant un comportement spécifié**, par l'assemblage de « briques » réutilisables et standardisées (p.ex., circuit de régulation synthétique pour le contrôle de l'homéostasie de l'urate chez la Souris) ;
2. **la synthèse de génomes minimaux**, afin de mieux appréhender le fonctionnement des cellules, et afin de créer des cellules-hôtes (châssis) capables d'une bio-production efficace ou de fonctions simples pré-déterminées (synthèse complète d'un petit génome bactérien et sa transplantation dans une bactérie-hôte par la société Craig Venter).

III - ÉMERGENCE ET ÉVOLUTION

Au cours de ces 15 dernières années, une **fertilisation croisée** s'est opérée entre les découvertes des sciences biologiques et celles d'autres disciplines, comme la physique, la chimie, les mathématiques, l'informatique, l'automatique et les sciences de l'ingénieur. Les développements en biologies moléculaire, structurale et systémique, et en modélisation et simulation, ont ouvert la voie à la BS.

En voici **quelques jalons**. En 1995, le premier génome bactérien est séquencé, et le premier long gène synthétisé. En 1999, le premier génome viral est synthétisé. En 2000 est démontrée la faisabilité de concevoir rationnellement des circuits de régulation et de les implanter dans des bactéries ; le génome humain est séquencé. En 2003, un repli ("fold") protéique non naturel est conçu et réalisé. En 2008 un génome bactérien est pour la première fois entièrement re-synthétisé de façon artificielle. En 2010 il est introduit avec succès dans une bactérie hôte.

1) Sur le plan fondamental

Il est devenu clair qu'une compréhension du fonctionnement de la cellule ou de l'organisme requiert plus qu'une simple liste des composants telle que la livrent certaines technologies '-omiques'. Il s'agit de comprendre comment les gènes, les protéines etc. interagissent pour former des circuits biochimiques, et d'en avoir une vision causale et dynamique. Ces circuits biochimiques sont soit régulatoires (influences multiples entre gènes et leurs produits), soit métaboliques (série de transformations de molécules par des enzymes). Cette compréhension, qui progresse par les approches dites de "biologie systémique", fournit les outils conceptuels requis ensuite dans le cadre de la BS pour le design et la construction rationnelle de circuits biochimiques ; on parle d'ingénierie régulatoire ou métabolique.

2) Au niveau technologique

Les méthodes standard de la biochimie et des biologies moléculaire et structurale, qui permettent de modifier les protéines et de réarranger l'information génétique, ont progressé au point d'être utilisables pour la conception de circuits biochimiques dans et hors des cellules vivantes. Les méthodes d'implémentation moléculaire de ces circuits connaissent une robotisation croissante. Point essentiel pour le futur, nos capacités à lire et écrire l'ADN progressent exponentiellement. L'état avancé de l'art consiste à synthétiser entièrement un génome bactérien, et à l'introduire en remplacement du génome naturel très similaire d'une cellule hôte. En corollaire, on voit aussi l'importance de la progression exponentielle des capacités de calcul pour la conception assistée par ordinateur de biomolécules, et pour les simulations numériques de leurs structures et activités.

Les moteurs d'évolution actuels de la BS pourraient être :

1. **Les convergences "NBIC"** (Nano-Bio-Info-Cogno), entre nano-techno-sciences, sciences de la vie, de l'information et de la cognition, caractérisent une tendance de fond depuis 2005. Actuellement on observe des convergences par paire mais rarement par trio. Or la BS s'appuie au moins sur le trio NBI.
2. **L'amélioration des méthodes computationnelles** appliquées en biologie. Aujourd'hui l'état avancé de l'art permet de concevoir et réaliser des protéines-enzymes et de nouveaux replis protéiques; des modèles permettent de prédire le résultat de modifications des chemins métaboliques.

3. **La découverte assistée en biologie**. Il ne s'agit plus seulement de robotiser l'expérimentation, mais bien d'assister l'ensemble du cycle cognitif de la découverte (formation d'hypothèses plausibles, déduction de conséquences testables, induction expérimentale).
4. **Parmi les technologies de miniaturisation/robotisation, la microfluidique** offre la possibilité de diminuer drastiquement les coûts (petits volumes), de paralléliser et de mieux contrôler les processus. Cette technologie innovante et en pleine expansion, devrait permettre à terme d'appréhender la complexité biologique au niveau de la cellule et de la molécule unique.
5. **L'hybridation entre nano-électronique et nano-biologie** commence à s'envisager. La BS peut ainsi par exemple permettre de réaliser un nano-capteur dans lequel la mesure est effectuée par des macromolécules biologiques, hybridées avec des éléments nano-électroniques pour le calcul et l'affichage du résultat. Des applications existent, comme les "laboratoires" dans des pilules ou sur des puces.
6. **L'utilisation de codes génétiques ou de chimies différentes** ("xénobiologie") a l'intérêt de rendre les produits issus de la BS dépendants de composés absents de l'environnement. Elle permet aussi de mieux s'affranchir des interférences entre cellule et composant synthétique.

IV - ENJEUX DE SOCIÉTÉ

La fraction de la BS qui s'intéresse aux conditions d'émergence de la vie est condamnée par certains comme prométhéenne. D'autre part la capacité de la BS à manipuler le Vivant soulève des craintes exacerbées par sa liberté créatrice. En outre des Organisations Non Gouvernementales (ONG) [2] reportent sur la BS le débat sur les plantes génétiquement modifiées.

Ces objections devraient s'exprimer dans des débats prenant en compte enjeux éthiques, coûts et bénéfices sociétaux.

1) Sûreté et sécurité

Quelques inquiétudes ont vu le jour concernant les risques associés à la pratique de la BS (problème de « sûreté ») et à la possibilité de détourner celle-ci à des fins malveillantes (problème de « sécurité »), tels que des organismes pathogènes ou des produits chimiques nocifs créés *de novo*.

Le dialogue public organisé par les conseils de recherche britanniques (BBSRC et EPSRC) a souligné l'inquiétude du public sur la difficulté à évaluer les impacts de systèmes nouveaux.

Les produits de la BS sont déjà soumis aux règlementations pertinentes en cours selon le domaine d'application concerné[3]. Notons aussi que les produits finaux et intermédiaires de la BS seront nécessairement soumis aux investigations (éco-)toxicologiques selon le règlement REACH.

Parmi les méthodes possibles d'implémentation moléculaire de la BS, la seule qui ait été débattue concernant sûreté et sécurité est le génie génétique. Or ce dernier est l'objet d'un moratoire, levé il y a plus de 30 ans. Un danger potentiel plus réaliste réside dans la possibilité de synthétiser des fragments d'ADN dotés de pouvoirs pathogènes (virus par exemple). Ce danger n'est en fait pas spécifique de la BS, mais résulte de l'augmentation de capacité en synthèse d'ADN, et relève de la règlementation sur la biosécurité.

La Délégation Générale pour l'Armement (DGA) a réalisé une base des données des acteurs de la BS et a identifié les options biosécuritaires. Le Secrétariat Général de la Défense et de la Sécurité Nationale (SGDSN) propose de maintenir une veille sur les problématiques de défense et sécurité liées aux domaines de la BS, et d'organiser une réunion interministérielle annuelle de concertation. L'agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) va mettre en place une veille scientifique prospective sur la BS.

2) Propriété intellectuelle

La BS ne connaîtra un véritable essor économique que lorsque les investissements publics initiaux seront relayés par une florissante industrie. Aussi le traitement du droit à la propriété intellectuelle est-il déterminant. À terme, il faudra résoudre les difficultés nouvelles liées à la dualité de la BS, qui mêle parfois étroitement la phase de conception fondée sur des logiciels, et celle de construction biotechnologique. Actuellement, les modèles de propriété intellectuelle envisagés en BS sont le brevet, et l'open source par analogie avec l'informatique [4]. Il y a généralement consensus sur l'intérêt des brevets à spectre étroit en biotechnologies, et sur le danger de ceux à spectre large, plus attaquables et susceptibles d'étouffer l'innovation. L'open source est le modèle favori des tenants de

[2] Voir par exemple ETC group, Canada.
[3] Par exemple l'autorisation de mise sur le marché des médicaments.
[4] Lorsque l'invention est combinatoire, des droits de protection forts sur les entités élémentaires peuvent bloquer l'invention en induisant des coûts de transaction rédhibitoires et une distribution non optimale des rentes de l'invention entre les différents acteurs.

la BS constructiviste utilisant les biobriques (iGEM, BIOFAB). En Europe, il existe un lien entre la propriété intellectuelle et l'éthique qui pourrait mener à un examen plus étroit des brevets de BS dans l'UE par rapport aux USA. Cependant, il est vraisemblable que la BS pose moins de problèmes que la protection par brevet d'objets naturels, même s'il faut évaluer le risque d'une éventuelle monopolisation de la BS par quelques entreprises multinationales.

3) Éthique

Par delà les questions de sécurité et de propriété intellectuelle, chaque technique et chaque avancée de la BS pose des difficultés spécifiques car l'artificialisation du vivant peut heurter certaines valeurs des sociétés dans lesquelles elle se développe. Il importe donc de réfléchir sur les significations morales de pratiques qui visent à éliminer l'imprédictibilité du vivant, au profit d'une conception rationnelle de systèmes organisés pour assumer des fonctions technologiques. La recherche en BS ne peut se développer qu'à l'écoute du milieu culturel et social qui la nourrit. Les instances scientifiques doivent donc contribuer à la diffusion des connaissances sur la BS et accepter d'être interpellées par la société civile. Le dialogue public organisé par les conseils de recherche britanniques (BBSRC et EPSRC) a souligné l'ouverture du public vis-à-vis de la BS si les bénéfices attendus sont clairement expliqués. Enfin, le bio-art volontiers provocateur qui se développe aujourd'hui fera probablement partie de l'imaginaire induit par la BS, susceptible de jeter un pont entre science et société.

V - APPLICATIONS ET MARCHÉS

Cette nouvelle technologie pourrait offrir des bénéfices en matière de santé, d'environnement et de société. Parmi les champs d'application de la BS, on peut citer :

1. **de nouvelles techniques moins polluantes de bio-production** confinée de composés biologiques ou chimiques, classiques ou innovants ; cela inclut les ingrédients alimentaires, les bio-fuels et les matériaux issus de la pétrochimie ; la synthèse complète d'un petit génome bactérien et sa transplantation dans une bactérie-hôte viennent d'être annoncés, ouvrant le (long) chemin vers des microorganismes de synthèse pour la bio-production ;
2. **des outils diagnostiques améliorés, des médicaments et des vaccins nouveaux** ; une première preuve de principe vient d'être apportée dans le cas du contrôle de l'homéostasie de l'urate chez la Souris, permettant d'envisager une thérapeutique par un circuit régulatoire de synthèse ;
3. **des bio-senseurs** ; ceux-ci ont un spectre d'application potentiel très large, qui inclut la lutte contre le bio-terrorisme ;
4. **des outils innovants de bio-remédiation** pour traiter les milieux contaminés ou les eaux usées ;
5. **des outils supplémentaires au service des matériaux « intelligents »** ou bio-matériaux.

Les développements de la BS devraient permettre l'émergence d'un nouveau marché et une redistribution des cartes dans le secteur industriel, notamment en matière de biotechnologies, d'énergie et de pétrochimie. La structuration du secteur comprend actuellement deux types d'entreprises : les **"Gene Foundries"** (Fonderies à gènes), qui synthétisent à façon des gènes et leurs compositions ; et les **"BioSynTechs"** (Biotech de synthèse), qui développent des microorganismes à partir de ces gènes synthétisés dans le but de produire par ingénierie métabolique des biocarburants, des médicaments ou des produits chimiques. Ces entreprises sont au cœur d'un tissu économique plus vaste qui intègre des acteurs académiques, tels les universités ou les organismes de recherche, et des acteurs privés, tels les industries pharmaceutique ou pétrochimique. Une stratégie d'intégration verticale voit le jour au travers des partenariats et alliances établis entre les différents acteurs.

Depuis peu, des produits issus de plusieurs domaines d'application de la BS arrivent sur le marché. Ainsi, un premier outil de diagnostic, Versant™ (Siemens), permet le suivi annuel de 400.000 patients atteints de viroses multiples, soit un chiffre d'affaire de 100 M$ par an. En bio-production, un puissant traitement anti-malaria concernant 500 millions de patients, l'artémisinine vient d'être approuvé aux USA par la FDA (Amyris Biotechnology a cédé une licence d'exploitation à Sanofi Aventis pour production et mise sur le marché à prix coûtant). Dans le domaine du textile, les sociétés Du Pont et Tate&Lyle produisent déjà à partir de sucre céréalier une molécule communément utilisée dans les tissus synthétiques.

Une étude du département de l'énergie américain (US DOE) estime que le marché global du séquençage du génome et des services associés (liés ou non à la BS) dépassait les 5 milliards d'euros en 2006. Le marché annuel de la BS était estimé à 0,5 milliard d'euros en 2006 et il devrait atteindre 3 milliards en 2016. D'autres estimations sont plus optimistes ; en particulier, la firme indépendante Lux Research estime qu'avant 2015 un cinquième du chiffre d'affaire de l'industrie chimique américaine (estimé actuellement à 1 800 milliards de dollars) pourrait dépendre de la BS.

Les pays de l'OCDE et les économies émergentes investissent en BS car elles perçoivent son énorme potentiel pour la croissance économique et pour répondre à certains défis globaux (substituts à la pétrochimie, procédés moins polluants etc.). A titre d'exemple l'Inde a prévu d'investir 1,6 milliards de dollars pour sa recherche en BS sur 5 ans.

VI - ÉTAT DES LIEUX INTERNATIONAL ET NATIONAL

Au plan des publications, les États-Unis d'Amérique (USA) pèsent 68%, l'Union Européenne (UE) 17% (8% pour l'Allemagne, 2% chacun pour le Royaume-Uni, l'Espagne et la France). Ce décalage notable entre USA et UE se retrouve au niveau des financements publics.

Aux USA, la National Science Foundation (NSF) finance, outre des projets de recherche, le réseau SynBERC (16 M$) et la fabrique BIOFAB (42 M$); la Fondation Gates finance des applications médicales (43 M$); le département de l'Énergie et la société British Petroleum financent le Joint Bioenergy Institute (600 M$). La société Exxon finance des travaux du J.C. Venter's Institute.

L'UE a financé 18 projets durant son 6eme programme cadre (PCRD) (NEST [5] - total 25 M€), et quelques projets isolés durant le 7eme PCRD (KBBE [6] - 3 M€ par projet).

En 2008, **le Royaume-Uni** a créé 7 réseaux thématiques de BS, et lance bientôt un homologue de BIOFAB. Les conseils de recherche BBSRC et EPSRC ont organisé une enquête d'opinion dont les résultats ont été publiés à l'été 2010 : des ateliers publics ont été organisés avec 160 citoyens et 40 experts ou acteurs de la BS qui ont produit une synthèse de leurs débats en 12 points, très utile et non polémique. En 2009, un rapport de l'Académie Royale des Technologies a recommandé 2 actions principales :

1. la création de centres de recherche pluridisciplinaires, chacun comptant 30-35 personnels de recherche et d'appui, chacun pour un montant de 80 M€ sur 10 ans ;
2. un programme d'écoles doctorales, chacune pour 0,8 M€ par an.

La présence française dans 5 des 18 projets européens NEST et dans 2 projets KBBE a été significative. TESSY, un des projets NEST de coordination, avait en 2008 recensé 38 équipes françaises impliquées dans la BS ou susceptibles de l'être. Selon des critères académiques stricts de reconnaissance internationale en BS, ne subsistent que 4 équipes de recherche affichées en BS, qui se concentrent à Genopole Évry. Ceci place proportionnellement la France au-dessus de la moyenne européenne, mais souligne avec acuité le problème de masse critique dans toute l'Europe. Un réseau de BS regroupant 20 laboratoires français s'est constitué en 2005 et internationalisé en 2008. Sept entreprises de biotechnologie ont un profil de BS, dont une à Clermont-Ferrand (n°2 mondial), une à Nîmes, et cinq en Île-de-France . La compagnie Total a créé en 2009 un département de R&D Biotech avec un axe BS (Paris La Défense). Enfin, la première équipe française ayant participé à la compétition étudiante internationale de BS — iGEM — avait remporté au MIT en 2007 un premier prix de recherche fondatrice. Il existe donc en France un gisement significatif d'expertise et un potentiel à développer dans le domaine de la BS.

Par ailleurs, la France participe à **plusieurs activités transnationales en BS** :

1. **un ERA-Net en Biologie Systémique**, ERASysBio (terme en 2011), qui a un lot de travail dévolu à un état des lieux des activités européennes en BS ;
2. **un groupe de travail collaboratif (CWG) en BS**, qui a démarré ses travaux en 2009 et prépare un ERA-Net spécifiquement dédié à la BS pour 2011 ;
3. **une réflexion sur la BS lancée par l'OCDE**, qui a conduit entre autres à la conférence de Washington en 2009 ;
4. **des ateliers** sur la normalisation, la propriété intellectuelle, la sûreté et la sécurité, qui sont organisés par diverses instances.

[5] NEST : Science et technologie nouvelle et émergente.
[6] KBBE : Bio-économie basée sur la connaissance.

VII - FORCES ET FAIBLESSES EN FRANCE

1) Recherche et Développement

+ Grande force à l'échelle européenne en ingénierie métabolique, avec un tissu industriel émergent de BioSynTech ;

+ Originalités en ingénierie épigénétique et en microfluidique ;

+ Haut niveau international mais faibles effectifs en ingénierie régulatoire ;

+ Un appui possible sur l'excellence en mathématiques, nano-techno-sciences et nano-galénique ;

± Des effectifs supérieurs à la moyenne européenne, mais un peu en-deçà du Royaume-Uni, et bien en-deçà des États-Unis ; une amorce de concentration depuis 2008 ; un réseau informel depuis 2005 ;

– Quasi-absence de sociétés de synthèse à façon de gènes ou génomes (1 Fonderie à gènes) ;

– Déficit de structuration des relations entre académie et industrie ;

– Persistance de barrières culturelles, faisant obstacle à la transdisciplinarité ; les biologistes ont une perception profondément analytique de leur discipline ; et alors que la chimie contribue traditionnellement à la biologie, l'inverse — pourtant utile en biocatalyse — reste exceptionnel.

2) Enseignement

+ Au niveau master, une formation spécialisée, une autre semi-spécialisée, apparues en même temps qu'au Royaume-Uni, en avance sur le reste de l'Europe ;

± Au niveau ingénieural, quelques formations de qualité en biotechnologie et génie des procédés, mais ces dernières n'incorporent pas encore de méthodes issues de la BS dans leur champ pédagogique ;

– Globalement, une perte d'influence de la physiologie microbienne, de la biochimie et du métabolisme, requis pour certains sous-domaines de la BS ; une désaffection des SHS dans les filières scientifiques, importantes pour sensibiliser les acteurs de la BS aux enjeux sociétaux ;

– Défaut de manuels et autres outils pédagogiques en BS (à l'échelle mondiale).

3) Programmation

– Absence de vision et de coordination des efforts au niveau national.

4) Débat Science et Société

+ Un débat autour de la BS organisé en 2009 par VivAgora ;

– Défaut d'informations validées, rigoureuses et compréhensibles, mises à la disposition de tous.

VIII - FACTEURS CLÉS DE SUCCÈS

1. Fédérer les talents en sciences dures, humaines, sociales et de l'ingénieur autour de la BS ;
2. Forger une identité forte à vocation européenne et proposer un cadre réglementaire ;
3. Créer une attractivité et une visibilité internationales ;
4. Mettre en synergie Formation / Recherche / Plateforme / Développement / Industrie ;
5. Favoriser un dialogue sociétal transparent, impliquer la société dans la programmation.

IX - PROPOSITIONS POUR DÉVELOPPER LA BIOLOGIE DE SYNTHÈSE

Comme techno-science émergente, la biologie de synthèse (BS) porte le même potentiel de développement au 21eme siècle que la chimie de synthèse depuis le milieu du 19eme siècle. Tout en diminuant l'impact environnemental des procédés industriels, elle peut permettre la création de richesses et d'emplois. Il existe en France un gisement de compétences à mobiliser autour de la BS, en s'appuyant sur quelques acquis solides, permettant de viser une position mondiale de second ou troisième. Ainsi, la BS répond précisément aux critères de programme Investissements d'Avenir définis par le gouvernement.

Les propositions ci-dessous visent au développement harmonieux de la BS dans ses diverses facettes. Leur mise en œuvre devrait assurer à la France un standing dans le concert international qui garantisse son plein accès aux technologies avancées et aux bases de données, ainsi qu'aux décisions normatives.

1) Créer des centres d'excellence multidisciplinaires, alliant recherche et formation en BS

1.1. Créer des centres d'excellence reliés en un réseau

La réussite dans un domaine à forte compétitivité nécessite une mise en réseau des acteurs et une mutualisation des moyens. L'émergence de centres d'excellence académiques sera soutenue, en s'appuyant sur quelques critères parmi lesquels : a) une recherche de haut niveau international, dans les disciplines constitutives de la BS, mais aussi transdisciplinaire, et b) la présence sur le même campus d'au moins deux des trois composantes suivantes : une formation spécialisée, un acteur industriel et une plateforme technologique dédiée.

1.2. Développer une formation initiale ambitieuse

Il est impératif que la formation initiale en BS soit développée en lien avec ces centres afin de constituer un vivier de compétences pour les milieux académique et industriel. Une formation spécialisée de master permet de servir de référence, mais dans le futur ce seront surtout des aménagements de cursus qui permettront de généraliser les concepts et méthodes issus de la BS dans les formations de biotechnologie des Instituts Universitaires de Technologies, Universités et Écoles d'ingénieurs, ainsi que dans les Écoles Doctorales. Les aspects éthiques et sociétaux feront partie intégrante des enseignements spécialisés en BS.

1.3. Créer un forum national de la BS

Pour favoriser l'unité du futur tissu national de BS, pour permettre l'échange de bonnes pratiques en recherche, développement et formation, un forum national de la BS devrait rassembler les principaux acteurs de la recherche, de la formation et de la société. Ce forum permettra de faire le lien entre les grands et petits centres, et les initiatives internationales. Il contribuera à mettre en place un dialogue entre science et société, établira des synergies en enseignement, et suscitera de l'intérêt pour la BS auprès des formations réputées, en visant des implémentations en 2012-2014. Ce forum pourra également promouvoir l'urgente introduction de la BS au niveau des écoles doctorales. Le groupe interministériel recherche et innovation autour des sciences et technologies du vivant auquel participent des représentants des Alliances et de l'ANR supervisera ce forum et déléguera chacune des actions ci-dessus à l'entité la mieux appropriée.

2) Promouvoir un véritable dialogue entre science et société

2.1. Informer le public et motiver des personnes-relais

Le défi crucial est de créer les conditions pour que les avancées de la BS s'opèrent résolument dans un climat de confiance citoyenne et d'innovation manifestement responsable, en phase avec les grands enjeux sociétaux que sont la santé, le climat, la biodiversité et la qualité de vie. La confiance citoyenne devra être alimentée par une transparence de la recherche. Une information validée, rigoureuse et compréhensible sur la BS sera accessible dès que possible. Des "ambassadeurs" seront identifiés pour sensibiliser les structures intervenant auprès des étudiants et collégiens.

2.2. Organiser le dialogue et l'intégrer au processus de programmation

Des actions de concertation à long-terme seront lancées par le forum national de la BS (point 1.3) en lien avec le Groupe de Travail "Risques émergents" mis en place dans le cadre du "deuxième Plan National Santé Environnement" [7]. Il s'agit d'organiser des espaces de dialogue où les publics concernés, les ONG, les journalistes, les enseignants et les acteurs du domaine pourront échanger sur les bénéfices de la BS et leurs éventuelles inquiétudes concernant ses développements. Ces dialogues devront bien préciser le champ d'activité concerné et éviter d'englober sous le vocable de "biologie de synthèse" les activités qui lui pré-existaient. Egalement, les agences de financement et les Alliances impliqueront les représentants de la société dans leur processus de programmation. Par ailleurs, les demandes sociétales s'expriment également par le canal parlementaire ; l'Office Parlementaire d'Évaluation des Choix Scientifiques et Technologiques pourrait organiser les consultations nécessaires pour orienter les priorités publiques de recherche.

3) Mobiliser en synergie les acteurs institutionnels, publics et industriels

3.1. Mobiliser les acteurs institutionnels

L'objectif de l'engagement national au long cours doit être de rationaliser l'usage des moyens et de soumettre toute décision à un processus d'expertise clair et multi-acteurs. Les applications de la BS couvrant des secteurs divers de l'activité économique, cette stratégie nécessite de maintenir la concertation interministérielle, lancée depuis 2009 en réponse à une initiative de l'OCDE. En effet, l'OCDE joue un rôle important dans la concertation internationale en BS. Les acteurs de la programmation nationale devraient être parties prenantes, afin d'intégrer ces réflexions dans leurs feuilles de route. Le développement de cette stratégie devra s'appuyer sur l'avis d'experts scientifiques qui bénéficient d'une reconnaissance internationale en BS, et sur la consultation des porteurs d'enjeux sociétaux et économiques. Cette stratégie devra s'inscrire dans un cadre européen, et viser le développement des points forts de la France, à mettre en synergie avec ceux de nos principaux voisins (Allemagne, Royaume-Uni, Espagne).

3.2. Impliquer les acteurs industriels

De manière croissante, les développements futurs de la BS seront promus en combinant l'exploration et la connaissance du vivant avec la réponse aux problématiques de l'industrie. Afin d'obtenir un bon retour sur investissement, l'industrie doit être impliquée dès la définition du plan stratégique, en direct ou via les pôles de compétitivité. La prise en compte des questions éthiques et sociétales sera nécessaire pour la définition de ce plan. Les centres d'excellence devront être fortement incités à créer des partenariats avec l'industrie afin d'optimiser le transfert technologique. Ces liens devront favoriser l'introduction des méthodes de la BS dans l'industrie existante et la création de nouvelles

[7] "Action 44" : Renforcer la concertation sur les risques liés aux nouvelles technologies "Créer un espace de concertation dans le domaine de l'identification et de la prise en charge des risques émergents … en lien avec le comité de prévention et de précaution et les agences sanitaires".

entreprises dédiées. Le lien entre recherche fondamentale et appliquée sera favorisé par des appels à projets impliquant de manière croissante les industriels.

3.3. Investir dans des infrastructures pérennes

Une plateforme constitue une remarquable plaque tournante entre acteurs publics et privés. Dans ce domaine en pleine évolution technologique, elle doit être vue, non comme un investissement initial, mais à l'instar de ce qui se fait aux USA, ou dans les centres de séquençage nationaux, comme un investissement continu et conséquent permettant le renouvellement rapide des concepts et des équipements. Au niveau national, il faut envisager 2 à 4 plateformes à visées complémentaires, tournées vers l'innovation technologique et la valorisation, et s'inscrivant dans la ligne des moteurs d'évolution décrits plus haut.

3.4. Poursuivre l'effort de veille et de prospective

Il importe que le gouvernement poursuive son effort en faveur de l'essor responsable de la BS, en l'inscrivant de nouveau dans l'actualisation de la Stratégie Nationale de Recherche et d'Innovation. La vision à moyen terme doit être consolidée par un travail de veille et de prospective au sein des alliances concernées. Cet essor doit s'appuyer sur toutes les disciplines (biologie, chimie, physique, informatique, mathématiques appliquées et sciences de l'ingénieur, sciences humaines et sociales) et inciter à la transdisciplinarité.

4) Créer une politique de financement incitatrice

4.1. Financer des centres d'excellence et des projets compétitifs impliquant les SHS

La BS européenne n'a pas atteint sa masse critique. Un centre viable doit atteindre une masse critique en termes de personnel, savoir-faire, locaux et services communs. Une estimation basée sur des centres comparables indique que le coût total par centre (incluant salaires et locaux) serait de 15 M€ d'investissement initial et de 5 M€ par an de fonctionnement. Comme toute techno-science émergente, la BS devra bénéficier, notamment pour ses aspects les plus fondamentaux, d'une programmation soutenue. Afin de donner dès le départ toute leur mesure aux aspects éthiques et sociétaux, la recherche en BS devra être conduite en collaboration avec les sciences humaines et sociales (SHS). De véritables partenariats scientifiques seront donc requis dans les réseaux de recherche et encouragés dans les projets.

4.2. Tirer parti des investissements d'avenir

La BS entre maintenant en phase de décollage dans les pays les plus avancés. Le cadre des Investissements d'Avenir financés par l'Emprunt National offre à la France l'occasion de faire fructifier ses atouts dans ce domaine. La BS est concernée par plusieurs des 29 propositions faites par Mme Pécresse le 6 octobre 2009 pour l'Emprunt National (propositions 2 et 9; propositions 23-27 en synergie avec les nano-technologies pour créer des hybrides à l'échelle nano-métrique). Les appels d'offres 'Démonstrateurs pré-industriels en biotechnologie' 'Biotechnologies et Bioressources' et 'Nanobiotechnologies' de l'action Santé-Biotechnologies répondent à ces propositions.

Le démonstrateur 'Toulouse White Biotech' et le projet SYNTHACS, financés par la première vague de ces appels, s'inscrivent dans une démarche de biologie de synthèse.

Le programme Investissements d'Avenir soutient la biologie de synthèse ; le projet SYNTHACS sélectionné à l'issue de l'appel à projets 'Biotechnologies et Bioressources' propose de développer des voies métaboliques nouvelles permettant de produire des molécules 'plate-forme' à partir de biomasse. Il illustre parfaitement les perspectives offertes par la BS, qui permet de concevoir de nouvelles voies métaboliques chez un micro-organisme en combinant la modélisation, l'enzymologie et l'ingénierie métabolique. Ce projet est né d'un partenariat entre la société ADISSEO et l'Institut National des Sciences Appliquées de Toulouse. L'INSA propose déjà des modules de formation sur la BS, illustrant particulièrement bien l'association entre formation, innovation et partenariat.

4.3. Proposer à l'échelon Européen un guichet unique de la BS

Alors que le 8eme PCRD entre en phase préparatoire, la France pourrait proposer un guichet unique de la BS afin de lui conférer une vraie visibilité, à l'instar du 6eme PCRD, mais à rebours du 7eme PCRD. Le soutien de l'Allemagne est attendu sur ce point, l'Allemagne étant un membre actif du CWG cité au chapitre VI. Un projet d'ERA Net a été déposé en février 2011, auquel participent le CNRS et l'ANR.

5) Harmoniser les politiques et maîtriser les risques à l'échelle Européenne et Internationale

5.1. Développer en partenariat Européen un cadre réglementaire et normatif

S'il est essentiel de rassembler les compétences académiques et de créer les conditions d'un transfert vers l'industrie, la stratégie nationale doit aussi se préoccuper de développer, dans un partenariat européen, un cadre réglementaire et normatif pour accroître l'efficacité des échanges entre acteurs et garantir la sécurité des innovations de la BS pour la société. Les travaux de normalisation sont fondateurs pour l'industrialisation et la réglementation. Ce cadre normatif permettra d'implémenter les "demandes" économiques et sociales ; ainsi, des règles de production plus respectueuses de l'environnement en chimie ou pétrochimie peuvent avoir un effet incitatif majeur sur les entreprises de BS. Il sera donc essentiel de motiver des scientifiques français à s'y impliquer, notamment en valorisant cette activité dans leur carrière.

La France devra être présente sur tous les fronts internationaux d'harmonisation des politiques en matière de BS. La préparation de la position française pourrait s'appuyer sur le forum national proposé plus haut.

5.2. Maîtriser les risques potentiels sans entraver le développement scientifique et technologique

Afin de ne pas pénaliser les avancées de la recherche dans ce domaine, il faut intégrer le risque nouveau avec une attitude d'incertitude positive. La responsabilisation des chercheurs doit certes être encouragée. Cependant, un code de conduite pour les expérimentateurs sera promulgué au plus tôt. Ce code fondera des campagnes de sensibilisation par les Commissions d'Hygiène et de Sécurité, ciblées sur la pratique quotidienne des acteurs. Des formations en biosécurité seront mises en place.

Enfin, il est important d'inciter à la recherche sur les méthodes de confinement [8], au-delà du classique confinement physique. Concernant la sécurité, la question principale est de savoir si la réglementation en vigueur ou à venir permet les développements scientifiques et technologiques nécessaires à la BS, tout en garantissant la maîtrise des risques potentiels. Les recommandations de l'étude approfondie de la DGA (2010) concernant les options biosécuritaires en BS serviront ici de référence. Il s'agit principalement de la sécurisation des activités de synthèse d'ADN à façon avec : a) la création d'une cellule étatique d'aide à la décision concernant un client ou une commande "à risque" ; b) la mise en place d'une synergie forte entre sociétés de synthèse d'ADN et acteurs étatiques ; et c) le suivi des appareils de synthèse d'ADN. Les problèmes potentiels devront être surmontés et maîtrisés à l'échelon international.

Perspectives

Ce document est produit en 2010 à l'initiative du Groupe de Concertation Thématique "Sciences du Vivant" mis en place par le MESR, qui rassemble des représentants des ministères, des agences, des alliances, des pôles de compétitivité et quelques experts *intuitu personae*. Dans l'hypothèse où le MESR retiendrait les propositions qu'il contient, les perspectives à 2, 5 et 15 ans pourraient être les suivantes.

[8] Par exemple on peut contrôler la prolifération d'organismes issus de la BS en les rendant dépendants d'un composé chimique qu'on ne trouve pas dans la nature et qu'ils ne peuvent pas fabriquer eux-mêmes. Autre approche, l'usage de matériel héréditaire qui ne soit ni ADN ni ARN préviendrait tout transfert horizontal de gènes vers les êtres naturels.

Objectifs à 2 ans (2012) : phase de montée en puissance

Constituer un réseau français original en BS avec une ambition internationale :

1. organiser le dialogue science et société, l'intégrer dans le processus de programmation ;
2. mettre à disposition du public des informations rigoureuses ;
3. attirer les meilleurs scientifiques vers ces défis transdisciplinaires, et renforcer les positions autour des quelques forces de recherche déjà présentes ;
4. susciter des rapprochements scientifiques et amorcer une structuration territoriale par des actions incitatives telles que des appels d'offre généralistes autour de projets, centres et plateformes;
5. motiver des établissements d'enseignement supérieur à incorporer une part de BS dans certaines filières biotechnologiques ;
6. créer un lien entre recherche publique et petite/moyenne industrie ;
7. contribuer à toute initiative européenne significative pour mettre en œuvre la feuille de route TESSY : jalons scientifiques, transfert de connaissances, financement, règlementation et code de conduite du chercheur.

Objectifs à 5 ans (2015) : phase de consolidation

1. amplifier le dialogue science et société et renforcer sa place dans le processus de programmation ;
2. poursuivre et étendre la structuration du territoire ;
3. renforcer et structurer le lien entre recherche publique et petite/moyenne industrie ;
4. susciter une implication croissante de la R&D des grands comptes via les pôles de compétitivité ;
5. habiliter des filières de formation incorporant une part de BS ;
6. consolider la position française dans le réseau européen, et contribuer au développement d'une règlementation européenne ;
7. réaliser un premier bilan des actions, assorti de perspectives.

Objectifs à 15 ans (2025) : phase de généralisation

1. pérenniser le dialogue science et société ;
2. renouveler les compétences pour ces défis transdisciplinaires ;
3. ouvrir quelques formations spécialisées supplémentaires ;
4. susciter de nouvelles plateformes de niveau européen ;
5. amener à l'autofinancement les cellules de transfert technologique (SATT) impliquées dans le domaine.

XI - LEVIERS D'ACTION

La réalisation des projections envisagées ci-dessus à 2, 5 et 15 ans devra mobiliser plusieurs leviers d'action.

1. **Formation initiale et continue** : intégrer la pluridisciplinarité et la formation à la BS dans le dialogue contractuel entre les universités et l'Etat.
2. **Plateformes technologiques** : utiliser l'appel d'offres 'Démonstrateurs pré-industriels en biotechnologie' de l'action Santé-Biotechnologies du programme Investissements d'Avenir ; inscrire la BS dans les priorités de l'appel d'offres plateformes du Fonds Unique Interministériel (FUI). Inscrire le besoin de plateformes en BS dans les conclusions (recommandations) du groupe de travail "Infrastructures" du GCT "Sciences du Vivant".
3. **Recherche et développement industriel** : soutenir les initiatives en BS et en recherche transdisciplinaire structurés autour de sites d'excellence mobilisés par la loi L.R.U. et les appels d'offre du programme Investissements d'Avenir ; utiliser le bilan des mesures d'aide à l'innovation en cours de réalisation dans le champ des biotechnologies (groupe de travail "Plan Biotech" du GCT Sciences du Vivant) pour renforcer, remplacer ou créer des mesures d'aide ; consulter les pôles de compétitivité concernés.
4. **Mise en réseau européen** : participer à l'ERA-Net de BS en cours de préparation en réponse au prochain appel d'offres de la priorité KBBE du 7eme programme cadre.
5. **Communication et vulgarisation** : développer et diffuser des textes de référence ; organiser des espaces de dialogue où les publics concernés, les journalistes, les enseignants et les acteurs du domaine pourront échanger sur les bénéfices de la BS et leurs éventuelles inquiétudes concernant ses développements.
6. **Méthodes d'évaluation de l'atteinte des objectifs :** mettre en place ces méthodes et critères en amont à travers un groupe de travail.

XII - ANNEXES

1) Documents de référence (classés du plus récent au plus ancien)

1. Biologie synthétique, génie biologique et biomimétique. J. Weissenbach (Rapport ITMO BMSV ; 2010)
2. Des nano-technologies à la biologie de synthèse. Réalités Industrielles (Annales des Mines ; fév 2010)
3. Les options biosécuritaires face aux risques potentiels induits par la Biologie Synthétique. Délégation Générale pour l'Armement (2010)
4. Five hard truths for synthetic biology. R. Kwok. Nature 463, 288-290 (2010)
5. Self-sufficient control of urate homeostasis in mice by a synthetic circuit. C. Kemmer et al. Nature Biotechnology 28, 355-60 (2010)
6. Notes de veille 136 & 137 du Centre d'Analyse Stratégique (2009)
7. The farther, the safer. P. Marlière. Syst Synth Biol 3:77-84 (2009)
8. The Bioeconomy to 2030. Desiging a policy agenda. Main findings and policy conclusions. (OCDE; 2009) http://www.oecd.org/futures
9. Synthetic Biology: scope, applications and implications. The Royal Academy of Engineering (2009)
10. Télégramme Diplomatique de l'Ambassade de France aux Etats-Unis d'Amérique (juillet 2008)
11. Succès de la première équipe française lors de la compétition iGEM de biologie synthétique. D. Bikard & F. Képès. Médecine / Sciences 24, 541-544 (2008)
12. Biologie synthétique, quel business model ? F. Le Fèvre. Mémoire de Master en administration des entreprises (2008) fhr.lefevre.googlepages.com/Synthia_quel_business_model.pdf
13. Final roadmap towards synthetic biology in Europe. TESSY (2007) http://www.tessy-europe.eu/public_docs/Final-Roadmap-towards-Synthetic-Biology-in-Europe.pdf
14. Synthetic Genomics – options for governance. The J. Craig Venter Institute, MIT & Center for strategic and international studies (2007)
15. Berkeley Center for Synthetic Biology. M. Bucci. Nature Chemical Biology 3:527 (2007)
16. Extreme genetic engineering – an introduction to synthetic biology. etc Group (2007) http://www.etcgroup.org/
17. Synthetic Genomics – options for governance. The J. Craig Venter Institute, MIT & Center for strategic and international studies (2007)
18. Synthetic Biology. A NEST pathfinder initiative. European Commission (2007) ftp://ftp.cordis.europa.eu/pub/nest/docs/5-nest-synthetic-080507.pdf
19. An Analysis of Synthetic Biology Research in Europe and North America. Synbiology (2006) http://www2.spi.pt/synbiology/documents/news/D11%20-%20Final%20Report.pdf
20. Numéro spécial de "Nature" n° 438 (24 novembre 2005).

Sites Internet :

21. Association VivAgora ; cycle 2009 sur la BS : http://www.vivagora.org/spip.php?rubrique70
22. Laboratoire français virtuel : http://www.epigenomique.genopole.fr/index.php?n=Workgroups.NewSynBio
23. Site francophone d'information : http://www.biologiesynthetique.fr/
24. Le consortium TESSY : http://www.tessy-europe.eu/
25. About Knowledge-Based Bio-Economy ("KBBE"). European Commission http://cordis.europa.eu/fp7/kbbe/about-kbbe_en.html
26. Le consortium d'entreprises de synthèse d'ADN à façon "ICPS" : http://pgen.us/ICPS.htm
27. International Association Synthetic Biology "IASB" : http://www.ia-sb.eu/

28. La communauté USA de BS : http://syntheticbiology.org/
29. Le consortium USA financé par NSF "SynBERC" : http://www.synberc.org/
30. Le consortium USA financé par NSF "BIOFAB" : http://www.biofab.org/
31. Le consortium USA financé par DOE et BP "JBEI" : http://www.jbei.org/
32. La compétition étudiante internationale "iGEM" : http://www.igem.org/
33. Bibliographie partielle de la BS : http://www.synthetic-biology.info/

2) Lexique

- *-omiques* : ensemble des méthodes de la biologie moléculaire s'appliquant à l'échelle du génome (génomique, transcriptomique, protéomique, métabolomique etc.).
- *biobrique [BS]* : courte chaîne d'ADN servant de composant de base pour la BS, tel que la partie codante d'un gène, ou la région nécessaire à son expression.
- *biologie systémique* : approche analytique visant une compréhension intégrée d'un système biologique. Cette approche fait appel à la modélisation mathématique et à la simulation informatique, et s'enracine dans les données -omiques.
- *chassis [BS]* : hôte cellulaire optimisé pour accueillir un objet biologique de synthèse.
- *dispositif [BS]* : assemblage de biobriques remplissant une fonction de bas niveau tel qu'un interrupteur ou un oscillateur.
- *génie génétique* : ensemble des méthodes de la biologie moléculaire permettant de modifier ou créer les chaînes d'ADN.
- *microfluidique* : science et technologie des systèmes manipulant des petits volumes (microlitre) de fluides et dont au moins l'une des dimensions caractéristiques est de l'ordre du micromètre.
- *système [BS]* : assemblage de dispositifs remplissant une fonction de haut niveau tel qu'un appareil photosynthétique.
- *xénobiologie [BS]* : science s'intéressant à des formes de vie basées sur des biochimies différentes de celle des êtres naturels.

3) Le Groupe de Travail "Biologie de Synthèse"

Liste des membres

Bernadette Bensaude-Vincent (Univ Sorbonne Paris 1, philosophie)
Jean-Michel Besnier (MESR, secteur Science et Société)
Nathalie Blin (ANR)
François Képès (CNRS & Genopole d'Evry, animateur du Groupe, biologie des systèmes)
Claude Lambré (Ministère du Travail, de l'Emploi et de la Santé)
Lionel Moulin (MEDDTL)
Michael O'Donohue (ANCRE, Agreenium, biotechnologies industrielles)
Daniel Richard-Molard (MESR, secteur Bioressources-Ecologie-Agronomie)
Anna Rocca (MESR, secteur Biologie-Santé)
Alain Rochepeau (MESR, département de la coordination et des politiques transverses)
Francoise Roure (Conseil général de l'industrie, de l'énergie et des technologies
Ministère de l'Economie, des Finances et de l'Industrie)
Frédéric Sgard (OCDE)
Michèle Tixier-Boichard (MESR, secteur Bioressources-Ecologie-Agronomie)
Jean Weissenbach (AVIESAN, génomique)

Auditions d'experts

Recherche académique (3)
Alfonso Jaramillo (iSSB, Genopole et Université d'Evry)
Denis Pompon (CGM, CNRS, Gif)
Franck Molina (SysDiag, CNRS/BioRad, Montpellier)

Recherche industrielle et Développement, Propriété Intellectuelle (4)
Vincent Schächter (Total, Paris)
Philippe Soucaille (Metabolic Explorer Biopôle, Clermont)
Marc Delcourt (Global Bioenergies, Evry)
Pierre-Benoît Joly (INRA/SenS & IFRIS, Université Paris-Est, Marne-la-Vallée)

Formation et Éducation (2)
François Taddei (CRI, Université Paris 5)
Jean-Loup Faulon (iSSB, Genopole et Université d'Evry)

Éthique et Société (2)
Bernadette Bensaude-Vincent (Université Sorbonne Paris 1)
Gérard Lambert (journaliste et écrivain, Paris; grand témoin du cycle Vivagora)

Sécurité et Sûreté (1)
Julien Thourot (DGA, Arcueil).

Ordres du jour des réunions du groupe

Réunion du 7 juin 2010

14h00 Tour de table - présentation des membres du GT
14h15 Cadre général du travail du groupe - Michèle Tixier-Boichard
14h45 Débat sur le cadre général
15h00 Introduction aux problématiques de la biologie de synthèse - François Képès
15h45 Discussions autour des problématiques
16h15 Pause
16h30 Organisation du travail du groupe - Mise au point du plan du texte de vision
18h00 Fin de session

Réunion du 28 juin 2010

10h00 Alfonso Jaramillo (iSSB, Genopole et Université d'Evry)
10h30 Denis Pompon (CGM, CNRS Gif)
11h00 Franck Molina (SysDiag, CNRS/BioRad, Montpellier)
11h30 Vincent Schächter (Total, Paris)
12h00 Discussion interne au GT

12h30 Déjeuner
13h30 Philippe Soucaille (Metabolic Explorer Biopôle, Clermont)
14h00 Discussion interne au GT
14h45 François Taddei (CRI, Université Paris 5)
15h15 Jean-Loup Faulon (iSSB, Genopole et Université d'Evry)
15h45 Discussion interne au GT
16h00 Bernadette Bensaude-Vincent (Université Paris 10 Nanterre)
16h30 Gérard Lambert (écrivain, Paris; grand témoin du cycle Vivagora]
17h00 Julien Thourot (DGA, Arcueil)
17h30 Discussion interne au GT
17h45 Préparation des étapes suivantes
18h00 Fin de session

Réunion du 9 juillet 2010

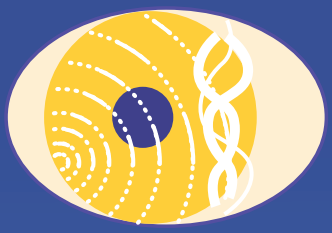
9h00 Marc Delcourt (Global Bioenergies, Evry)
9h30 Pierre-Benoît Joly (INRA/SenS & IFRIS, Université Paris-Est, Marne-la-Vallée)
10h00 Discussion interne au GT
10h30 Travail sur la version 1 du texte de vision
13h00 Fin de session

Groupe européen d'éthique en science et nouvelles technologies

« Ethics of Synthetic Biology »

Avis n° 25 du 17 novembre 2009

(version anglaise)



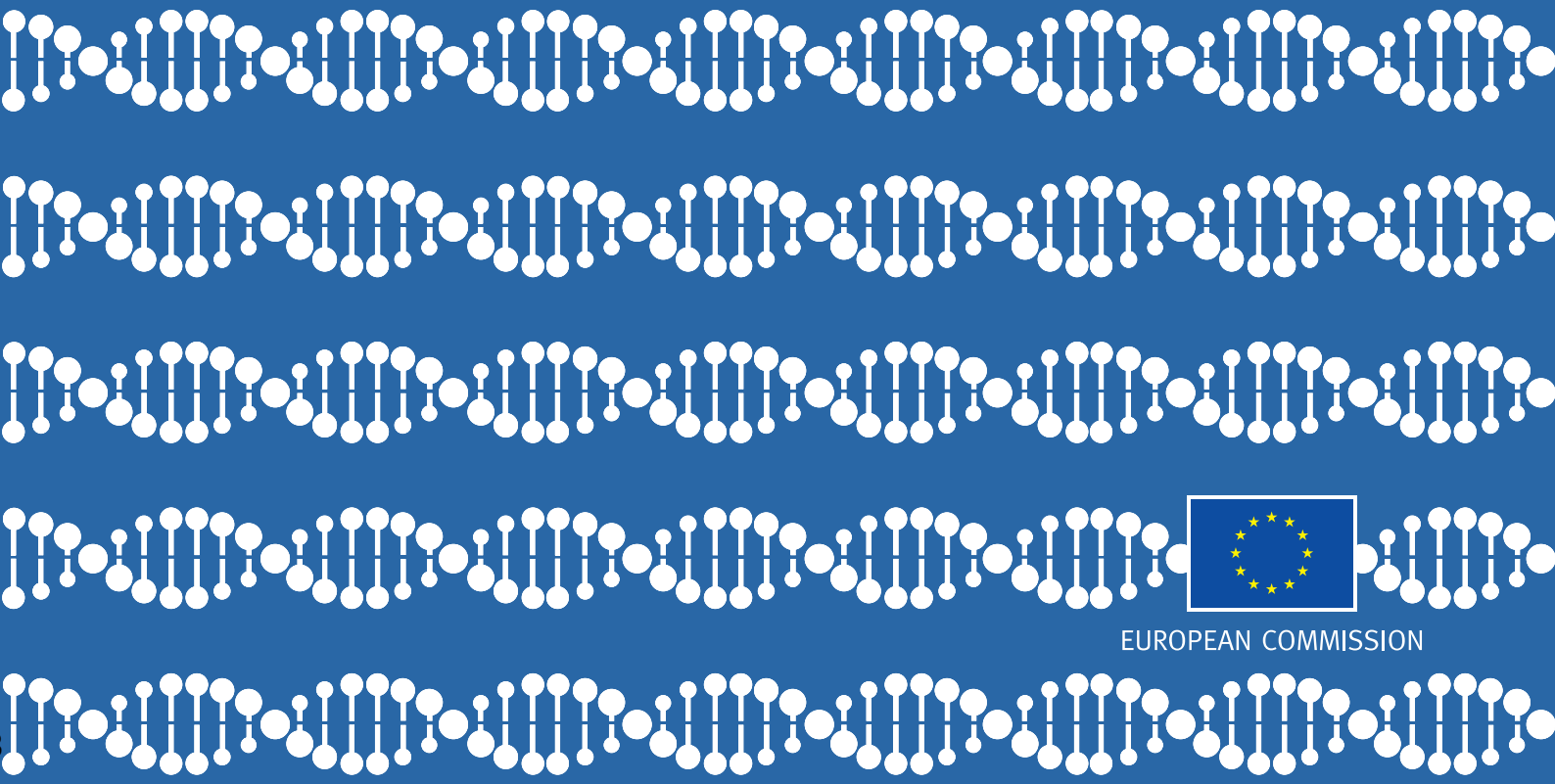
The European Group
on Ethics in Science
and New Technologies
to the European Commission

Ethics of synthetic biology

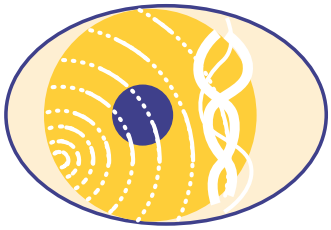
Opinion No

25

Brussels, 17 November 2009



EUROPEAN COMMISSION



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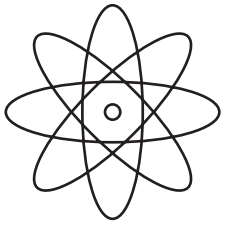
Ethics of synthetic biology



Brussels, 17 November 2009

25
Opinion No

European Commission

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OPINION OF THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES TO THE EUROPEAN COMMISSION

Ethics of synthetic biology No **25** 17/11/2009

Reference: *Request from President Barroso*
Rapporteurs: *Rafael Capurro, Julian Kinderlerer, Paula Martinho da Silva and Pere Puigdomenech Rosell*

THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE),

Having regard to the Treaty establishing the European Community, and in particular Article 6 of the common provisions concerning respect for fundamental rights,

Having regard to the EC Treaty, and in particular Article 152 on public health,

Having regard to the Charter of Fundamental Rights of the European Union of 28 September 2000, approved by the European Council in Biarritz on 14 October 2000 and proclaimed solemnly in Nice by the European Parliament, the Council and the Commission on 7 December 2000, and in particular Article 1 (Human dignity) and Article 3 (Right to the integrity of the person), ([1])

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, ([2])

Having regard to the Convention on the grant of European patents (European Patent Convention) of 5 October 1973 (text as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996, 10 December 1998 and 27 October 2005 and comprising the provisionally applicable provisions of the act revising the EPC of 29 November 2000), ([3])

Having regard to Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, ([4])

Having regard to Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, ([5]) as amended in 2003 and 2005,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, ([6])

Having regard to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, ([7])

Having regard to Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, ([8])

([1]) Official Journal C 364 of 18 November 2000, pp. 1–22.
([2]) OJ L 136 of 30 April 2004, pp. 1–33.
([3]) http://www.european-patent-office.org/legal/epc/e/ma1.html.
([4]) OJ L 159 of 27 June 2003, pp. 46–94.
([5]) OJ L 121 of 1 May 2001, pp. 34–44.
([6]) OJ L 311 of 28 November 2001, pp. 67–128.
([7]) OJ L 169 of 12 July 1993, pp. 1–43.
([8]) OJ L 189 of 20 July 1990, pp. 17–36.

Having regard to Directive 76/768/EC of the European Parliament and of the Council of 27 July 1976 on the approximation of the laws of the Members States relating to cosmetic products, ([9])

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC,

Having regard to Council Directive 80/68/EEC of 17 December 1979 on the protection of groundwater against pollution caused by certain dangerous substances, ([10])

Having regard to Council Directive 85/337/EEC of 27 June 1985 on the assessment of the effects of certain public and private projects on the environment, ([11])

Having regard to the Treaty of Amsterdam of 17 June 1997, and in particular to the sustainable development strategy (SDS) and Article 152 thereof concerning public health,

Having regard to Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms, as amended by Directive 98/81/EC, ([12])

Having regard to Council Directive 91/676/EEC of 12 December 1991 concerning the protection of waters against pollution caused by nitrates from agricultural sources ([13]) in order to reduce overall use of nitrates,

Having regard to Council Regulation (EEC) No 2078/92 of 30 June 1992 on agricultural production methods compatible with the requirements of the protection of the environment and the maintenance of the countryside, ([14])

Having regard to the United Nations Convention on Biological Diversity of 6 June 1992, ratified by the European Union on 25 October 1993, and to the Cartagena Protocol on Biosafety, approved by the European Community on 11 September 2003,

Having regard to Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control, ([15])

Having regard to the Kyoto Protocol, adopted on 11 December 1997 with the aim of reducing greenhouse gas emissions in order to fight global climate change (for the period 2005-2012),

Having regard to Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market, ([16])

Having regard to the Commission communication 'Directions towards sustainable agriculture', ([17])

Having regard to the World Trade Organisation (WTO) Sanitary and Phytosanitary (SPS) Agreements of 1995, in particular Article 5.1, 5.2 and 5.3 thereof on health risk assessments,

Having regard to Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients, ([18])

([9]) Official Journal L 262, 27.9.1976, p. 169.
([10]) OJ L 20, 26.1.1980.
([11]) OJ L 175, 5.7.1985.
([12]) OJ L 117, 8.5.1990.
([13]) OJ L 375, 31.12.1991.
([14]) OJ L 215, 30.7.1992.
([15]) OJ L 257, 10.10.1996.
([16]) OJ L 123, 24.4.1998.
([17]) COM(1999) 22, 27.1.1999.
([18]) OJ L 42, 14.2.1997.

Having regard to Council Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, in particular Article 6 thereof, ([19])

Having regard to Directive 2001/42/EC of the European Parliament and of the Council of 27 June 2001 on the assessment of the effects of certain plans and programmes on the environment, ([20])

Having regard to Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, ([21])

Having regard to Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed, ([22])

Having regard to Regulation (EC) No 1946/2003 of the European Parliament and of the Council of 15 July 2003 on Transboundary movements of genetically modified organisms, ([23])

Having regard to Council Regulation (EC) No 1234/2007 of 22 October 2007 establishing a common organisation of agricultural markets and on specific provisions for certain agricultural products (single CMO regulation) ([24]) , creating a horizontal legal framework for the agricultural markets,

Having regard to the Commission communication '2006 environment policy review' describing the action taken by the EU on the environment, ([25])

Having regard to the Commission communication 'Mid-term review of the Sixth Community Environment Action Programme' with reference to protection of the environment, biodiversity and natural resources, ([26])

Having regard to the Commission communication on 'Implementation of the Community strategy for dioxins, furans and polychlorinated biphenyls', ([27])

Having regard to the Council Regulation (EC) No 1334/2000 setting up a Community regime for the control of exports of dual-use items and technology ([28]) and its amendments,

Having regard to the Commission communication 'Preparing for the 'health check' of the CAP reform' on the overview of the adjustments needed in the CAP, ([29])

Having regard to the Treaty of Lisbon, signed on 13 December 2007 and currently open for ratification,

Having regard to Article 6 of the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007-2013), which states that 'All the research activities carried out under the Seventh Framework Programme shall be carried out in compliance with fundamental ethical principles',

Having regard to the Commission communication 'Supporting early demonstration of sustainable power generation from fossil fuels', ([30])

([19]) OJ L 213, 30.7.1998.
([20]) OJ L 197, 21.7.2001.
([21]) OJ L 106, 17.4.2001.
([22]) OJ L 268, 18.10.2003.
([23]) OJ L 287, 5.11.2003.
([24]) OJ L 299, 16.11.2007.
([25]) COM(2007) 195, 30.4.2007; OJ C 181, 3.10.2007.
([26]) COM(2007) 225, 30.4.2007; OJ C 181, 3.10.2007.
([27]) COM(2007) 396, 10.7.2007; OJ C 191, 17.8.2007.
([28]) OJ L 159/1, 30.6.2000 and for the amendments 2000R1334 — EN — 12.04.2006 — 007.001 — 1
([29]) COM(2007) 722, 20.11.2007.
([30]) COM(2008) 13, 23.1.2008.

Having regard to the Commission communication on a 'Proposal for a Directive on the promotion of the use of energy from renewable sources', ([31])

Having regard to the Council of Europe Convention on Human Rights and Biomedicine, signed on 4 April 1997 in Oviedo, ([32])

Having regard to the Additional Protocols to the Council of Europe Convention on Human Rights and Biomedicine, in particular the Additional Protocol on Prohibition of Human Cloning and the Protocol on Biomedical Research,

Having regard to the Universal Declaration on the Human Genome and the Rights of Man adopted by UNESCO on 11 November 1997, ([33]) the Declaration on Human Genetic Data adopted by UNESCO on 16 October 2003 and the Universal Declaration on Bioethics and Human Rights adopted by UNESCO on 19 October 2005,

Having regard to the European Commission (2003) Reference Document on Synthetic Biology, ([34])

Having regard to the European Commission Report (2005) on Synthetic Biology, Applying engineering to biology, by a NEST high-level expert group ([35]) and the European Commission Paper (2007) on Synthetic Biology: A NEST pathfinder initiative, ([36])

Having regard to the hearings of experts and Commission departments by the EGE during their January 2009, February 2009, March 2009, April 2009 and May 2009 meetings, ([37])

Having regard to EGE Opinion No 21 on 'Ethical Aspects of Nanomedicine', ([38])

Having regard to the Roundtable organised by the EGE on 19 May 2009 in Brussels,

Having heard the EGE rapporteurs ***Rafael Capurro***, ***Julian Kinderlerer***, ***Paula Martinho da Silva*** *and* ***Pere Puigdomenech Rosell***,

Hereby adopts the following opinion.

([31]) COM(2008) 19, 23.1.2008.
([32]) http://conventions.coe.int/treaty/en/treaties/html/164.htm.
([33]) http://portal.unesco.org/shs/en/ev.php-URL_ID=2228&URL_DO=DO_TOPIC&URL_SECTION=201.html.
([34]) ftp://ftp.cordis.europa.eu/pub/nest/docs/synthetic_biology.pdf.
([35]) FTP://FTP.CORDIS.EUROPA.EU//PUB/NEST/DOCS/SYNTHETICBIOLOGY_B5_EUR21796_EN.PDF.
([36]) ftp://ftp.cordis.europa.eu/pub/nest/docs/5-nest-synthetic-080507.pdf.
([37]) See agendas on the EGE website: http://europa.eu.int/comm/european_group_ethics/index_en.htm.
([38]) http://europa.eu.int/comm/european_group_ethics/docs/avis20en.pdf.

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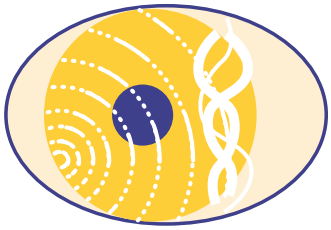


European Group
on Ethics in Science
and New Technologies
to the European Commission

OPINION OF THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES TO THE EUROPEAN COMMISSION

Ethics of synthetic biology

Reference: Request from **President Barroso**
Rapporteurs: **Rafael Capurro**, **Julian Kinderlerer**, **Paula Martinho da Silva** and **Pere Puigdomenech Rosell**

25
Opinion No

Scope of the opinion

On May 28, 2008 President José Manuel Barroso asked the EGE to issue an Opinion on the ethical, legal and social implications that may derive from synthetic biology. In his letter, the President advocated that '(…) the debate about the legitimacy of engineering new life forms has mainly focused on safety issues and a work on the ethical, legal and social implications that may derive from this specific use of biotechnology is still missing.'

The EGE is aware that synthetic biology raises philosophical, anthropological, ethical, legal, social and scientific issues. It is equally aware that the convergence of multiple technologies in synthetic biology, each based on different scientific paradigms, increases the complexity of assessing the ethics of synthetic biology and its products. The EGE has, however, agreed that, apart from safety issues associated with synthetic biology, an ethical, legal, and political governance of synthetic biology is needed in the EU and worldwide to ensure that the interests of society are respected. The Group has therefore accepted President Barroso's request.

1. Scientific Aspects

Synthetic biology is a new research field within which scientists and engineers seek to modify existing organisms by designing and synthesising artificial genes or proteins, metabolic or developmental pathways and complete biological systems in order to understand the basic molecular mechanisms of biological organisms and to perform new and useful functions. This research sector is heterogeneous and results from the convergence of different technological and scientific tools (from information technology to chemistry, engineering, biology, mathematics and computer modelling). Synthetic biology has two main goals: 1) to be a tool to improve understanding of biological systems, their complexity and emergent properties that derive from the interaction of complex pathways and 2) to use the organisms as factories to obtain products which may have a direct, clear and immediate use (pharmaceuticals, bio-fuels, raw materials or biomedical tools (e.g. vaccines), or new bio-defence agents). This distinction diversifies not only the potential uses of synthetic biology but also the goals on which current research activities are being developed across the world by private or public research bodies. The following paragraphs aim to describe the research activities currently ongoing and to indicate potential future uses of this research field.

1.1. Historical overview

The desire to know and understand the world around us has been deeply rooted in humans since ancient times. The first approach to the study of life has been *analytical* ([39]): to break down complex systems into smaller and simplified ones to facilitate their observation and understanding.

During the early XIX century a *synthetic* approach emerged in biology as a complementary approach to analysis. Using the knowledge of the time, the first synthesis experiments of biological compounds were carried out in the field of organic chemistry. For example in 1828, ([40]) urea, a component of human urine and an important fertiliser, was first synthesised from ammonium salts, showing that organic compounds could be chemically synthesised from inorganic compounds. This was revolutionary news, as common knowledge was that, although organic matter could be decomposed into inorganic constituents (e.g. through heating or other treatments), the reverse would be impossible because inorganic matter would lack the 'vital force' to transform it into organic matter.

As time passed and research advanced, the same pattern (from *analysis* to *synthesis*) was observed not only in chemistry, but also in genetics. In 1953, the DNA structure was described by Watson and Crick. ([41]) For the first time, the double helix structure was revealed in DNA, which is a polymer formed from monomers constituted of sugar molecules (deoxyribose) linked to a nitrogen containing base (A=adenine, T=thymine, C=cytosine, G=guanine) and a phosphate group.

From the mid 1950's onwards, molecular biology research focused on the study of DNA regulation, replication and repair (the *analytical* period). In the early 1970's the first restriction endonucleases ([42]) were discovered and purified, which allowed scientists to precisely 'cut' and 'paste' DNA fragments from one source to another, paving the way for the *synthetic* era of molecular biology.

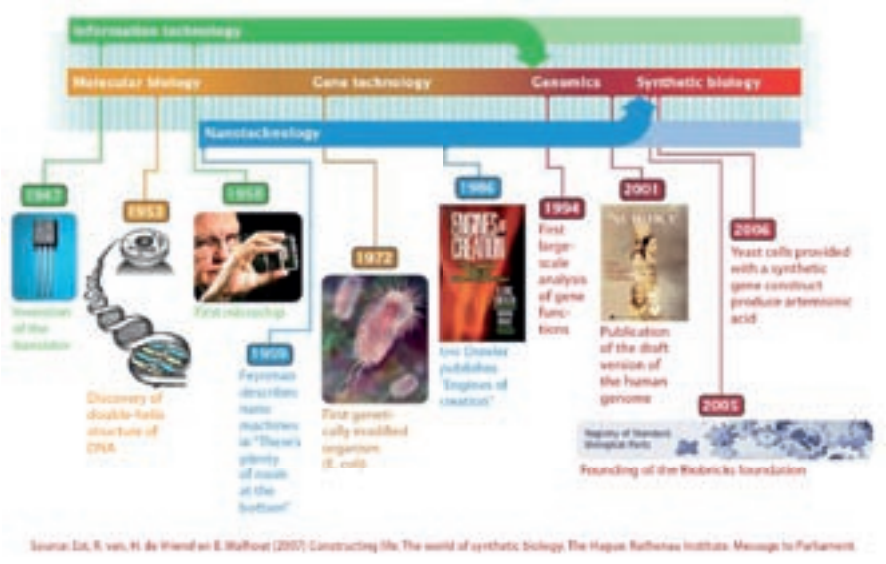
([39]) Such an approach has been used since before the time of Aristotle, and, in a more formal way, by Descartes, G. Galilei and Newton.

([40]) F. Woehler, Poggendorff's Ann. Phys., 12, 253-256 (1828).

([41]) J.D. Watson and F.H. Crick, 'Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid', Nature, 171(4356):737-8, 25 April 1953.

([42]) For this discovery the Nobel Prize for Medicine was awarded in 1978 to W. Arber, D. Nathans and H. Smith.

Technology key in shifting paradigms



In 1973, Cohen and Jalal published the first paper on the recombinant DNA technique, through which a functional plasmid produced by joining different DNA fragments was inserted into *E. Coli* to produce transgenic bacteria. ([43])

Recombinant DNA technologies have evolved constantly since they first appeared in the 1970's. Biology research has moved increasingly towards the study of molecular actors and their interaction through signalling pathways and complex network dynamics. Due to the great advances made since the 1970's with regard to molecular techniques, scientists have been able to address complicated issues by being able to analyse more and more complex molecular model systems.

Another important development for molecular biology occurred in 1984 with the discovery of the Polymerase Chain Reaction (PCR) by K. Mullis. ([44]) It allowed the enzymatic replication of DNA fragments by using a DNA polymerase, nucleotides (dNTPs, the building blocks of DNA) and the repetition of cycles (denaturing, annealing and elongation) through which a DNA template is amplified. PCR relies on the availability of small pieces of DNA (oligonucleotides) that are produced by chemical synthesis. The development into a routine technique of oligonucleotide synthesis was a landmark in synthetic biology. This was made possible in the early '80s and the development of automatic synthesisers resulted in a technique accessible to most molecular biology laboratories.

1.2. Moving from analytical molecular biology to synthetic biology

As W. Szybalski foresaw in 1974 'Up to now we are working on the descriptive phase of molecular biology. […] But the real challenge will start when we enter the synthetic biology phase of research in our field. We will then devise new control elements and add these new modules to the existing genomes or build up wholly new genomes. This would be a field with unlimited expansion potential and hardly any limitations to building 'new better control circuits' and […] finally other 'synthetic' organisms […].'

Synthetic biology was born, therefore, at least theoretically, in 1974, although the term synthetic biology can be traced back at least to 1912 when Stephane Leduc published his *Biologie Syntetique*. ([45]) However, in practice, the term was not used for a further twenty years, until scientists began to think about assembling synthetic genetic regulatory networks (circuits) in the

([43]) S.N. Cohen et al., 'Construction of biologically functional bacterial plasmids in vitro.' PNAS 70, 3240-44 (1973).

([44]) K. Mullis et al., 'Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction', Cold Spring Harb Symp, Quant Biol. (1986).

([45]) Stephane Leduc, *La Biologie Synthétique*, Paris 1912. Also see Szostak, J.W., Bartel, D.P., Luisi, P.L.*(2001) Synthesizing life. Nature 409:387–390.*

laboratory. ([46]) The first formal conference on synthetic biology was held in 2004, showing that by that time a scientific community grouped under the name of synthetic biology was present and active.

Synthetic biology experts believe that the field should not be defined only by its applications and that it may contribute significantly to the progress of biology. For instance, knowledge of the minimum number of genes needed to support a microorganism is relevant to understanding the essential functions of living beings. They also claim that knowing whether the components of basic biological machinery can differ from those existing in present organisms including, for instance, the genetic code, may enlighten us as to the origins of life. All these important basic biological questions are key to research into what we call synthetic biology, which has a number of objectives in a variety of fields of application. From a biological point of view, interactions between different cellular pathways in metabolic or developmental processes are essential for understanding cell dynamics. Synthetic biology may therefore be a heuristic tool to improve our understanding of the main biological mechanisms of life.

1.3. Towards a working definition of synthetic biology

It is not easy to find a working definition of synthetic biology. It depends on the desired outcomes, either on its applications (or aims) or more in general on the broad concept of basic research and therefore its experimental nature. It may not be possible to find an unequivocal definition and it could change over time as awareness of this discipline increases and becomes more widespread.

A recent (2008) description of synthetic biology reads: *The fundamental idea behind synthetic biology is that any biological system can be regarded as a combination of individual functional elements — not unlike those found in man-made devices. These can therefore be described as a limited number of parts that can be combined in novel configurations to modify existing properties or to create new ones.* ([47])

Another description can be found at the website of the EU Project 'Towards a European Strategy for Synthetic Biology' (TESSY, 2007-2008):

- *Synthetic biology uses nucleic acid elements or complex systems that are predefined and chemically synthesised in the laboratory by a modular approach. This approach aims to: 1. engineer and study biological systems that do not exist as such in nature, and 2. use this approach for i) achieving better understanding of life processes, ii) generating and assembling functional modular components, iii) developing novel applications or processes.* ([48])

([46]) M.B. Elowitz and S. Leibler, 'A Synthetic Oscillatory Network of Transcriptional Regulators'; Nature. 2000 Jan 20; 403(6767):335-8.

([47]) A. Danchin, 'Synthetic biology: discovering new worlds and new words', EMBO reports; doi:10.1038/embor.2008.159 (2008).

([48]) See http://www.tessy-europe.eu/.

Other definitions of synthetic biology put forward so far include:

- *[Synthetic biology] attempts to recreate in unnatural chemical systems the emergent properties of living systems … [the] engineering community has given further meaning to the title…to extract from living systems interchangeable parts that might be tested, validated as construction units, and reassembled to create devices that might (or might not) have analogues in living systems*. (Benner and Sismour, 2005)

- *The development of well characterised biological components that can be easily assembled into larger functioning devices and systems to accomplish many particular goals*. (Jay Keasling speaking at the Synthetic Biology 2.0 conference at Haas Business School, UC Berkeley)

- *To advance knowledge and create products that can promote human welfare, synthetic biologists seek to create biological systems that do not occur naturally as well as reengineer biological systems that do occur naturally.* (Hastings Center, USA)

- *[Synthetic biology is] the design and construction of new biological parts, devices and systems that do not exist in the natural world and also the redesign of existing biological systems to perform specific tasks.* (Erosion, Technology and Concentration (ETC) Group, Canada)

- *[Synthetic biology] describes research that combines biology with the principles of engineering to design and build standardised, interchangeable biological DNA building-blocks. These have specific functions and can be joined to create engineered biological parts, systems and, potentially, organisms. [Synthetic biology] may also involve modifying naturally occurring genomes… to make new systems or by using them in new contexts*. (UK Parliamentary Office of Science and Technology, POST)

- *[Synthetic biology] is broadly understood as the deliberate design of novel biological systems and organisms that draws on principles elucidated by biologists, chemists, physicists and engineers... in essence it is about redesigning life.* (UK Royal Society)

It therefore appears that a general consensus on a standard classification of synthetic biology does not exist. The definitions so far provided depend on the scientific approach taken or the applications carried out by biologists. From the range of descriptions of the technologies it is, possible to identify the core elements of synthetic biology that include the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements. It centres on the intentional design of artificial or re-worked biological systems, rather than primary understanding of the biology of existing organisms in nature. A definition of synthetic biology should therefore include:

1. The design of minimal cells/organisms (including minimal genomes);

2. The identification and use of biological 'parts' (toolkit);

3. The construction of totally or partially artificial biological systems.

In addition, several experts emphasise the potential of **synthetic genomics**. Synthetic genomics may be defined as a field within synthetic biology that uses the increasing wealth of genomic information including the tools of oligonucleotide synthesis and of genetic modification with the aim of producing new genomes that will allow the fabrication of a product or a desired behaviour. One of the ways to achieve these goals is to use minimal genomes that become the basic framework into which a new set of genes are added to achieve new biological functions. It may make use of custom-designed base pair series, though in a more expanded and hitherto unprecedented sense, synthetic genomics could use genetic codes that are not composed of the four base pairs of DNA currently used in life forms.

1.3.1. To what extent does synthetic biology differ from other existing disciplines?

A key issue to address in synthetic biology is its difference from other disciplines, such as those based on the insertion of recombinant DNA into organisms. For example, techniques used in synthetic genomics (e.g. the use of synthetic DNA within an existing cell may be considered to be a recombinant DNA application rather than synthetic biology). It nevertheless appears that no clear boundary can be drawn between genetic engineering that is based on recombinant DNA and synthetic biology: the first is the starting point and merges into the second without a clear cut limit. Nevertheless, recognition of the complexity of biological systems and the intention to construct an organism with radically new properties may be described as a feature of the new discipline.

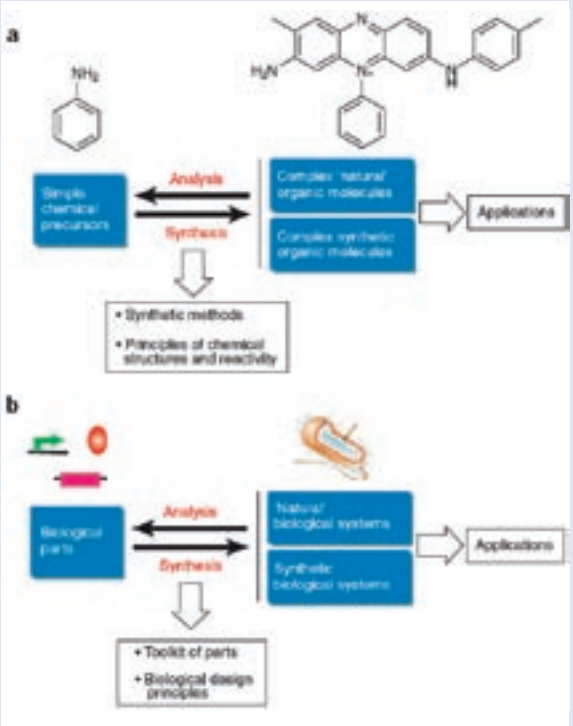


Figure 1. a) Analysis and synthesis in organic chemistry; b) Analysis and synthesis in synthetic biology ([49]).

Balmer A. and Martin P. have underlined ([50]) that the word 'synthetic' is ambiguous since it can mean either 'constructed' or 'artificial'. The former meaning is preferred by synthetic biologists (BBSRC/EPSRC, 2007), but it is inevitable that the 'artificial' aspect of synthetics is to some extent associated with the term. In fact, attempts have been made to avoid the word 'synthetic' by naming the field 'constructive biology' or 'intentional biology' (Carlson, 2006), but these terms have not become widely adopted.

The scientific community is still debating whether synthetic biology has introduced a paradigm shift compared with other biotechnologies. Some have indicated that, in order to distinguish between synthetic biological fabrications and other approaches, like transgenic organisms, the key difference could be that transgenic organisms are the result of introducing naturally occurring foreign or mutated DNA (genes) into the organism ([51]). Synthetic biology, in contrast, would result in the manufacturing of elements with synthetic raw materials and with no natural counterpart. ([52]) Some reserachers are producing protocells, that mimic the systems found in biology but differ in that the DNA contains nucleotides not found in already existing organisms. ([53]) Synthetic biology therefore involves the use of standardised parts and follows a formalised design process (Arkin and Fletcher, 2006). In parallel, synthetic biology involves a different level of sophistication and complexity of the work done in genetic engineering (where one gene at a time is inserted into an existing biological system), contrary to synthetic biology, where a whole specialised metabolic unit can be constructed (Stone, 2006 and Breithaupt, 2006:22).

One novelty that synthetic biology has introduced in the design and use of different bioengineering technological tools is the notion of intentionality. Synthetic biology uses biotechnology to ***intentionally*** design and build engineered biological systems that process information, manipulate chemicals, fabricate materials and structures, produce energy, provide food, and maintain and enhance human health and our environment. In parallel, synthetic biology ***synchronically uses*** multiple technologies, such as chemistry, engineering, biology, information technology and nanotechnology. In that respect, synthetic biology uses technology to manufacture products that are designed to give rise to knowledge or which serve a given aim, defined by the application area on which they are built, from bioremedies to ICT, biomedicine, biofuels or biomaterials. What is also distinctive in synthetic biology is recognition of the ***complexity*** of the systems that researchers want to reproduce, the fact that they work on not just molecular cloning of single genes or gene components as in standard molecular biology, but on whole interacting genetic networks, genomes and ultimately entire organisms. In this sense, the results of systems biology, a discipline that studies the relations of differ-

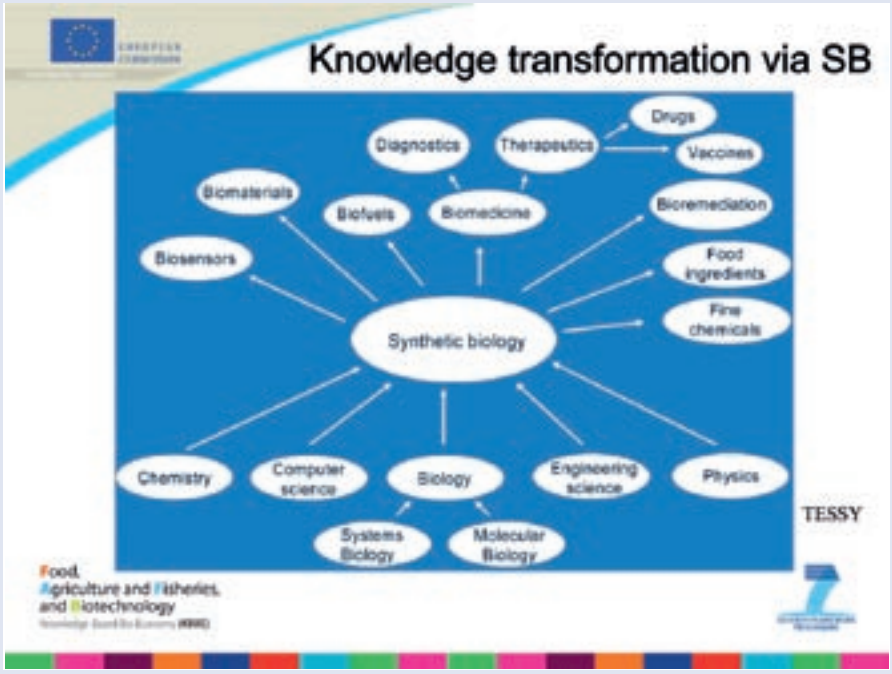
([49]) http://www.nature.com/nchembio/journal/v3/n9/pdf/nchembio0907-521.pdf.

([50]) Balmer A., Martin P., 2008, Synthetic Biology: Social and Ethical Challenges, Institute for Science and Society, University of Nottingham.

([51]) This could include copy DNA where codons have been modified to reflect the codon usage of the modified organism.

([52]) Bhutkar A., 2005, Synthetic Biology: Navigating the Challenges Ahead, J. BIOLAW & BUS., Vol. 8, No 2, p. 19-29.

([53]) "Protocells are defined as self-assembling and self-reproducing chemical systems created through human artifice (but not merely by manipulating a natural living organism) that produce the following interlocking chemical properties: (1) spatial localization of components by containment (2) utilization of energy and raw materials from the environment by metabolism and (3) control of the containment and metabolism by chemical information that can be replicated and can mutate." From Mark A. Bedau, Emily C. Parke, Uwe Tangen, Brigitte Hantsche-Tangen (2009) Social and ethical checkpoints for bottom-up synthetic biology, or protocells Syst Synth Biol (2009) 3:65–75



ent metabolic or developmental pathways within an organism, are important to synthetic biology.

1.4. The conceptual basis of synthetic biology

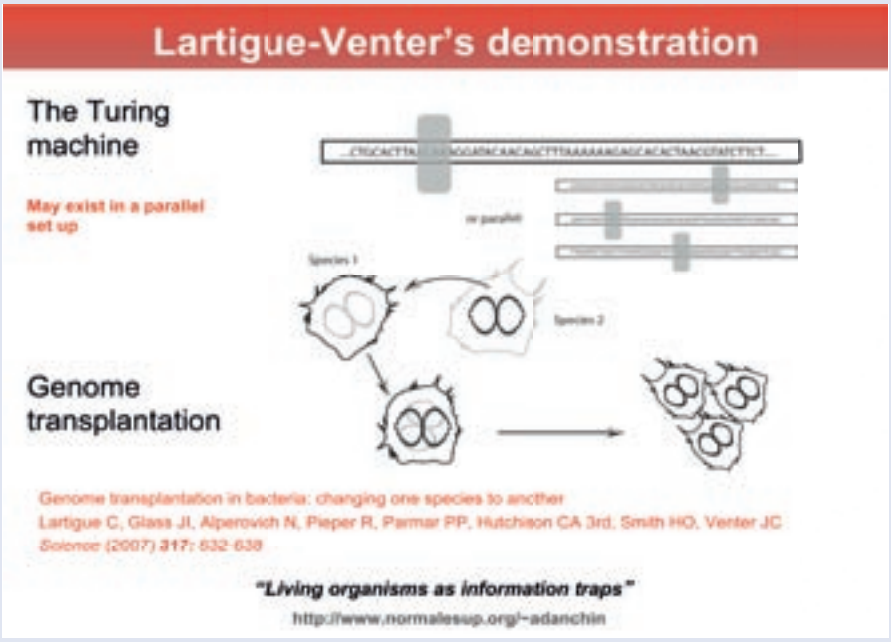
The conceptual basis underlying many modern approaches to biology is a reductionist view, which accepts that biological phenomena are expressions of chemical-physical processes. There are numerous examples of this paradigm, including Monod (1967), Eigen (1975) and Watson (1998). According to this view, the phenotypic expression of genes is a physicochemical phenomenon and interaction with this fundamental biological matrix would offer us the possibility of the synthesis of life ([54]). This paradigm has dominated the development of modern biology for several decades. Many modern geneticists, however, are now calling for a more complex concept of the gene, based on not only its DNA sequence, but also its epigenetic interaction manual, which in turn may be defined by complex protein-DNA interaction. The relevance of mechanistic approaches to synthetic biology is particularly strong since the attempt to manufacture intentionally designed organisms relies on the assumption that their expression will be controlled by the synthesised DNA sequences.

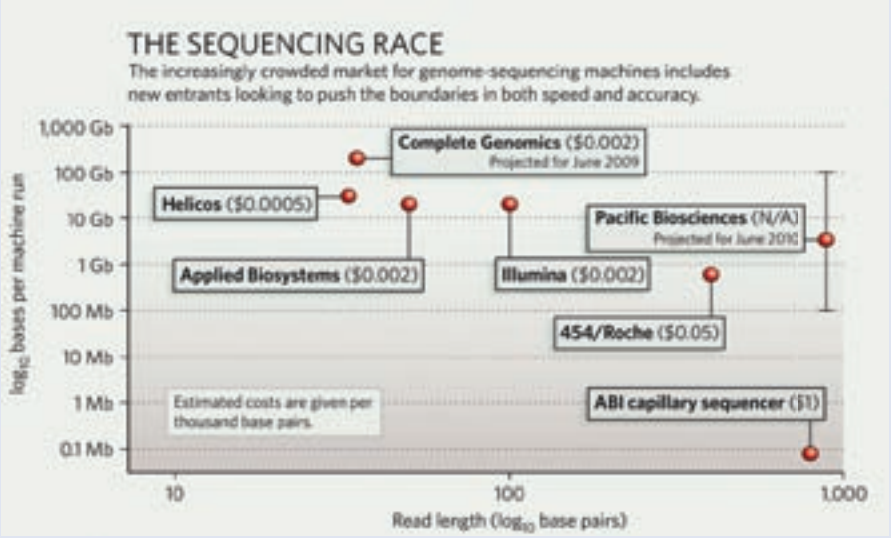
Some of the basic disciplines of modern biology such as biochemistry and molecular biology are based on a reductionist approach. The hope was that by deconstructing the systems and understanding individual parts of the system in great detail it would be possible to reconstruct pathways, cell systems and cellular interactions. This has been facilitated by the new methods available to scientists that permit the removal of parts of the organism. A number of scientists including Venter and colleagues have attempted to identify a minimal organism where the only remaining genes are those absolutely essential for a functional organism. Synthetic biology can then use a less complicated approach than the total synthesis of a new organism – using the basic cellular structures of micro-organisms or combinations of existing parts in a new cellular environment.

1.4.1. Key enabling approaches to synthetic biology

There are several key enabling technologies that are critical for the growth of synthetic biology. The key

([54]) An antagonistic approach to determinism is organismic biology (Ritter 1919). The central point is that an organism is a highly organised system where its biological meaning (and the meaning of its activity) cannot be understood as the sum of the activity of the parts, of its biological constituents. This means that when we wonder about the meaning of a living being we cannot explain its existence as a physicochemical phenomenon or attribute a contingent value to a singular organisms' constituent (for example, the brain). On the contrary, an organism is considered as a locus of integrated complexity, whose meaning refers to its composite nature. Eigen M. & Schuster P. (1978) *The Hypercycle*. Berlin; Eigen M. (1988) Perspektiven der Wissenschaft. Jenseits von Ideologien und Wunschdenken. Deutsche Verlags-Anstalt; Jonas H. (1979) *Das Prinzip Verantwortung* Insel Verlag; Jonas H. (1987) 'Creazione dell'uomo' *il Mulino* (XXXVI) Bologna pp. 615-626; Monod J. (1967) *Chance and Necessity* N.Y. Vintage Books; Ritter W. E. (1919) *The Unity of the Organism* 2 vols. Boston.





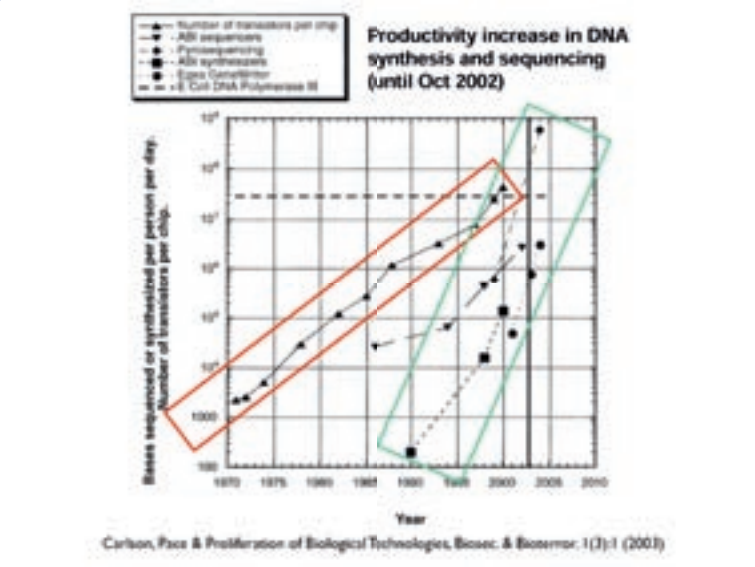
http://www.nature.com/news/2009/090206/pdf/news.2009.86.pdf

issues include standardisation of biological parts and hierarchical abstraction to permit the use of those parts in increasingly complex synthetic systems. ([55]) Achieving this is greatly aided by basic technologies to read and write DNA (sequencing and synthesis), which are exponentially improving in price/performance (Kurzweil, 2001). Measurements under a variety of conditions are needed for accurate modelling and computer-aided-design (CAD).

Sequencing

Synthetic biologists use DNA sequencing to obtain information about naturally occurring organisms (large-scale genome sequencing). The information obtained for many organisms will (eventually) permit the construction of biological components and devices. Other goals of DNA sequencing for synthetic biology aim at verifying that the manufactured engineered systems correspond to the expected goals and to facilitate rapid detection and identification of synthetic systems and organisms. Over the last twenty years, astonishing progress has been made in increasing the efficiency of DNA sequencing, synthesis and amplification.

([55]) Group, Bio FAB; Baker D, Church G, Collins J, Endy D, Jacobson J, Keasling J, Modrich P, Smolke C, Weiss R (June-2006). 'Engineering life: building a fab for biology'. Scientific American 294 (6): 44–51. PMID 16711359.



Progress in DNA sequencing has been constant and extraordinarily rapid. It started with the conversion from manual to automatic DNA sequencers that used fluorescence techniques and from sequencers that used electrophoresis gels to capillary sequencers. During the last two or three years, a new generation of DNA sequencers has emerged that allow the sequencing of gigabases (1 x 10^9 basepairs of DNA sequence) per run and new machines are in the pipeline. That means that the possibility of sequencing a single human individual's genome in a single experiment for about 10.000 USD could soon be reached.

DNA synthesis

As of now, the manufacturing of engineered genetic sequences is time consuming and the cycle of design, fabrication, testing and redesign used in bioengineering may be accelerated by the techniques developed for synthetic biology because it may provide rapid and reliable *de novo* DNA synthesis and assembly of fragments of DNA. The acceleration of technical and heuristic capacity in this use of synthetic biology is impressive. In 2002, researchers at SUNY Stony Brook succeeded in synthesising the 7741 base poliovirus genome from its published sequence, producing the first synthetic organism. ([56])

In 2003, the 5386 bp genome of the bacteriophage Phi X 174 was assembled in about two weeks. ([57]) In 2006, the same team at the J. Craig Venter Institute constructed and patented a synthetic genome of a novel minimal bacterium, *Mycoplasma laboratorium*, and is working on getting it to function in a living cell. ([58]) In 2007, it was reported that several companies were offering the synthesis of genetic sequences up to 2000 bp long, for a price of about USD 1 per base pair and a turnaround time of less than two weeks. ([59])

Modelling

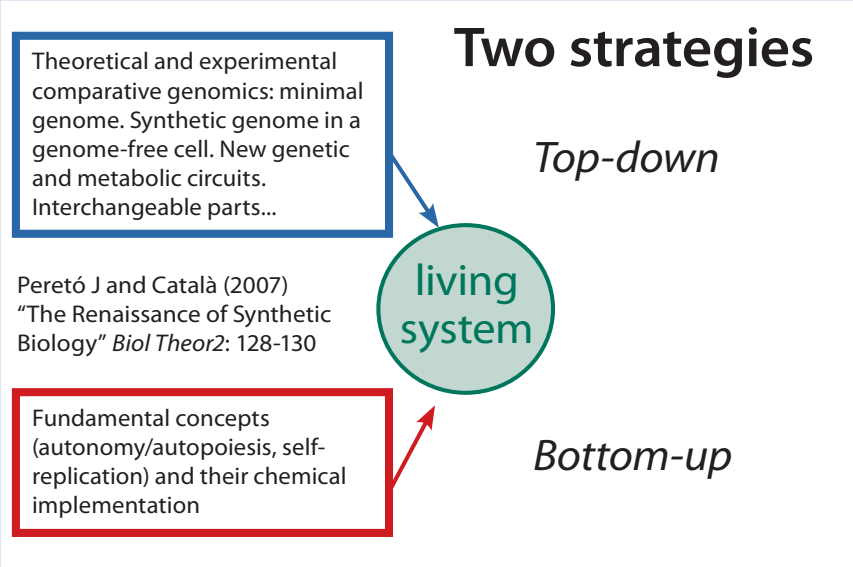
Synthetic biology models are informative tools for the design of engineered biological systems to better predict system behaviour prior to fabrication. Because of the intentional nature of manufacturing synthetic biology products, modelling is a key factor allowing

([56]) Couzin J (2002). 'Virology. Active poliovirus baked from scratch'. Science 297 (5579): 174–5. doi:10.1126/science.297.5579.174b.

([57]) Smith, Hamilton O.; Clyde A. Hutchison, Cynthia Pfannkoch, J. Craig Venter (2003-12-23). 'Generating a synthetic genome by whole genome assembly: {phi}X174 bacteriophage from synthetic oligonucleotides'. Proceedings of the National Academy of Sciences 100 (26): 15440-15445. doi:10.1073/pnas.2237126100.

([58]) Wade, Nicholas (2007-06-29). 'Scientists Transplant Genome of Bacteria'. The New York Times. ISSN 0362-4331; Gibson, DG; Benders GA, Andrews-Pfannkoch C, Denisova EA, Baden-Tillson H, Zaveri J, Stockwell TB, Brownley A, Thomas DW, Algire MA, Merryman C, Young L, Noskov VN, Glass JI, Venter JC, Hutchison CA 3rd, Smith HO. (2008-01-24). 'Complete chemical synthesis, assembly, and cloning of a Mycoplasma genitalium genome'. Science 319 (5867): 1215–20.

([59]) Pollack, Andrew (2007-09-12). 'How Do You Like Your Genes? Biofabs Take Orders'. The New York Times. ISSN 0362-4331.



Source: Modified graphic from a presentation by Andrés Moya "Synthetic Biology: Goethe's Dream", available at http://ec.europa.eu/european_group_ethics/activities/docs/ege_moya.pdf

synthetic biologists to predict how the functions of biological systems will develop, for example how biological molecules bind substrates and catalyse reactions, how DNA encodes the information needed to specify the cell and how multi-component integrated systems behave. Multiscale models of gene regulatory networks are being developed to focus on synthetic biology applications. Simulations have been used to predict biomolecular interactions in transcription, translation, regulation, and induction of gene regulatory networks, guiding the design of synthetic systems. ([60]) Research is also ongoing into improving accurate quantitative measurements of biological systems to elucidate how biological systems work and provide the basis for model construction and validation. Technologies which allow many parallel and time-dependent measurements will be especially useful in synthetic biology.

In addition, since biological systems are extremely complex and often involve thousands of interacting components, bioinformatic methods are useful to elucidate interdependencies in various biological processes. ([61]) For instance, insights into the distributions of mutational effects are vital for understanding robustness, and thus for both the genetic engineering of synthetic biological systems and the genetic modification of existing systems. ([62]) Thanks to the use of *'in silico'* methodology, it may be possible to provide accurate predictions of the underlying networks from expression data generated with artificial genomes and explore computationally future genome-wide redesign experiments in synthetic biology. ([63])

Cell-free approach

For certain applications of synthetic biology, there is now a developing trend towards using a cell-free approach, an alternative to developing minimal cells. The cell-free approach uses a different strategy, where only biochemical extracts containing the components necessary to operate the synthetic DNA circuit or a complex metabolic process are employed. ([64])

1.5. State of art and medium- to long-term forecast

There are two complementary approaches to synthetic biology, which take opposite starting points for

([60]) Y. N. Kaznessis, (2007) 'Models for Synthetic Biology', BMC Systems Biology, 2007, 1:47 doi:10.1186/1752-0509-1-47.

([61]) Jane Synnergren*, Björn Olsson and Jonas Gamalielsson. Classification of information fusion methods in systems biology. In Silico Biology 9, 0007 (2009).

([62]) Loewe L. A framework for evolutionary systems biology. BMC Syst Biol. 2009 Feb 24;3:27.

([63]) Carrera J, Rodrigo G, Jaramillo A. Model-based redesign of global transcription regulation. Nucleic Acids Res. 2009 Apr;37(5):e38. Epub 2009 Feb 2.

([64]) 24. Forster AC & Church GM, Molecular systems biology 2: 45 (2006 Ref. in Synthetic Biology: scope, applications and implications, Royal Academy of Engineering 2009.

research but share the same aim, namely to artificially reconstruct biological systems.

The first is called the ***'top-down'*** approach because it takes as a starting point an existing organism (e.g. a bacterium or a virus) and 'strips down' redundant genetic elements to get to the 'minimal' cell configuration (see C. Venter).

The second approach is called ***'bottom-up'*** because it takes as a starting point the creation of an inventory of 'standard parts' (e.g. MIT's registry of biological parts ([65])), which constitute the building blocks of the biological systems to be reconstituted. This approach is based on the idea of modularity, meaning that all biological systems can ultimately be decomposed into independent functional modules; the reconstitution of even complex networks can therefore be seen and designed as the combination of several modules according to the properties one wants the system under investigation to have. ([66])

1.5.1. Current research in synthetic biology

Pan-European research funded through the EU research programme on synthetic biology address the following areas:

- To produce generic capabilities in 'bio-inspired' tools and processes that will offer breakthrough answers to many needs of industry and the economy; ([67])
- To fabricate engineered biological devices based on modular assemblies of genes and proteins to (a) detect and combat disease at a very early stage and (b) for tissue repair and cell regeneration purposes;
- To fabricate synthetic biology products to produce useful materials, such as biodegradable plastics from cheap and renewable raw materials, or to convert sustainable feedstocks to fuels;
- To fabricate synthetic biology products to give rise to materials with new and improved properties. The ability to control biological structures at molecular level could also lead to devices such as machines and electronic circuitry on an ultra-small scale;
- To control cell membrane behaviour to develop innovative applications, such as biosensors, mainly in the pharma-industry.

According to the UK Parliamentary Office of Science and Technology - POST ([68]), the potential applications of synthetic biology research could include:

New biological production techniques for existing or novel biological materials and chemicals, including food ingredients and biofuels

Engineering organisms to produce hydrocarbons has received considerable interest as a possible outcome of synthetic biology given the aspiration to develop new and more sustainable sources of energy (POST, 2008). A major focus is to examine the potential for using synthetic or modified organisms to generate ethanol from plant matter. There are many ways of engineering microorganisms to produce carbon-neutral (or more environmentally friendly) sources of energy. For example, bacteria could be engineered to synthesise hydrogen or ethanol by degrading cellulose, although further work is needed to overcome technical barriers. Plants and algae could also be engineered to produce biodiesel (Shreeve, 2006). The University of California recently received 600 million USD from BP and the USA Department of Energy for bioenergy research. Several biotech companies are researching industrial applications to produce biofuels using bioengineered organisms. They speculate that fuels could be on the market within five years. Similar to genetically engineered bacteria for degrading oil residues, synthetic organisms

([65]) See http://partsregistry.org/Main_Page.

([66]) Please note that the concept and definition of 'module' is somewhat arbitrary and can be subjective. As a general rule, a 'module' should be the smallest functional entity of a biological system, but it is not very clear cut in an absolute sense.

([67]) For example, while some pharmaceutical compounds are already produced bio-technologically using genetically engineered organisms, the capacity to design synthesis pathways based on pre-existing elements could greatly accelerate the development speed and the complexity achievable in this novel application.

([68]) POSTNOTE — Synthetic Biology, January 2008, No 298 report

and their metabolic pathways could be engineered to breakdown specific environmental pollutants at a much lower cost than we see today. Researchers aim to engineer bacteria which produce isoprenoids (naturally-occurring substances) that have the right characteristics to substitute for petrol. There are also plans to engineer microorganisms which produce hydrogen fuel from water, using sunlight as the energy source.

New bio-based manufacturing and chemical synthesis

The development of alternative production routes could also be used for the production of new bio-based manufacturing and chemical synthesis. For example, Du Pont and Tate & Lyle are involved in making corn produce a compound used in the textile industry (POST, 2008). Plants have also been engineered to produce a synthetic analogue of spider silk, which has qualities of extreme strength and elasticity (De Vriend, 2006). Along similar lines, synthetic mollusc shells could lead to the production of material which is light but also strong (Academy of Medical Sciences & Royal Academy of Engineering, 2007). Bacteria have been engineered to produce spider silk by a process that is non-toxic to the cells. ([69]) Spider silk has significant industrial potential, being as strong as Kevlar and ten times more elastic. Future research now aims to scale up production to an industrially useful level. Micro-organisms that produce the bulk of today's raw material for the organic chemical industry have been envisaged.

New and improved diagnostics, drugs and vaccines

The production of some drugs or vaccines may need important modifications of living organisms and therefore the approach of synthetic biology may be useful in this case.

Artemisinin is a naturally occurring, effective anti-malarial drug. It is currently obtained through extraction from a plant at high cost and with low efficiency. A 43 million USD project at the University of California at Berkeley funded by the Gates Foundation has extensively engineered new pathways in yeast which produce a precursor to the active drug. This potentially high-yield method may mean that the drug may become cheaper, of consistent quality and more widely available.

Synthetic biology models of human physiology may also give rise to a number of medical applications, such as regulatory circuits designed to trigger insulin production in diabetes (ITI Life Sciences, 2007), and bacteria or viruses programmed to identify malignant cancer cells and deliver therapeutic agents (Serrano, 2007). Viruses have also been engineered to interact with HIV-infected cells, which could prevent the development of AIDS ([70]) (De Vriend, 2006). Synthetic biology uses for new vaccines have been hypothesised for SARS and Hepatitis C (Garfinkel et al., 2007).

European scientists are combining their expertise in immunology and molecular biology to develop a new technique for producing monoclonal antibodies with the aim of creating a library of over one million cells, each expressing unique antibodies. A novel screening technique, based on cell signalling, should enable cells that specifically bind an antigen to be selected and purified.

By carefully linking certain genes and regulatory sequences, scientists are able to design and construct 'gene networks' that can sense and respond to specific conditions or signals in the cell. A multidisciplinary team is working to develop one such network that will sense errors in p53 signalling (a pathway implicated in almost all cancers) and respond either by killing the cell or by actually repairing detected mutations. The technology could have a wide range of applications from gene therapy to diagnostics.

([69]) See http://royalsociety.org/displaypagedoc.asp?id=31191, p. 6.

([70]) 'One of the avenues of synthetic biology that has wide application is the development of alternative production routes for useful compounds, and one of the most discussed of these is the construction of an artificial metabolic pathway in E. coli and yeast to produce a precursor (arteminisin) for an antimalarial drug (Martin et al. 2003, Ro et al. 2006). It has been suggested that an approach such as this could be used to produce other therapeutically useful compounds for cancer and HIV treatment (Voigt 2005). Polyketides are another important class of drugs which could potentially be produced using synthetic biology (Heinemann and Panke 2006).' Balmer A., Martin P., 2008, Synthetic Biology: Social and Ethical Challenges, Institute for Science and Society, University of Nottingham P. 10-11.

Biosensors

A team at the University of Edinburgh has designed and engineered bacteria as biological sensors for arsenic in water. A sequence of genes in the bacteria stimulates them to produce acid if arsenic is present above the safe level for human consumption. The resulting change in acidity can be read cheaply and simply using existing pH test devices. According to the Nuffield Council Background paper on Synthetic Biology (2009), a biosensor has been developed which can detect early-stage urinary catheter infections. ([71]) The biosensor consists of an engineered system suspended in a liquid that can be applied to the catheter end that is outside the body. The liquid contains a protein which binds the molecule AHL, associated with this kind of infection, thus activating a second protein that glows green and makes the liquid fluoresce. The system allows doctors to detect urinary catheter infection within 3 hours, whereas currently, doctors can often only identify urinary catheter infection once it has spread and infected the patient.

Bioremediation tools to process contaminants

Bioremediation is the use of biological systems to treat environmental contaminants. Researchers are using knowledge of natural processes to develop micro-organisms that can accumulate and/or degrade substances, such as heavy metals and pesticides. For example, a team at Berkeley has engineered a strain of *Pseudomonas* to degrade an organophosphate (commonly used as a pesticide). Synthetic biologists are endeavouring to engineer microorganisms that remediate some of the most potent environmental contaminants, such as heavy metals, pesticides and nuclear material. A strain of *Pseudomonas* bacteria has been developed to degrade an organophosphate that is commonly used as a pesticide. ([72]) Bacteria have also been designed to act as biosensors of arsenic in water. ([73])

Other research sectors in synthetic biology concern ***biosecurity*** and ***biodefence*** (military research and applications (warfare, bioterrorism). Synthetic biology could be used to produce biosensors to detect biological weapons or to create biological weapons, or single cellular organisms could be designed to emit a signal (e.g.: fluorescence) in the presence of certain environmental toxins. Examples of the dangerous synthesis of pathogen viruses already exist. For example, in 2002 scientists synthesised the polio virus, which had been previously eradicated. ([74]) In 2005, scientists synthesised the 1918 Spanish flu virus, ([75]) which prior to its extinction had caused a pandemic killing 20–50 million people. Military applications of biotechnology (including synthetic biology) could include biodefence, biowarfare, and bioweapons. The latter could be designed to target special groups of humans and/or other living beings. ([76])

The column labelled 'Difficulty of Synthesis' is the consensus of various virologists and molecular biologists who participated in our workshops and meetings. The judgment applies to someone with knowledge of and experience in virology and molecular biology and an equipped lab but not necessarily with advanced experience ('difficulty' includes obtaining the nucleic acid and making the nucleic acid infectious). ([77])

The military use of synthetic biology is often covered by secrecy clearance ([78]) (classified research). It should be noted that, according to a figure presented at the

([71]) See http://www.sciencedaily.com/releases/2007/11/071107103105.htm.

([72]) See http://pbd.lbl.gov/synthbio/aims.htm.

([73]) Aleksic J, Bizzari F, Cai Y et al. (2007) Development of a novel biosensor for the detection of arsenic in drinking water, Synthetic Biology, IET 1: 87–90.

([74]) Cello J, Paul AV, Wimmer E (2002) Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template, Science 297: 1016–8.

([75]) Tumpey TM, Basler CF, Aquilar PV (2005) Characterisation of the reconstructed 1918 Spanish influenza pandemic virus Science 310: 77–80.

([76]) See Alexander Kelle (2007). Synthetic Biology & Biosecurity. Awareness in Europe, http://www.synbiosafe.eu/uploads///pdf/Synbiosafe-Security_awareness_in-Europe_Kelle.pdf.

([77]) http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf. (page 16 of 66)

([78]) Garfinkel M., Endy D., Epstein GL., Friedman RM., 2007, Synthetic Genomics — Options for Governance.

Virus	Type: length of nucleic acid	Select Agent	Where Found	Difficulty of Synthesis
Variola	dsDNA;180kb	Yes	Locked lab	Difficult
1918 influenza	ssRNA, negative stranded; 8 segments ~10kb total	Yes	Locked lab	Moderately difficult
H2N2 influenza (extinct 1968)	ssRNA, negative stranded; 8 segments ~20kb total	No	Laboratories	Moderately difficult
Poliovirus	ssRNA, positive stranded; ~7.7kb	No	Laboratories; widely in nature, Africa and Asia	Easy
Filoviruses (Ebola, Marburg)	ssRNA, negative stranded; ~19kb	Yes	During active outbreaks	Moderately difficult to difficult
Foot-and-mouth disease virus	RNA, positive stranded; ~9kb	Yes	Certain hoofed animals	Easy
SARS	ssRNA, positive stranded; ~30kb	No	2003 strain in labs	Moderately difficult to difficult

Synthetic Biology 2007 World Conference, the USA spends 23 billion USD on biosecurity issues per year (civil part only) and synthetic biology is part of this research area. ([79]) Other countries may use synthetic biology for biosecurity or biowar. According to the United States Office of Technology Assessment (since disbanded), seventeen countries were believed to possess biological weapons in 1995: Libya, North Korea, South Korea, Iraq, Taiwan, Syria, Israel, Iran, China, Egypt, Vietnam, Laos, Cuba, Bulgaria, India, South Africa, and Russia.

1.5.2. Future uses of synthetic biology

Although the use of synthetic biology to manufacture new life forms of complex organisms does seem futuristic, some synthetic biologists have advocated the possible use of this science to synthesise new biological organisms or to extensively modify higher forms of life, including mammals.

One possibility so far envisaged to modify the genome of complex organisms, including humans, is via the use of ***artificial chromosomes***. *De novo* human artificial chromosomes have been generated in human cells following the introduction of bacterial artificial chromosomes or P1-derived artificial chromosomes containing large arrays of cloned or synthetic alphoid DNA repeats from chromosomes 5, 13/21, 14/22, 17, 18 and X. This has opened up the possibility of expressing large human transgenes in murine cells, and complement murine models of human genetic diseases. Human artificial chromosomes are therefore potentially useful vectors for gene therapy approaches where there is a need to transfer large segments of the genome. However, development of human artificial chromosomes to transfer large genomic loci into mammalian cells has been limited by difficulties in manipulating high-molecular weight DNA, as well as by the low overall frequencies of *de novo human artificial chromosomes*. ([80])

In April 2009, the creation of a ***self-replicating ribosome*** was announced. Although ribosomes were reconstituted 40 years ago, this appears to be the first time it has been done successfully and synthetically. Ribosomes provide the scaffolding for synthesising proteins, making them

([79]) USA Defense Department investment in synthetic biology for passive defence (by law [PL 103-160, all DoD work on chemical and biological defence is limited to passive defensive): From the forms submitted to Congress with the budget (called the Congressional R-form) detailing funding, inclusion of synthetic biology is mentioned under the Chemical and Biological Defence's Basic Research Program. The FY2009 budget request is available at http://www.dtic.mil/descriptivesum/Y2009/CBDP/0601384BP.pdf (page 4) The FY2010 budget request, which is the most recent, is available at http://www.dtic.mil/descriptivesum/Y2010/CBDP/0601384BP.pdf (page 3). In general, CBDP budget documents can be found at http://www.acq.osd.mil/cp/budget.html. Information on the Transformational Medical Technologies Initiative (TMTI) is available at http://www.acq.osd.mil/cp/cbdreports/tmti.pdf. Within DARPA's Defence Sciences Office (DSO), the program most involved in synthetic biology is the 'Protein Design Processes' http://www.darpa.mil/dso/thrusts/bwd/act/pdp/index.htm. DARPA's budget is available at http://www.darpa.mil/Docs/2010PBDARPAMay2009.pdf. Discussion of DSO's Biological Warfare Defence Program starts on page 103 of the pdf file.

([80]) See http://www.biomedcentral.com/1472-6750/5/21.

a main component of all living organisms'. A main goal of the Harvard team has been to fabricate a so-called 'mirror-image protein', a protein which is not susceptible to enzyme breakdown and can last longer than natural ones. This application of synthetic biology may have commercial applications to create basic molecular biology tool kits to synthesise proteins for molecular biology research or for therapeutic proteins. The proteins themselves could be engineered to undergo 'Darwinian evolution to evolve even better therapeutic proteins'. ([81])

Another use of synthetic biology converging with other new disciplines recently published in Science ([82]) was the combined use of synthetic biology and nanotechnology to produce ***genetically engineered high-power lithium ion batteries using multiple virus genes***. Scientists have adopted a strategy for attaching electrochemically active materials to conducting carbon nanotubes networks through biological molecular recognition. By manipulating two genes of the M13 virus, viruses were equipped with peptide groups with affinity for single-walled carbon nanotubes (SWNTs) on one end and peptides capable of nucleating amorphous iron phosphate (a-$FePO_4$) fused to the viral major coat protein. The produced virus has demonstrated, according to the research team involved, 10 times greater affinity for SWNTs, increasing their power performance in terms comparable to that of crystalline lithium iron phosphate. The electrodes produced with this technique have shown that this environmentally benign low temperature biological scaffold could facilitate the fabrication of electrodes from materials that have been excluded due to their extremely low electronic conductivity.

1.6. Research funding

To date, the embryonic stage of the research sector has mainly attracted investment from the public sector, but the vast range of applications of synthetic biology (if and when the science produces reliable products) is likely to attract private investment with the potential to open up new markets in the global economy. In the short term, application areas include materials, biofuels and industrial chemistry. The production of new medicines including synthetic viruses as vaccines could be promising from a scientific and socio-economic point of view. Synthetic biology is at this moment a domain which largely depends on public funding, both at EU and international level, but it is inevitable that private finance will follow developments.

The USA dominates research activities in synthetic biology in terms of numbers of scientific publications, number of scientists involved, number of post-graduate courses for students and research funding. In line with a broader international discussion, for example, President Obama's speech to the USA National Academy of Science on April 27, 2009, emphasizing the merit of knowledge for the good of humankind (and the subsequent decision to increase the USA budget allocated to this research sector). The majority of US funding comes from the National Institutes of Health (NIH), but other funding sources exist, such as from the government defence and energy agencies. The Massachusetts Institute of Technology (MIT) and some other US centres have so far dominated the field of synthetic biology, in particular with the creation of new terminology and language. Apart from the MIT registry of standard biological parts, the iGEM ('international genetically engineered machine') summer competition has been the main pillar of these activities.

According to data from the US research body Woodrow Wilson International Centre (Washington DC, USA), the US research budget in synthetic biology is in the order of 1 billion USD and 200 labs (100 universities and 60 companies) benefit from it. The US National Science Foundation has funded SynBERC (Synthetic Biology Engineering Research Centre) ([83]) , a network of USA institutions (especially universities) receiving 16 million USD over a period of five years. In addition, major investment from the private sector (Bill and Melinda Gates Foundation) has started in the USA. The Sloan Foundation supports activities on societal issues (ethics, risk perception, etc.).

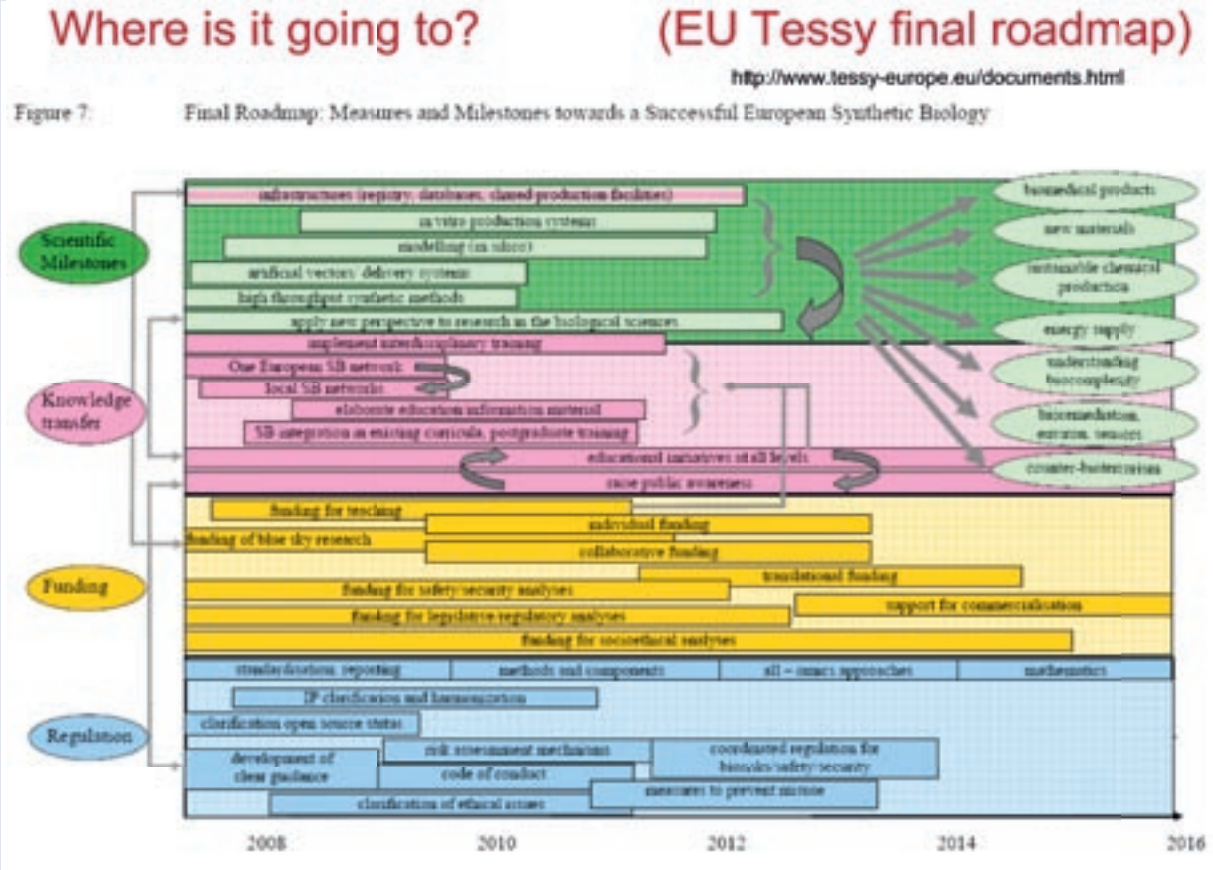
With some exceptions European national agencies and programmes are not yet very active ([84]). Europe has, so far, been relatively slow to embrace the potential opportunities from synthetic biology, despite the substantial pool of expertise which could be tapped to contribute towards an effective EU programme. Efforts have been made, however, to coordinate developments at pan-European level. In the EU Research Programme the budget is €30 million and 20 organisations benefit. EU funding for synthetic biology is mainly via the Framework Programmes for Research and Technological De-

([81]) http://www.masshightech.com/stories/2009/03/30/weekly15-George-Church-creates-building-block-for-artificial-life.html.

([82]) http://www.sciencemag.org/cgi/content/abstract/1171541?eaf.

([83]) http://www.synberc.org/institutions.html.

([84]) http://www.royalsoc.ac.uk/news.asp?id=6753.



velopment ([85]) (FP). For instance, FP6 funded NEST (New and Emerging Science and Technology), a part of which is dedicated to synthetic biology applications. In 2003, synthetic biology was identified as an emerging and innovative research area and a NEST High-Level Expert Group reported on the subject. As a result, FP6 funding was granted to 18 synthetic biology research and policy projects. Five current EU-funded projects will run to the end of 2009 and aim to stimulate and coordinate synthetic biology research in Europe. Some examples of EU-funded research projects include:

BIOMODULAR H2, specifically aims to generate building blocks to harvest solar energy for the production of useful chemicals. The project seeks to pave the way for designing a standards-based methodology using engineered bacteria to photosynthesise hydrogen, an environmentally-friendly potential replacement for dwindling fossil fuels. ([86])

The CELLCOMPUT project proposes a highly innovative approach to defining basic cellular computation systems. By combining expertise in molecular cell and chemical biology, complex systems design and mathematical modelling, CELLCOMPUT aims to demonstrate reliable fault-tolerant designs based on predictable communications between engineered yeast cells. This solution makes it much easier to build complex biological circuitry, such as memory units and programmable structures. ([87]) The resulting biological-based computers would have potential in many areas, not least in developing modular assemblies of genes and proteins that would be able to

([85]) European Commission (2006), Synbiology. An Analysis of Synthetic Biology Research in Europe and North America, http://www2.spi.pt/synbiology/document/news/D11%20-%20Final%20Report.pdf.

([86]) In BIOMODULAR H2, six European universities are collaborating to solve this problem by constructing an artificial photosynthetic bacterium containing suitably engineered chemical pathways. At the same time, they will lay the foundation for an engineering approach that will provide the next generation of synthetic biology engineers with a toolbox to design complex circuits of high potential, for even more industrial applications.

([87]) While the focus is on well-documented yeast cells and their cell-to-cell communication pathways, the long-term aim would be to build programmable biodevices using other cells as well. These engineered systems would have standardised functionalities and be substantially different from naturally-existing systems.

detect and respond to changes in the body and so combat diseases at a very early stage. Similar devices could also be used for tissue repair and cell regeneration.

The possibility of artificial systems controlling living cells and influencing the genetic information processes might seem like science fiction to many, but the ORTHOSOME project is doing just that. A multidisciplinary consortium is building an artificial genetic system which will be able to be used in genetic engineering without the danger of contaminating natural systems. Such a system will represent a major breakthrough for synthetic biology and will give the EU's pharmaceutical sector the leading edge against its competitors.

The COBIOS project aims to develop synthetic biology devices for therapy in medicine, in particular to create methods to treat diabetes through the innovative use of novel biological delivery systems. Among its objectives, COBIOS intends to deliver a systematic approach to developing well characterised, engineered biological devices in higher eukaryotes that will constitute reusable 'building blocks' for future engineered systems design. The project will also provide computer-aided design tools for the building and simulation of synthetic gene circuits, tools that will be available to the scientific community.

EU-funded research projects ([88]):

BIOMODULAR H2: Energy project promises a new biotechnology
BIONANO-SWITCH: Matching up living organisms with computers
CELLCOMPUT: Building computers in the body
COBIOS: Solution for complex diseases
EMERGENCE: Coordination puts synthetic biology on firm footing
EUROBIOSYN: A sweeter way to make saccharine
FuSyMEM: Functional synthetic membranes to mimic nature's sense of smell
HIBLIB: Monoclonal antibody production made quick and easy
NANOMOT: Nature's motors tuned for delivery on demand
NEONUCLEI: Synthetic analogues of cell nuclei
NETSENSOR: Genes join up to detect and defend
ORTHOSOME: When artificial nucleic acids control microbial genetics
PROBACTYS: Programming bacterial catalysts *à la carte*
SYBHEL: Synthetic biology for human health – ethical and legal issues
SYNBIOCOMM: Pushing the boundaries further
SYNBIOLOGY: A European perspective on synthetic biology
SYNBIOSAFE: Safety and ethics of synthetic life
SYNTHCELLS: The bare necessities of life
SYNTH-ETHICS: Ethical and regulatory challenges raised by synthetic biology
TESSY: Foundations for a European synthetic biology.

([88]) ftp://ftp.cordis.europa.eu/pub/nest/docs/5-nest-synthetic-080507.pdf.

2. Legal, Governance and Policy Aspects

Specific legislation on synthetic biology has not been introduced in European Union Member States. Most of the existing regulations result from transposing EU legislation into national legal systems. This is supplemented by some global provisions, issued by the World Trade Organisation (WTO), and an international framework on ethics and human rights. The latter is only to a limited extent legally binding. These rules are described briefly below according to their legal force, focusing on their importance for synthetic biology, with special reference to definitions, procedures and the content of the provisions. The legislative framework applying to synthetic biology is strictly dependent on the applications of this scientific sector and include legal and policy provisions at different levels:

(A) **European Union** (EU) legislation on GMOs, biomedicine, bio-safety, chemicals, data protection and patents;

(B) **Global provisions** issued by the World Trade Organisation (WTO) and bio-safety standards issued by the World Health Organisation (WHO);

(C) **International framework on ethics and human rights**.

At the moment virtually all approaches to synthetic biology involve the use of genetic modification techniques. Therefore within the EU they are regulated through the Directives and Regulations for genetic modification introduced initially in 1990 and substantially modified during the ensuing years.

Legislation adopted by the European Union is binding for the Member States, but there are differences in the nature of obligations. Legislation related to the placing of products on the EU market, e.g. medical devices, medicinal products and cosmetics, is harmonised at Member State level, whereas legislation on Good Clinical Practice may be supplemented by national rules, as Community law establishes minimum provisions. Data protection and patent provisions are binding for the EU Member States.

WTO agreements ratified by a great number of nations form the legal ground rules for international commerce. They are binding for the States that have signed and ratified them.

The international framework on ethics and human rights is legally binding only to a limited extent. The Council of Europe Convention on Bioethics (1997), based on the Convention for the Protection of Human Rights and Fundamental Freedom (4.11.1950), is binding for the States that have signed and ratified it, but not all EU countries have done so. ([89]) However, European projects funded under the EU research framework programmes also have to comply with the principles enshrined in that Council of Europe Convention. The UNESCO Declarations and the EU Charter of Fundamental Rights are not legally binding, but they have moral authority. All three types of rules may be supplemented by national regulations.

2.1. EU legislation

There is a wide range of EU legislation related to issues relevant for synthetic biology, either existing or in preparation. These issues primarily concern risk assessment.

European Union legislation of specific importance for ***risk assessment*** and ***risk management*** includes Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms (replacing Council Directive 90/220/EC ([90])) Regulation (EC) No 1946/2003 on transboundary movements of genetically modified organisms that implemented the provisions of the Cartagena Protocol on Biosafety within the European Union; ([91]) and Council Directive 98/81/EC amending Directive 90/219/EEC ([92]) on the contained use of genetically modified micro-organisms. ([93])

Most of the work in synthetic biology falls within the remit of Directive 98/81 which deals with the contained use of genetically modified micro-organisms. It regulates ***the contained use of genetically modified micro-organisms*** (GMM) and therefore has environmental

([89]) As of November 2006, the Convention has been signed by 21 EU Member States and ratified by 13. (http://www.coe.int/t/e/legal_affairs/legal_cooeration/bioethics/texts_and_documents/1Treaties_COE.asp#TopOfPage.

([90]) http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_106/l_10620010417en00010038.pdf.

([91]) http://europa.eu/eur-lex/pri/en/oj/dat/2003/l_287/l_28720031105en00010010.pdf.

([92]) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0219:EN:HTML.

([93]) http://europa.eu/eur-lex/pri/en/oj/dat/1998/l_330/l_33019981205en00130031.pdf.

and human health protection purposes as stated under Article 1 of the Directive. ([94])

A microorganism is defined in Article 2 of the directive to be "any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, animal and plant cells in culture". This includes cultures of cells derived from human tissue. The Article also defines a genetically modified microorganism as "a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural Recombination". Hence any new organism produced through synthetic biology will be regulated through this directive.

The Directive provides the regulatory framework for assuring the safety of organisms used in containment (whether physical or biological) ([95]). At the very least, any organization working with genetically modified organisms has to register with a Competent Authority within a Member State (Article 7). If the organism (synthetic or otherwise) poses no conceivable risk to human health or the environment, no further action is necessary. If, however, there is a risk (even a low risk) of damage to human health or the environment the authorities must be informed of each individual 'experiment'. If the risk is moderate or high, prior assent must be obtained from the Competent Authorities.

Directive 98/81/EC also defines the 'user' as "any natural or legal person responsible for the contained use of GMMs" and 'notification' as "the presentation of the requisite information to the competent authorities of a Member State." A difference is made between first and subsequent uses and as regards to risk classification category.

Moving from the laboratory to the commercial world, whether for the introduction into the environment of an organism or for marketing brings Directive 2001/18/EC ([96]) into play. It defines a 'genetically modified organism' (GMO) as an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Within the terms of this definition, a genetic modification occurs at least through the use of one of the techniques listed in Annex IA of the Directive. ([97]) Risk assessment, marketing and labelling requirements are spelled out in Regulations (EC) 1829/2003 and 1830/2003.

The definitions in the Directives differ significantly. Directive 2001/18/EC regulates the ***deliberate release into the environment of genetically modified organisms*** and therefore has environmental and human health protection purposes as stated under Article 1 of the Directive. In accordance with the precautionary principle, the objective of this Directive is to approximate the laws, regulations and administrative provisions of the Member States and to protect human health and the environment when: 1) carrying out the deliberate release into the environment of genetically modified organisms for any other purposes than placing on the market within the Community, 2) placing on the market genetically modified organisms as or in products within the Community. The Directive defines a GMO as an 'organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'. The techniques covered in the Directive include:

> (1) recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;
>
> (2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;

([94]) This Directive lays down common measures for the contained use of genetically modified micro-organisms with a view to protecting human health and the environment.

([95]) "contained use" shall mean any activity in which micro-organisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with the general population and the environment (Article 2)

([96]) Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

([97]) Regulations (EC) No 1829/2003 and 1830/2003 refer to the definition of GMO laid down in Directive 2001/18/EC.

(3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally. (2001/18/EC, Annex 1A).

Deliberate release under Article 2.3 'means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment.'

The standard authorisation procedure for deliberate release of GMOs for any other purpose than for placing on the market is laid down in Article 6 of the Directive, whilst placing on the market of GMOs as or in products is regulated by specific provisions on the notification procedure in Article 13. Both procedures lay down a number of requirements that need to be met in order for the competent authorities to take a decision on authorisation of GMO release. Furthermore, Article 9 of Directive 2001/18/EC on 'Consultation of and information to the public' provides for active involvement of the public and groups.

In addition, the Commission has recently prepared a replacement Draft Directive on the contained use of genetically modified micro organisms (GMM) to amend Directive 98/81/EC. The above Directive aims to establish common measures to evaluate and reduce the potential risks arising in the course of all operations involving the contained use of GMMs and to set appropriate conditions of use. The Directive also seeks to lay down requirements for risk assessment and advocates that contained uses of GMMs should be classified in relation to the risks they present to human health and the environment. It states that where there is any uncertainty, appropriate containment and other protective measures for higher classification should be applied until less stringent measures are justified by appropriate data. Appropriate containment measures should be applied at the various stages of an operation to control emissions and the disposal of material from contained uses of GMMs, and to prevent accidents.

The above EU regulatory framework addresses the biosafety of synthetic biology but, as the Nuffield Council underlines in its 2009 background paper, under the current regulatory framework, risk assessments of genetically modified organisms (GMOs) compare the altered organism with the natural organism on which it is based, considering the individual traits introduced. Synthetic biology will produce organisms with multiple traits from potentially several different donor organisms. The use of an artificially expanded genetic information system or the insertion of multiple genetic traits or the synthesis of new synthetic biology products, while not excluded *per se* in the EU biosafety framework may not provide sufficient reliability to the risk assessment and analysis framework.

The application areas of synthetic biology are already regulated at EU level and synthetic biology products will have to comply with the existing regulations. In addition to the requirements identified above, there are further requirements depending on the use to which the products of synthetic biology might be put. A list of possible uses of synthetic biology is provided in Chapter 1.5 of this Opinion, hence the regulatory framework that would apply to the various synthetic biology applications would include:

- ***new medicinal products*** (Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2003/94/EC and Directive 2003/63/EC);
- ***medical devices*** (Directive 93/42/EEC and 90/385/EEC);
- ***gene therapy, cell therapy and tissue engineering*** (Regulation (EC) No 1394/2007 amending Directive 2001/83/EC and Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2004/23/EC and Directive 2002/98/EC);
- ***clinical trials*** (EC 2001/20 amended in 2003 ([98]) and 2005 ([99]));
- ***cosmetic products*** (Directive 1976/768/EC);
- ***data protection*** (Directive on the processing of personal data and the protection of privacy in the electronic communications sector ([100]));
- ***chemicals*** (REACH rules ([101]));

([98]) Directive 2003/63/EC.

([99]) http://clusters.wallonie.be/servlet/Repository/Directive_2005/28/EC_EN__comp.PDF? IDR=5482.

([100]) Directive 2002/58/EC, Directive 95/46/EC.

([101]) The REACH Regulation was formally adopted on 18 December 2006 by the Council of Environment Ministers fol-

- ***biological risks*** (Council Directive 82/894/EEC and Council Directive 2000/29/EC of 8 May 2000 ([102]));

- ***safety and health for workers exposed to biological agents at work*** (Directive 2000/54/EC).

The above regulations are described and discussed in the EGE Opinion on Nanomedicine ([103]) (biomedicine), the EGE Opinions on animal cloning for food supply ([104]) (food safety, IPR) and modern developments in agriculture technologies ([105]) (biosafety, IPR). There are however, three regulatory frameworks which will apply to synthetic biology products that have not been fully addressed in previous Opinions: 1) patenting, 2) open access, 3) security policy and Chemical, Biological, Radiological or Nuclear (CBRN) substances.

The Patent Directive, ([106]) deals specifically with the protection of biotechnological inventions and is designed to ensure effective legally harmonised protection of patents. In doing so it aims to encourage innovation and promote investment in the field of biotechnology and establish legal certainty. The inventor secures exclusive rights to control commercial exploitation of his invention for 20 years and, in return, he must disclose a detailed description of his invention, making the new knowledge publicly available. This disclosure enables others (researchers etc.) to build on the knowledge gained. The patent may be a product claim, a process claim or both. ([107]) The standard criteria for patentability include novelty, inventive steps and industrial application. According to Article 3, 'biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature'. The Directive contains provisions laying down restrictions based on ethical concerns, i.e. *ordre public* or morality (Article 6 ([108])). The applicability of the morality clause to patents for some synthetic biology products may be controversial. The Directive above also states (Article 7) that the EGE 'evaluates all ethical aspects of biotechnology'. Article 7 is the only Article of the Directive that has not been implemented in the rules of European Patent Office or any Member State's Patent Office.

Open Access (OA) is broadly defined as 'free access to knowledge at no charge to the user.' ([109]) Under open access policies, authors published in research publications grant free internet access to their scientific contributions, as well as the possibility to use them, subject to proper attribution of authorship. ([110]) This means

lowing the vote in second reading of the European Parliament on 13 December 2006. REACH will enter into force on 1 June 2007. The text of the Regulation was published on 30 December 2006 in Official Journal of the European Union L 396 (Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. See: http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm). See also: Council Directive 96/82/EC of 9 December 1996 on the control of major accident hazards involving dangerous substances (Seveso II) aims at mitigating the consequences of accidents. It focuses on safety, the formulation of emergency plans, and information exchange in case of incident. Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work lays down the requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents. The Standing Committee of Experts on Precursors addresses the risks posed by chemical precursors. The standing committee has been meeting since the beginning of 2008.

([102]) This directive creates a compulsory notification system: when an outbreak occurs, Member States have to notify the Commission. Member States have also to notify the Commission when there is an interception at the customs on imported/exported goods, http://europa.eu/scadplus/leg/en/lvb/f85001.htm.

([103]) http://ec.europa.eu/european_group_ethics/activities/docs/opinion_21_nano_en.pdf.

([104]) http://ec.europa.eu/european_group_ethics/activities/docs/opinion23_en.pdf.

([105]) http://ec.europa.eu/european_group_ethics/docs/opinion24_en.pdf.

([106]) Directive 98/44/EC.

([107]) See also EGE Opinion No 16 on 'Ethical aspects of patenting inventions involving human stem cells' (http://ec.europa.eu/european_group_ethics/docs/avis16_en.pdf).

([108]) According to the Directive on biological inventions, 'inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation'. Directive 98/44/EC, Article 6(1).

([109]) EU handbook on open access — http://ec.europa.eu/research/science-society//document_library/pdf_06/open-access-handbook_en.pdf.

([110]) http://europa.eu/rapid/pressReleasesAction.do?reference

free, immediate, permanent and full access to texts, online for any user of internet Scientific and Digital Scholarship material, mainly research articles published in scientific journals . Although there is no specific legislation applicable, there are at least three main international declarations on the subject: the first one, BOAI (Budapest Open Access Initiative) dated February 2002, followed by the 'Bethesda Statement on Open Access Publishing' (June 2003) and the 'Berlin Declaration on Open Access knowledge in the Sciences and Humanities' (October 2003).

In an open access publication, 'the author(s) and copyright holders(s) grant(s) to all users a free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, transmit and display the work publicly (...)' (Bethesda Declaration). This is viewed, by some, as a potential way of improving access to and dissemination of publicly funded scientific information, in particular peer-reviewed scientific publications. In fact this approach, although not new to synthetic biology, has been discussed over the last few years regarding the sharing of scientific information. It is now emphasised where synthetic biology models are mostly used in modelling synthetic biology structures. Including in concept of OA and applicable to software, Open Source software is software that includes source code and is usually available at no charge, but carries a general licence that may identify that which may (or may not) be done with the software ([111]).

In 2008, the European Commission launched a pilot project that was planned for in Commission Communication (COM(56)2007) on 'scientific information in the digital age: access, dissemination and preservation' ([112]) in reaction to which European research ministers adopted Council Conclusions inviting the Commission to experiment with open access in FP7. ([113]) The pilot project is to give unrestricted online access to EU-funded research results (covering around 20 % of the €50 billion FP7 program budget) in areas such as health, energy, environment, social sciences and information and communication technologies. The legal basis for the pilot project is the so-called special clause 39 on Open Access ([114]) adopted in August 2008 that requires a) deposit of an electronic copy (published version or final manuscript) in an institutional or subject-based repository at moment of publication and b) best efforts to ensure that this electronic copy becomes available 'open access' (freely and electronically available to anyone). ([115])

2.1.1. EU biosecurity policy frame

Either through an Open Access system or illegal action (such as biopiracy), access to DNA sequences and synthetic biology models may raise ***biosecurity concerns***. Concerns raised regarding safety have triggered important legislation in the EU ([116]) as well as in the Council of Europe with the Convention on Cybercrime (Budapest, 23.11.2001) as tools to 'deter action directed against the confidentiality, integrity and availability of computer systems, networks and computer data as well as the misuse of such systems, networks and data' at international level. Additionally, open access may apply to synthetic biology project results where information related to pathogenic and/or dangerous synthetic biology products are published.

Over the past ten to fifteen years, the threat of a terrorist group acquiring ***Chemical, Biological, Radiological or Nuclear (CBRN)*** materials has led governments and international organisations to adopt far-reaching regulations ([117]) and programmes to defend populations against the associated risks. Tackling terrorist access to CBRN material is currently considered a key priority for the European Union. ([118]) This is acknowledged by the

=MEMO/08/548&format=HTML&aged=0&language=EN&guiLanguage=en. See also the 2003 Berlin Declaration on Open Access to Knowledge in the Sciences and Humanities, http://oa.mpg.de/openaccess-berlin/berlindeclaration.html.

([111]) See http://creativecommons.org/licenses/by-nc-sa/2.0/uk/ and http://www.bios.net/daisy/bios/home.html.

([112]) http://ec.europa.eu/research/science-society/document_library/pdf_06/communication-022007_en.pdf.

([113]) http://ec.europa.eu/research/science-society/index.cfm?fuseaction=public.topic&id=1680.

([114]) http://ec.europa.eu/research/press/2008/pdf/annex_1_new_clauses.pdf.

([115]) http://ec.europa.eu/research/science-society/document_library/pdf_06/ec-open-access-pilot-ppt_en.pdf.

([116]) Directive 2006/24/CE of the European Parliament and of the Council of 15 March 2006 on the retention of data generated or processed in connection with the provision of publicly available electronic communications services or of public communications networks and amending Directive 2002/58/EC

([117]) Such as UN Security Council Resolution 1540.

([118]) The Council Conclusions of 6 December 2007 'addressing Chemical, biological, radiological and nuclear risks and on bio-preparedness' provide the most recent EU-level overview of the ongoing activities.

European Union Counter-Terrorism Strategy adopted by the Council on 1 December 2005, and by the 'EU Strategy against proliferation of weapons of mass destruction and their means of delivery (WMD)' adopted by the European Council on 12 December 2003. ([119]) In addition, the Council adopted specific Conclusions in 2007 that called for further EU level work on CBRN security. ([120])

The Member States are responsible for protecting their citizens from CBRN threats by a host of different measures, and with the involvement of a wide range of authorities. The Ghent European Council of 2001 instigated the first steps in countering the CBRN threat at EU level, ([121]) followed by the adoption of the 'Programme to improve cooperation in the European Union for preventing and limiting the consequences of chemical, biological, radiological or nuclear terrorist threats' in December 2002. ([122]) The Programme was superseded by the Council and Commission's EU Solidarity Programme of 3 December 2004 on the consequences of terrorist threats and attacks, that extended, revised and replaced the 2002 CBRN Programme following the attacks in Madrid on 11 March 2004. ([123]) Aspects of the Solidarity Programme were included in the overall Strategy and Action Plan on Combating Terrorism established in 2005 after the London attacks. ([124]) Whilst the responsibility for responding to CBRN incidents rests with the Member States, robust crisis management procedures and tools to support the Member States in the event of a crisis with cross-border implications have been developed at EU level. In order to prepare the current CBRN policy, in February 2008 the Commission established a CBRN Task Force. The final report of the Task Force was published in January 2009 and contained 264 separate recommendations. On June 24 2009, ([125]) the Commission adopted an action plan defining the new EU CBRN policy. ([126]) The Action Plan sets out three main areas of CBRN security work: 1) Prevention — ensuring that unauthorised access to CBRN materials of concern is as difficult as possible; 2) Detection — having the capability to detect CBRN materials in order to prevent or respond to CBRN incidents; 3) Preparedness and response — being able to efficiently respond to incidents involving CBRN materials and recover from them as quickly as possible.

The most important part of current EU external relations policy related to the CBRN threat is the EU Strategy against Proliferation of Weapons of Mass Destruction — also known as the EU WMD strategy, adopted in December 2003. This Strategy was recently updated and reviewed, resulting in the adoption by the Council of 'New lines for action by the European Union in combating the proliferation of weapons of mass destruction and their delivery systems' in December 2008. ([127]) Issues related to the threat of CBRN materials are also discussed in a significant number of international fora ([128]), and are dealt with by international organisations such as the International Atomic Energy Agency (IAEA), the Organisation for the Prevention of Chemical Weapons (OPCW), the BTWC Conference, Interpol and the Global Health Security Initiative (GHSI). In a more general sense, counter-terrorism efforts form part of many cooperation agreements in place or being negotiated between the EU and third countries. The Council decided in 2002 that a standard counter-terrorism clause should be inserted in all agreements with third countries. Additionally, since November 2003, WMD clauses have been inserted in all new or renewed mixed agreements now covering almost 100 countries. Work on CBRN issues with strategic partners, such as the United States, can be further developed based on the current policy package. From the public health perspective, the Commission will present a Communication on health security in 2009, outlining the internal and external aspects of health security.

([119]) 15708/03 and SN 400/03, no 68. See also *infra*, paragraph 7.

([120]) 16589/07, of 17 December 2007.

([121]) SN 4292/01 REV 2.

([122]) 14627/02.

([123]) 15480/04.

([124]) 14469/4/05, paras 20 and 31.

([125]) COM(2009) 273 final; SEC(2009) 874; SEC(2009) 790; SEC(2009) 791.

([126]) The EU CBRN Action Plan is not a legal instrument. Therefore, immediate legal and budgetary consequences for the EU could only derive from possible future legal instruments implementing the Action Plan, which would be subject to separate prior impact assessment — including an assessment of their impact on economic sectors and research environments and systematic and rigorous monitoring to ensure compatibility with the Charter of Fundamental Rights of the European Union.

([127]) 17172/08, 17 December 2008.

([128]) Such as the Global Initiative to Counter Nuclear Terrorism (GICNT), and dual-use export control regimes such as the Nuclear Suppliers Group, the Wassenaar Arrangement, the Australia Group and the Missile Technology Control Regime.

2.2. Global provisions

2.2.1. WHO biosafety standards

The World Health Organisation (WHO) published the first edition of the *Laboratory bio-safety manual* in 1983. The manual encouraged countries to accept and implement basic concepts in biological safety and to develop national codes of practice for the safe handling of pathogenic microorganisms in laboratories within their geographical borders. Since 1983, many countries have used the expert guidance provided in the manual to develop such codes of practice. Subsequent editions of the manual were published in 1993 and in 2005. The last edition of the WHO bio-safety manual ([129]) stresses the importance of personal responsibility and addresses risk assessment, safe use of recombinant DNA technology and transport of infectious materials. It also introduces biosecurity concepts — the protection of microbiological assets from theft, loss or diversion, which could lead to the inappropriate use of these agents to harm public health.

2.2.2. The Cartagena Protocol

On 29 January 2000, the Conference of the Parties to the Convention on Biological Diversity adopted a supplementary agreement to the Convention known as the Cartagena Protocol on Biosafety. ([130]) The Protocol seeks to protect biological diversity from the potential risks posed by living modified organisms resulting from modern biotechnology. It establishes an advance informed agreement (AIA) procedure for ensuring that countries are provided with the information necessary to make informed decisions before agreeing to the import of such organisms into their territory. The Protocol contains a reference to the precautionary approach and reaffirms the precautionary language in Principle 15 of the Rio Declaration on Environment and Development. The Protocol also establishes a Biosafety Clearing House to facilitate the exchange of information on living modified organisms and to assist countries in the implementation of the Protocol. Countries shipping GMOs for intentional introduction into the environment will have to give prior notification to the importing country that they are party to the Protocol under the Advance Informed Agreement (AIA) procedure if it is not intended for food, feed or processing and is the first such movement of that GMO between the countries. The notification must provide the information needed to enable the importing country to make informed decisions. The Protocol contains documentation requirements for shipments of GMOs and establishes a Biosafety Clearing House (BCH) to facilitate the exchange of information on GMOs and to assist countries in implementing the Protocol.

The Protocol is designed to protect biological diversity and human health from the potential risks arising from genetically modified organisms (GMOs) by providing a clear legal framework for transboundary movement. The Advanced Informed Agreement (AIA) procedure established by the Protocol will ensure that countries can make informed decisions on whether to import GMOs intended for introduction into the environment. To date, 153 instruments of ratification or accession have been deposited with the UN Secretary-General from the Parties to the Convention on Biological Diversity. The EU and all EU Member States have ratified the protocol. ([131]) (Regulation (EC) No 1946/2003 on transboundary movements of genetically modified organisms is the regulatory instrument that implements the provisions of the Cartagena Protocol on Biosafety within the European Union ([132])). The risk assessment requirements of the Protocol are similar to those identified in the EU legislation identified earlier.

2.2.3. World Trade Organisation (WTO) agreements and Trade-Related Aspects of Intellectual Property Rights (TRIPS)

The World Trade Organisation (WTO) has developed a multilateral system of trade to lower customs and trade barriers, and abolish discrimination in international trade. WTO agreements are the legal ground rules for international commerce which were negotiated and signed by a large majority of the world's trading nations and ratified by their parliaments. The General Agreement on Tariffs and Trade (GATT) and the Sanitary and Phytosanitary (SPS) agreement include measures that may be relevant for trading synthetic biology products.

Most nations of the world are party to the World Trade Organisation. As part of their agreement to join the organisation, they have agreed and largely ratified all the component treaties of the General Agreements on Tar-

([129]) http://www.who.int/csr/resources/publications/biosafety/Biosafety7.pdf.

([130]) http://www.cbd.int/biosafety/background.shtml.

([131]) http://www.cbd.int/biosafety/signinglist.shtml.

([132]) http://europa.eu/eur-lex/pri/en/oj/dat/2003/l_287/l_28720031105en00010010.pdf.

iffs and Trade (GATT). The last successful round of trade negotiations culminated in all ratifying Member States endorsing all agreements in the WTO package under the 'single undertaking'. No opting out of individual treaties (over 17 in total) was allowed as they were to be ratified all at once. One of these is the TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights). TRIPS provides for each country to institute a minimum set of laws protecting intellectual property, so that where inventors so wish, they may protect that which they have created or invented in any jurisdiction. Countries may not discriminate between domestic and international 'creations'. ([133])

A business has a competitive advantage if it develops, maintains and exploits its assets appropriately. These must include its intellectual property where it has an advantage over its competitors if it has information which it has not shared (secrecy) or where it has asserted rights that permit it to assure that others cannot use or copy without permission. A relatively new concept is that the portfolio of intellectual property constitutes a currency that is negotiable for use in commercial or research interactions with others. Patents may then be used as such, without the intention to use them in advancing technology.

The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement also contains a provision (Article 25(2)) allowing Member States to exclude from patentability inventions that are contrary to *ordre public* or morality or in order to protect human, plant or animal life, or in order to avoid serious detriment to the environment. ([134])

([133]) TRIPS Article 27.1 provides that '…patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.'.

([134]) In the Patent Directive (98/44/EC) there are two major exclusions from patentability: 'ordre public' and 'morality'. Where the commercial exploitation or publication of the invention would be contrary to morality or affect *ordre public*, patentability is excluded (not immoral experimentation leading to the invention). The TRIPS agreement permits exclusion on these grounds. There have been few exclusions on the grounds of morality, although Article 6(2) of the Patent Directive provides examples (stressing that these are non-exhaustive) of possible 'immoral' inventions which shall be unpatentable: (a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; (c) uses of human embryos for industrial or commercial purposes; and (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

In most jurisdiction, patents may only be granted if they meet specific criteria. They must be new, involve an inventive step and be susceptible of industrial application and can be for processes, products or both.

1. 'An invention shall be considered to be new if it does not form part of the state of the art' ([135]), which includes that which has been communicated to the 'public' by oral or written means.

2. 'An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.' ([136])

3. 'An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.' ([137])

2.2.4. Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction ([138])

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction — more commonly known as the Biological and Toxin Weapons Convention (BTWC) — was simultaneously opened for signature in Moscow, Washington and London on 10 April 1972 and entered into force on 26 March 1975. The Convention bans the development, production, stockpiling, acquisition and retention of microbial or other biological agents or toxins, in types and in quantities that have no justification for prophylactic, protective or other peaceful purposes. It also bans weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict. The actual use of biological weapons is prohibited by the 1925 Geneva Protocol and Article VIII of the BTWC recognises that nothing contained in the Convention shall be construed as a derogation from the obligations contained in the Geneva Protocol. As of November 2001, 162 states had signed the BTWC and 144 of these had ratified it.

([135]) European Patent Convention, Article 54.

([136]) European Patent Convention, Article 56.

([137]) European Patent Convention Article 57.

([138]) http://www.opbw.org/.

Article I defines the scope of the BTWC's prohibition (the general purpose criterion). This includes all microbial and other biological agents or toxins and their means of delivery. Subsequent Review Conferences have reaffirmed that the general purpose criterion encompasses all future scientific and technological developments relevant to the Convention. The objects themselves (biological agents or toxins) are not prohibited, only their purpose. Permitted purposes are defined as prophylactic, protective and other peaceful purposes. The objects may not be retained in quantities that have no justification or which are inconsistent with the permitted purposes. Article IV requires States Parties to take any necessary national measures (e.g. passing national laws) to prohibit and prevent the misuse of biological agents, toxins, weapons, equipment and means of delivery within their territories. Only a small number of signatory states have implemented this provision. 155 countries have signed the BTWC, including all 27 EU Member States. However, the BWC includes no verification and enforcement mechanisms for preventing states from applying synthetic genomics in this way, and many would argue that effective measures for that purpose are not feasible. The BTWC does not cover research for defensive measures and dual use considerations.

2.3. *International Framework on ethics and human rights*

The Council of Europe Convention on Human Rights and Biomedicine (the Oviedo Convention) is legally binding for those States that have signed and ratified it ([139]). Other relevant documents (such as the UNESCO Declaration and the EU Charter of Fundamental Rights) are not legally binding, but have moral authority.

(a) In 1997 the *Council of Europe* adopted the Oviedo Convention — Convention on Human Rights and Biomedicine. Its main purpose is to protect individuals against exploitation arising from treatment or research. The articles on the purpose and object of the Convention state that the Parties 'shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine'. The Convention also concerns equitable access to health care, professional standards, protection of genetic heritage and scientific research. The Convention is supplemented by a number of protocols. ([140])

(b) The *Universal Declaration on the Human Genome and Human Rights*, adopted by the UNESCO General Conference in 1997 and subsequently endorsed by the United Nations General Assembly in 1998, deals with the human genome and human rights. Since the Declaration was drafted in 1997 it does not refer explicitly to synthetic biology, but modifications concerning DNA may fall within its scope. It states, among other things, that the 'human genome underlies the fundamental unity of all members of the human family as well as the recognition of their inherent dignity and diversity'. The Declaration asserts that 'dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity'. Moreover, the Declaration prohibits financial gain from the human genome in its natural state, and affirms that the benefits of advances in the technologies should be made available to all, and that freedom of research is 'necessary for the progress of knowledge'.

The UNESCO *Universal Declaration on Bioethics and Human Rights* (adopted on 19 October 2005) also contains specific provisions on ethical issues related to medicine, life sciences and associated technologies and advocates several ethical principles, including human dignity, consent, autonomy and responsibility, privacy, equity and justice, solidarity and benefit sharing. ([141]) The Declaration is not legally binding, but is a reference point for the protection of human rights and ethics.

(c) The most recent version of the World Medical Association (WMA) *Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects* ([142]), was adopted by the 18th WMA General Assembly in Seoul in October 2008. The WMA Declarations of Geneva, Helsinki and Tokyo clarify the duties and responsibilities of the medical profession to preserve and safeguard the health

([139]) Whilst the EU is party to the convention, many member states neither signed nor ratified and are therefore not Party to the Convention. These include Austria, Belgium, Germany, Malta, Ireland, and the United Kingdom. Finland, France, Italy, Latvia, Luxembourg and the Netherlands have signed but not ratified the Convention and others have indicated reservations and declarations. See http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf for detailed information.

([140]) http://www.coe.int/t/e/legal_affairs/legal_cooperation/bioethics/texts_and_documents/1Treaties_COE.asp#TopOfPage.

([141]) http://portal.unesco.org/shs/en/file_download.php/46133e1f4691e4c6e57566763d474a4dBioethicsDeclaration_EN.pdf.

([142]) http://www.wma.net/e/policy/b3.htm.

of the patient and to be dedicated to the service of humanity. The Declaration advocates ethical principles for medical care. In its constitutive articles, the Declaration states that it is the duty of the physician to promote and safeguard the health of patients, including those involved in medical research. Concerning potential military uses of medicine, the WMA adopted in October 1998 (text amended by the WMA General Assembly, Seoul, Korea, October 2008) a *Statement on Nuclear Weapons*. ([143]) The WMA condemned the development, testing, production, stockpiling, transfer, deployment, threat and use of nuclear weapons; asked all governments to refrain from the development, testing, production, stockpiling, transfer, deployment, threat and use of nuclear weapons and to work in good faith towards the elimination of nuclear weapons; and all National Medical Associations to join the WMA in supporting the Declaration and to urge their respective governments to work towards the elimination of nuclear weapons. All these principles, although they address nuclear weapons, may also apply to other weapons, such as biological weapons.

(d) The *European Charter of Fundamental Rights* ([144]) emphasises that the Union is founded on the indivisible and universal values of human dignity, freedom, equality and solidarity and on the principles of democracy and the rule of law. It contributes to the preservation of these common values while respecting the diversity of the cultures and traditions of the peoples of Europe, as well as the national identities of the Member States and the organisation of their public authorities. The Charter formulates a common set of basic shared values at EU level. ([145]) Respect for human dignity, a ban on human reproductive cloning, respect for people's autonomy, non-commercialisation of biological components derived from the human body, prohibition of eugenic practices, protection of people's privacy and the freedom of science are examples of values enshrined in the Charter, which was adopted at the Summit of Nice in 2001 and is an integral part of the Lisbon Treaty.

([143]) http://www.wma.net/e/policy/n7.htm.

([144]) Approved on 28 September 2000 and proclaimed by the European Parliament, the Council and the Commission on 7 December 2000.

([145]) For example Article 1 (respect for human dignity), Article 3 (ban on human reproductive cloning, respect for people's autonomy, non-commercialisation of biological components derived from the human body, prohibition of eugenic practices), Article 8 (data protection issues), Article 13 (freedom of science).

2.4. Governance

Governance is an overarching concept including legal, political and ethical considerations. Since synthetic biology may result in major changes of traditional biology, governance needs to be reflected on all these levels, finally entering the legal sphere.

Governance of synthetic biology is being debated at EU and international level. Key issues relating to the governance of synthetic biology include, inter alia: 1) definition of the actors to regulate synthetic biology as well as the governing principles to be promoted; 2) definition of the applications area of the identified governance model (national, regional or international governance); 3) definition of boundaries between synthetic biology and other technological fields that often interact in synthetic biology trials (nanotechnology; ICT; biotechnology; chemistry etc.); 4) definition of synthetic biology governance reflecting the complex heterogeneity of this technological sector; 5) definition of a governance of synthetic biology in absence of specific target legislation (or regulation) on this technology sector; 6) definition of interrelation between different regulatory systems (from protection of worker to environmental protection, from medical and pharmaceutical products to bio-security) that may conflict with one another; 7) definition of a governance model where participative democratic processes are implemented etc. This indicative list shows that a governance model in synthetic biology, like other emerging technologies, is difficult to define.

The Group is aware that governance models should address several dimensions of synthetic biology policy and activities, such as: political level (monitoring research and safety issues); ethical level: (monitoring ethical criteria be properly implemented in each synthetic biology research sector); legal level (EU legislation and international legislation or regulation including clarification of grey areas); professional level (self-regulation and codes of conduct); scientific level (justification of expected scientific results, priority setting, resource allocation); institutional level (risks assessment; and implementing measures for risk management); societal level (public goods, citizens rights and liberties). The above components are interconnected and the prevalence of one of them may distort the proper approach to synthetic biology carried out in the EU and internationally.

Several models of governance of emerging technologies have been proposed, including synthetic biology. Governance models proposed by the Industry Association for Synthetic Biology contemplate actions covering

production, distribution and registration of potentially dangerous DNA sequences. Similar requests were indicated in a report delineating options for governance that was authored by members of the J. Craig Venter Institute ([146]).

The above soft law models are however confronted with the question of whether these regulatory attempts should be sort a kind of self regulation for the actors of synthetic biology research (and then opening issues related to the legitimacy, credibility and public trust of the codes prepared by the scientific community to be implemented by the scientific community itself ([147])) or whether the addressees of such codes should be public authorities having power to implement and monitor them. Additional questions relate to the role the public should play in the policy design of governance of synthetic biology, with subsequent issues related to market opening and social desirability of synthetic biology products. An editorial in Nature asserted: 'Self-governance need not and should not be exclusive – it does not preclude other forms of governance, any more than the possession of conscience makes redundant the strictures of law.' ([148])

2.5. *Public involvement and science-society dialogue*

Information, transparency and participation go hand in hand. Together, they create the sphere of trust that provides the space for new technologies to be developed as part of a societal endeavour – and not against it.

Research on the way the general public perceives risks of in particular new and emerging technologies show that certain risks will be perceived as more risky than others. Some risks might attract more than others the attention of the media and create headlines. Important factors include numbers and geographical distance: risks related to events and persons closer to us get more attention. Ethic and cultural factors also play an important role in the perception of risk. ([149]) This has a bearing on the perception of the risks of different possible applications of synthetic biology. The differences in risk perception between different ethnic groups and cultures have also been object of research.

In 2008 a first representative national survey ([150]) on public perception of synthetic biology was conducted in the USA showing that just over 30% of interviewees had already heard at all about synthetic biology. Notwithstanding this fact, 70% of respondents were ready to give their description on what they believed synthetic biology was and 66% expressed their opinion on the risk-benefit trade-off of the technology. In the EU, as the debate on GMOs has showed, proper involvement of society in discussing synthetic biology appears to be of significant importance, according to the 2006 Rathenau Institute paper ([151]). In different regions of the world, however, public discussions and consequently opinions are formed by various factors ([152]), with media

([146]) See: http://www.irgc.org/Synthetic-biology-genomics.html; Michele S. Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman, 'Synthetic Genomics: Options for Governance,' J. Craig Venter Institute, Center for Strategic and International Studies, and Massachusetts Institute of Technology, October 2007. Report available at www.jcvi.org.http://www.allacademic.com/one/www/research/index.php?cmd=www_search&offset=0&limit=5&multi_search_search_mode=publication&multi_search_publication_fulltext_mod=fulltext&textfieldsubmit=true&search_module=multi_search&search=Search&search_field=title_idx&fulltext_search=%3Cb%3EBioBricks+or+BioConflicts%3F+Building+Public+Trust+in+European+Governance+of+Synthetic+Biology%3C%2Fb%3E&PHPSESSID=77e51dd113d65622-bec5470855c62d05; http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf

([147]) A paper, detailing areas and ways in which oversight could be implemented by the scientific community, was dismissed as 'inadequate' by civil society organisations, who also raised concerns over scientists being allowed to act as 'judge and jury'. See http://www.etcgroup.org/upload/publication/pdf_file/602,, p46

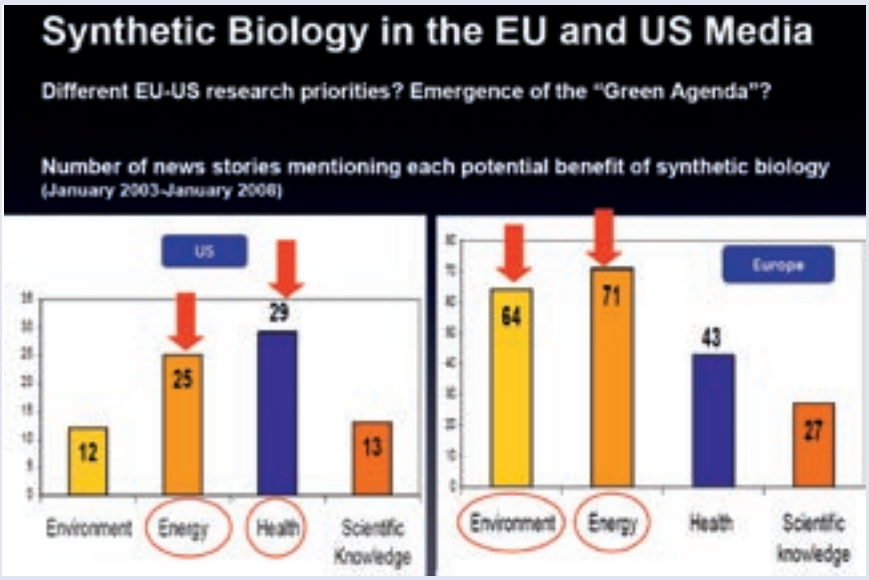
([148]) Nature Editorial (2006) Policing ourselves *Nature* 441: 383.

([149]) See P. Slovic: The Perception of Risk. Earthscan 2000, and MacGregor, D.G., Finucane,M.L., & Gonzalez-Caban, A. (2008). The effects of risk perception and adaptation on health and safety interventions. In Martin, W.E., Raish, C. & Kent, B. (Eds.), *Wildfire Risk: Human Perceptions and Management Implications* (pp. 142-155). Washington, DC: Resources for the Future.

([150]) Hart Research Associates (2008), Awareness of and attitudes toward nanotechnology and synthetic biology. Available at: http://www.synbioproject.org/process/assets/files/6019/hart_final_re8706b.pdf

([151]) 'Social and ethical issues will play an important role in the public and political acceptance of the technology', De Vriend, Huib. Constructing Life. Early social reflections on the emerging field of synthetic biology. The Hague: Rathenau Institute; Working Document 97. Available at http://www.rathenauinstituut.com/files/WED97%20Constructing%20Life%202006.pdf

([152]) There are two broad models for science communication: 1) the deficit model and 2) the contextual or dialogue model. The deficit model is based on an educational objective with the underlying assumption being that people are relatively uninformed about science, and that providing information



Source: Wodrow Wilson International Center for Scholars

playing an important role in making information available to and subsequently (co)shaping opinions of wide audiences.

The media coverage of synthetic biology addresses the question of public legitimacy and support for synthetic biology ([153]), with articles on synthetic biology regularly appearing in the press and popular science magazines ([154]). A 2008 study ([155]) analysed how synthetic biology had been introduced in the media looking at press coverage of synthetic biology in the USA and the EU between 2003 and 2008. In the US press 51% of articles focused on the potential benefits of synthetic biology while in the EU press only 26% of articles addressed these. The EU press focused on biosafety and biosecurity issues as well as ethics and creation of life whilst in the USA the press focused primarily on biosecurity.

Public opinion has already been shaped regarding some of the governance issues, e.g. firm opposition to the so-called soft law for synthetic biology was expressed in the response of civil society to the declaration on governance adopted by Second International Meeting on Synthetic Biology in 2006 ([156]). In parallel, the 2008 survey ([157]) on public perception of synthetic biology has showed that there is no public support for self-regulation of the industry in the synthetic biology field. The balance between potential risks and benefits seems to be the basis for public confidence in synthetic biology.

on scientific facts and benefits by independent scientists will lead to more positive attitudes towards science. Its critics argue that it is an approach based on one-way traffic of information from the 'informed' scientists to the public. The emphasis of contextual model is on dialogue and two-way streams of information exchange. It can be conceptualised along two broad ideas, namely 1) the notion of scientific literacy, according to which knowledge and understanding are key to public support and 2) the importance of social context for public support, with trust issues being seen as more important for public support than the knowledge of scientific facts. Contextual model provides a means to set science in a social context which seems to be especially relevant for the field of biotechnology. For further information see Osseweijer, Patricia: A Short History of Talking Biotech. Fifteen years of iterative research in institutionalising scientists' engagement in public communication. Vrije Universiteit Amsterdam, 2006.

([153]) Joachim Boldt, Oliver Müller, Giovanni Maio, Synthetische Biologie, op.cit., pp. 104-107

([154]) COGEM Report CGM/080925-01, pp. 25. Available at: http://www.cogem.net/ContentFiles/CGM080925-01-Biological%20machines1.pdf. See also http://ec.europa.eu/european_group_ethics/docs/avis20_en.pdf

([155]) See Eleonore Pauwels, Ioan Ifrim: Trends in American and European Press Coverage of Synthetic Biology. November 2008. Available at: http://www.synbioproject.org/process/assets/files/5999/synbio1final.pdf

([156]) Synthetic Biology: scope, applications and implications. The Royal Academy of Engineering, 2009, pp. 45. Available at: http://www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf

([157]) Hart Research Associates (2008), Awareness of and attitudes toward nanotechnology and synthetic biology. Available at: http://www.synbioproject.org/process/assets/files/6019/hart_final_re8706b.pdf

3. Ethical Aspects

3.1. General ethical aspects

Synthetic biology provides tools: (1) to improve our understanding of biological systems, their complexity and emergent properties that derive from the interaction of complex pathways (e.g. the minimal genome project) and methods; (2) to produce bio-products for different scientific, medical or market purposes (bio-remedies, bio-fuels, raw materials or biomedical tools (vaccines for example), or new bio-defence agents).

The ethics of synthetic biology is part of an ongoing larger debate on the ethics of emerging technologies and biotechnologies. Issues addressed by the EGE in its recent Opinions on Nanomedicine ([158]) and ICT implants into the human body ([159]) are therefore relevant to this Opinion.

3.1.1. The EU's fundamental ethical framework

As for other new technologies, the responsible development of synthetic biology must be based on fundamental ethical principles that have been enshrined in the conventions and declarations listed in the legal part (UN, UNESCO, Council of Europe and the Charter of Fundamental Rights). A consistent ethical framework is needed to undertake a thorough ethical analysis.

The Lisbon Treaty ([160]) states that *'Human dignity is inviolable. It must be respected and protected'* (Article II-61), goes on to explain that *'The dignity of the human person is not only a fundamental right in itself but constitutes the real basis of fundamental rights'* (Declaration concerning the explanations relating to the Charter of Fundamental Rights). This explanation does not strictly define human dignity and so various writers have attempted to fill this gap. One such attempt ([161]) suggests that human dignity be defined as follows: *'the exalted moral status which every being of human origin uniquely possesses. Human dignity is a given reality, intrinsic to human substance, and not contingent upon any functional capacities which vary in degree. (…) The possession of human dignity carries certain immutable moral obligations. These include, concerning the treatment of all other human beings, the duty to preserve life, liberty, and the security of persons, and concerning animals and nature, responsibilities of stewardship.'* This provides the basis for the following ethical principles, which are of direct relevance to this Opinion, where the general principle of human dignity is the core of the ethics framework for synthetic biology.

Bioethicists have often stated that the concept of dignity is vague and open to several interpretations. For example, as well as serving as a fundamental value, the principle of human dignity may be interpreted as a restrictive principle that protects human beings — who are principally vulnerable to violent acts by others — against actions or practices that run the risk of treating human beings as mere 'objects' of the interests of others to whose values they do not subscribe. D. Beyleveld and R. Brownsword define dignity *'as a particular practical attitude to be cultivated in the face of human finitude and vulnerability (and, concomitantly, the natural and social adversity that characterizes the human condition)'.* ([162]) Dignity can be understood as an enabling principle that guarantees individual freedom of action and autonomy in decision-making. The Kantian understanding of human dignity emphasises moral responsibility. A different view emphasises the need for individuals to consider the general effects their actions have on others, including other human beings, animals and the environment. Dignity is the basis for more specific principles, rights and obligations, and is closely connected to the principle of justice and solidarity.

As far as the debate on the ethics of synthetic biology is concerned, the difficulty stems from the overlap of several methodologies in ethics, depending on the main application fields. Although guiding principles have been established for quite some time in the biomedical field and can be used as a starting point for the ethical analysis of synthetic biology biomedicine, the same does not apply to environmental ethics, agriculture, or biotechnology in general. Furthermore, synthetic biology raises fundamental questions:

1. a conceptual analysis of life and nature ;
2. an analysis of procedural principles that aim to secure the freedom and autonomy of citizens with re-

([158]) http://ec.europa.eu/european_group_ethics/activities/docs/opinion_21_nano_en.pdf.

([159]) http://ec.europa.eu/european_group_ethics/docs/avis20_en.pdf.

([160]) Official Journal of the European Union, Volume 47, C 310, pages. 1–482, 16 December 2004.

([161]) William Cheshire, Ethics and Medicine, Volume 18:2, 2002.

([162]) Deryck Beyleveld and Roger Brownsword, *Human Dignity in Bioethics and Biolaw*, Introduction, p.2, Oxford University Press, Oxford-New York, 2001.

gard to the development of synthetic biology, such as transparency and access to information, democratic participation in fundamental issues of science and research and the principle of accountability and responsibility;

3. an analysis of substantial principles, depending on the different fields and applications.

3.1.2. Conceptual-ethical issues

The debate on synthetic biology addresses issues concerning or related to the ethical legitimacy of manufacturing living organisms. Some have advocated the ethical legitimacy of fabricating life ([163]) while critics have expressed serious concerns about the radical nature of this intervention.

In 1999, a group of bioethicists studied Venter's goal to fabricate a minimal genome organism. ([164]) They argued that the prospect of constructing minimal and new genomes did not violate fundamental moral precepts or boundaries, but did raise questions about the possible consequences of synthesising new free-living organisms in relation to the concept of life and our relation to it. ([165])

The concept of *life* has many interpretations according to the theoretical context in which it is used. Thought must be given to the terminology used to discuss ethical aspects of synthetic biology and its products, for instance, 'artificial cells,' or 'living machines'. ([166]) The terminology used to address the ethics of synthetic biology therefore needs to be ethically analysed in order to provide critical answers to questions concerning the difference between *life* and *non-life* ([167]) or between the *natural* and the *artificial*.

'Life' is the condition which distinguishes active organisms from inorganic matter, including the capacity for growth, functional activity and continual change preceding death. ([168]) A living organism can be seen as having a number of capacities that differentiate it from inorganic matter, such as metabolism, homeostasis, capacity to grow, reproduce and, through natural selection, adapt to its environment over successive generations. The concept of 'life' has also been addressed by several non-biological disciplines.

The distinction between life in a biological sense and its use in a social context is particularly relevant. ([169]) Some languages, such as Greek, have two words for this distinction, namely *zoe* and *bios*. *Zoe* applies to life processes common to all living beings, while *bios* refers to human

([163]) John Harris, *'Who's Afraid of a Synthetic Human?'* The Times, May 17, 2008. Colin Nickerson, *'A Quest to Create Life Out of Synthetics,'* Boston Globe, April 2, 2008. Erik Parens, *'Making Cells Like Computers,'* Boston Globe, February 18, 2008. Natalie Angier, *'Pursuing Synthetic Life, Dazzled by Reality,'* New York Times, February 5, 2008.

([164]) Cho MK, Magnus D, Caplan AL *et al.* (1999) *Ethical considerations in synthesising a minimal genome*, Science, 286: 2087–90.

([165]) The Roman Catholic Church has asserted that 'the human person does not commit an illicit act when, out of respect for the order, beauty and usefulness of individual living beings and their function in the ecosystem, he intervenes by modifying some of their characteristics or properties'. However, the Roman Catholic Church has also made a strong appeal for responsibility in this endeavour. See http://www.vatican.va/roman_curia/pontifical_councils/justpeace/documents/rc_pc_justpeace_doc_20060526_compendio-dott-soc_en.html, Article 473.

([166]) See Joachim Boldt, Oliver Müller, Giovanni Maio: *Synthetische Biologie. Eine ethisch-philosophische Analyse. Eidgenössische Ethikkommission für die Biotechnologie im Ausserhumanbereich* EKAH, Bern 2009. See also Nagel T. (1973) Mortal questions Cambridge University. Press; Nozick R (1981) Philosophical Explanations, Oxford University Press; Olson E. (1997) The Human Animal Personal Identity Without Psychology, Oxford University Press; Parfit D. (1984) Reasons and persons, Oxford University Press; Williams B. (1973) Problems of the self, Cambridge University Press; Wilson J. (1999) Biological Individuality Cambridge University Press; Salvi. M (2002) Rationalising individuality : the notion of individuality in biology, philosophy, (bio)ethics. Maastricht University Press, 300

([167]) See Arjun Bhutkar: *Synthetic Biology: Navigating the Challenges ahead*. Journal of Biolaw & Business, Vol. 8, No2, 2005: 'One of the main ethical concerns is drawing a distinction between an engineered machine and a living organism. Building a synthetic biological system from scratch or a [sic] constructing a minimal genome raises the question of the difference between life and nonlife.' (p. 26) (http://www.synbiosafe.eu/uploads/pdf/Bhutkar_Synthetic%20Biology_Navigating%20the%20Challenges%20Ahead.pdf).

([168]) The American Heritage Dictionary of the English Language, 4th edition, published by Houghton Mifflin Company, via Answers.com: 'The property or quality that distinguishes living organisms from dead organisms and inanimate matter, manifested in functions such as metabolism, growth, reproduction, and response to stimuli or adaptation to the environment originating from within the organism.' 'The characteristic state or condition of a living organism.'

([169]) For a thorough analysis of life concepts, see for instance: Hans Werner Ingensiep: *Lebensbegriffe — der Vergangenheit, der Gegenwart, der Zukunft.* In: H.W. Ingensiep and Anne Eusterschulte (Eds.): *Philosophie der natürlichen Mitwelt. Festschrift für Klaus Michael Meyer-Abich*. Würzburg 2002, pp. 103-119. See also: Sarah Franklin: Life. In: Warren Thomas Reich (Ed.): *Encyclopedia of Bioethics*. Revised Ed. Vol. 3, New York 1995, pp. 1345-1352.

life in its social and cultural dimension. ([170]) This distinction is echoed today in the two semantic perspectives we can address human life: firstly, as bodies-as-objects (having a body that is linked to all living beings), and secondly, as embodied beings (being a body, linked to the individual and irreducible experience of a self). ([171]) In the light of this, some bioethicists have advocated that from an ethical point of view, the human body should not be reduced to the concept of life proper to biosciences and biotechnology since it is also an expression of our social and cultural life deserving particular care and respect, which are at the core of the concept of human dignity. Some authors give *zoe* primacy over *bios*. ([172]) But this conceptual distinction does not necessarily advocate a hierarchy. From an ethical point of view, it is crucial to see that morality (accountability and responsibility) is connected to humans' specific capacity to decide upon the course of their actions.

The first reports on synthetic biology raise the question whether synthetic biology opens up radically new ways of fabricating life, and as a side-effect will change how we conceive of ourselves:

The production and/or modification of simple living organisms and their potential use to fabricate more complex ones raises the questions as to how far we want to assign a mere instrumental value of such organisms and our relation to the biosphere itself. ([173]) In this regard, the ethics of synthetic biology, addressed within the framework of ecological ethics, raises questions of uncertainty, potentiality, and complexity. ([174])

There are many different approaches to environmental ethics, mostly grouped as 'anthropocentric', 'biocentric', and 'ecocentric'. The EGE described the ethical debate on *eco-centric* theories in its Opinion on Modern developments in agriculture technology ([175]). It is important to underline that such theories have advocated the intrinsic value of the biosphere or the ethical dimension of nature. ([176]) Eco-centric environmental ethics questions the traditional ethics of rights and obligations, and asks instead in what kind of world we may wish to live in. Taken as such, ecological ethics advocates the change of traditional, if not modern values and goals at individual, national and global levels, and integrate the protection of the environment in a new view towards human beings, life, and nature.

Eco-centric theories apply to the use of synthetic biology to manufacture or modify life forms, as well as ecological considerations for synthetic biology in environmental protection. The relevance of such arguments should be considered in relation to uses of synthetic biology, although some theories of eco-centric ethics may intrinsically oppose synthetic biology when interacting with existing life forms or when (in a futuristic and hypothetical sense) synthesising complex organisms.

Anthropocentric theories, on the contrary, justify making instrumental use of nature for human purposes, although it is underlined that there are limits to human activities affecting the environment because they may damage the well-being of human beings now and in the future, since

([170]) See P. Hadot, H. Hübner, J. Vennebusch, R. Piepmeier, U. Dierse, K. Rothe, R. Toellner: Art. Leben. In J. Ritter and K. Gründer (Eds.): *Historisches Wörterbuch der Philosophie*, Darmstadt 1980, Vol. 5, pp. 52-103. See Martin G. Weiß (Ed.): *Bios und Zoe. Die menschliche Natur im Zeitalter ihrer technischen Reproduzierbarkeit* Frankfurt am Main 2009. See also Nicole C. Karafyllis (Ed.): *Biofakte. Versuch über den Menschen zwischen Artefakt und Lebewesen,* Paderborn 2003. The concept of 'biofact' is ambiguous if one makes a difference between *zoe* and *bios*. Products of synthetic biology are (until now) zoofacts. For a thorough analysis of life concepts, see for instance: Hans Werner Ingensiep: *Lebensbegriffe — der Vergangenheit, der Gegenwart, der Zukunft.* In: H.W. Ingensiep and Anne Eusterschulte (Eds.): *Philosophie der natürlichen Mitwelt. Festschrift für Klaus Michael Meyer-Abich*, Würzburg 2002, pp. 103-119. See also: Sarah Franklin: Life. In: Warren Thomas Reich (Ed.): E*ncyclopedia of Bioethics*. Revised Ed. Vol. 3, New York 1995, pp. 1345-1352 and Andreas Brenner: *Leben. Eine philosophische Untersuchung. Beiträge zur Ethik und Biotechnologie*, 3, *Eidgenössische Ethikkommission für die Biotechnologie* (Hrsg.), Bern 2007.

([171]) See Matthias Gutmann: *Biologie und Lebenswelt*. In: Ulrich Krohs, Georg Toepfer (Eds.): *Philosophie der Biologie*, Frankfurt am Main 2006, pp. 400-417. See also Simon Springmann, Asmus Trautsch (Hrsg./Eds.): Was ist Leben? Festgabe für Volker Gerhardt zum 65. Geburtstag. Berlin 2009

([172]) See Martin G. Weiß (Ed.): *Bios und Zoe. Die menschliche Natur im Zeitalter ihrer technischen Reproduzierbarkeit.* Frankfurt am Main 2009.

([173]) See Richard Maxwell, Toby Miller: *Ecological Ethics and Media Technology.* International Journal of Communication, 2 (2008), 331-353. (http://ijoc.org/ojs/index.php/ijoc/article/viewFile/320/151).

([174]) See Margaret Sommerville: *Creating the ethics of synthetic biology*, Ottawa Citizen, June 14, 2007. http://www2.canada.com/ottawacitizen/news/opinion/story.html?id=936d1e43-3dc3-48a2-bee5-b3164f6f4517.

([175]) http://ec.europa.eu/european_group_ethics/docs/opinion24_en.pdf

([176]) Rachel Carson, 'Silent Spring' (1963), which brought together a number of essays published earlier in the New Yorker magazine giving details of how pesticides, such as DDT, aldrin and dieldrin, concentrated along the food chain.

our well-being is essentially dependent on a sustainable environment. ([177]) Anthropocentric ethics argues strongly that humans ought to be at the centre of our attention and that it is right for them to be so. Anthropocentric approaches to synthetic biology focus much more on consequential considerations and issues related to potential consequences from the use of synthetic biology for human beings (risk assessment and management and hazard considerations ([178])). Where do we draw the line between what is certain, what could be certain and what remains, at least for the time being, uncertain?

3.2. Specific ethical issues

Specific ethical issues raised by synthetic biology concern its potential applications in the fields of biomedicine, biopharmaceuticals, chemicals, environment and energy and the production of smart materials and biomaterials, particularly but not exclusively from the viewpoint of bio-safety and biosecurity. ([179]) In addition, there have been discussions on aspects of risk governance, justice, public perception, intellectual property and co-modification. Synthetic biology raises issues of the governance of human practices related to scientific, technological, economic, political and cultural agents, no less than issues of security and organisational forms. ([180])

3.2.1. Biosafety

Unexpected interactions between synthetic microorganisms and the environment or other organisms produce risks to the environment and public health.

The risks have to be addressed in order to use synthetic biology responsibly. Synthetic microorganisms released into the environment could initiate processes of horizontal gene transfer and affect biotic balances, or evolve beyond their functionality and elicit unprecedented side-effects on the environment and other organisms. ([181]) Synthetic biology products must therefore address bio-safety issues when they have consequences for ecology and human health.

In the EU, the protection of human health is a key condition for the marketing of products resulting from synthetic biology, as with any other technology. Risk assessment procedures and methods have been established to safeguard this principle and include precaution, but long-term health-related risks associated with the ecological effects of synthetic biology are hard to predict.

As identified in the EGE Opinion on nanomedicine, which addresses analogous issues on the potential health impact of nano-pollutants, risk assessments used for synthetic biology are designed not only as a technical tool for the safe governance of synthetic biology in order to protect human dignity and the autonomy of persons directly (medical applications) or indirectly (exposure to synthetic biology products if released into the environment).

Similar considerations apply to environmental protection, where the precautionary principle plays a key role in EU policy design. The Nuffield Council on Bioethics' follow-up discussion paper, *The Use of Genetically Modified Crops in Developing Countries*, ([182]) stressed the possible interpretation of the precautionary principle and its application in the governance of biotechnology.

The precautionary principle requires:

a) that there are serious and irreversible risks,

b) a shift of the burden of proof from those potentially exposed to the hazards of a new technology to those who want to introduce it. ([183])

([177]) See Bookchin, M. 1990. *The Philosophy of Social Ecology*, Montreal: Black Rose Books.; Norton, B., Hutchins, M., Stevens, E. and Maple, T. L. (eds) 1995. *Ethics on the Ark*, Washington: Smithsonian Institution Press.; Passmore, J. 1974. *Man's Responsibility for Nature*, London: Duckworth, 2nd ed., 1980

([178]) See Antoine Danchin: *Nature and Artifice*, 2009. In: http://www.normalesup.org/~adanchin/causeries/Nature.html.

([179]) See Andrew Balmer & Paul Martin: *Synthetic Biology. Social and Ethical Challenges*, May 2008. http://www.bbsrc.ac.uk/publications/corporate/synthetic_biology.pdf .

([180]) See Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno: SYNBIOSAFE e-conference: online community discussion on the societal aspects of synthetic biology. In *Systems and Synthetic Biology* (2008) September 16. Online at: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf.
Paul Rabinow & Gaymon Bennett: *From Bio-Ethics to Human Practice*. Working Paper # 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf.

([181]) Nuffield Council background paper (2009).

([182]) See http://www.nuffieldbioethics.org/fileLibrary/pdf/GM_Crops_Discussion_Paper_2004.pdf.

([183]) The Commission Communication of February 2000 states that: 'The precautionary principle is not defined in the Treaty, which prescribes it only once — to protect the environment. But in practice, its scope is much wider, and specifically where preliminary objective scientific evaluation indicates that there

According to the European Commission, the precautionary principle is a dynamic tool to follow developments in a sector and continuously verify that the conditions for the acceptability of a given innovation are fulfilled — thereby improving governance. The precautionary principle does not, however, require refraining from action, as this may also involve risks, namely the risk of major environmental threats due to global pollution. For synthetically produced organisms, the precautionary principle is an important part of sound ethical debate and of legal, regulatory and political decisions.

An additional concern has to do with the dangers of potentially harmful organisms being inadvertently released during the experimental phase. Existing regulations in Europe contemplate these possibilities and different levels of confinement are defined, including a register for activities posing no risk for human health or the environment. In some cases these regulations may seem to contradict the freedom to use any available knowledge or tool for research or even recreation e.g. "bio-hackers". Freedom of research cannot be invoked if serious or irreversible risks to human health or the environment may occur. Existing regulations do not consider exceptions for such activities. In order to address some of the concerns regarding the safety of synthetic organisms (including protocells) suggestions have been made to assure that they are contained. This includes the traditional physical containment and disabling of the organisms in some way so as to ensure they cannot survive if accidentally or incidentally introduced into the environment.

3.2.2. Biosecurity

Ethical issues arise particularly from dangers of using synthetic lethal and virulent pathogens for terrorist attacks, bio-war, or maleficent uses ('garage terrorism', 'bio-hacking'), particularly if knowledge and skills on how to produce such pathogens are freely available. ([184]) Applications of synthetic biology for such purposes include the production of biological weapons, such as new and/or modified pathogenic viruses or bacteria ([185]) as well as synthetic organisms engineered to produce toxins. The literature on bio-war and the use of bioengineering for bio-defense, bio-offence and terrorism shows the potential of this technology, which may be amplified by synthetic biology. ([186])

This applies to the potential risks associated with the use of dangerous bio-material produced in governmental bio-defence laboratories as well as by terrorists. Given the present state of knowledge, the design and production of entirely novel pathogens for terrorist and/or maleficent uses may seem unlikely. There are technological difficulties and resources involved in producing existing and novel pathogens, and developing them into weapons. But states can mobilise resources and dangerous material can be obtained easily over the Internet or in other ways. ([187]) The ability to carry out DNA synthesis is

are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the Community' (Communication Summary, paragraph 3). http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf.

([184]) See the Report on the workshop *Technical solutions for biosecurity in synthetic biology* held on April 03rd, 2008 in Munich, Dr Hubert Bernauer et al., IASB (Industry Association Biology) http://ia-sb.eu.

([185]) The list of diseases considered for weaponisation, or known to be weaponised include anthrax, ebola, Marburg virus, plague, cholera, tularemia, brucellosis, Q fever, machupo, Coccidioides mycosis, Glanders, Melioidosis, Shigella, Rocky Mountain spotted fever, typhus, Psittacosis, yellow fever, Japanese B encephalitis, Rift Valley fever and smallpox (in addition naturally-occurring toxins that can be used as weapons include ricin, SEB, botulism toxin, saxitoxin and many mycotoxins).

([186]) See: Alibek, K. and S. Handelman. Biohazard: *The Chilling True Story of the Largest Covert Biological Weapons Program in the World – Told from Inside by the Man Who Ran it.* Delta (2000) ISBN 0-385-33496-6; Crosby, Alfred W., *Ecological Imperialism: The Biological Expansion of Europe, 900-1900* (New York, 1986); Endicott, Stephen and Edward Hagerman, *The United States and Biological Warfare: Secrets from the Early Cold War and Korea*, Indiana University Press (1998). ISBN 0253334721; Keith, Jim (1999), *Biowarfare In America*, Illuminet Press, ISBN 1-881532-21-6; Mangold, Tom and Goldberg, Jeff (1999), *Plague Wars: a true story of biological warfare*, Macmillan, London, ISBN 0-333-71614-0; Orent, Wendy (2004), *Plague, The Mysterious Past and Terrifying Future of the World's Most Dangerous Disease,* Simon & Schuster, Inc., New York, NY, ISBN 0-7432-3685-8: Preston, Richard (2002), *The Demon in the Freezer*, New York: Random House; Woods, Lt Col Jon B. (ed.), USAMRIID's Medical Management of Biological Casualties Handbook, 6th edition, U.S. Army Medical Institute of Infectious Diseases, Fort Detrick, Maryland (April 2005).

([187]) According to the Nuffield Council paper on synthetic biology (2009) 'In 2006, a journalist for the *Guardian* newspaper demonstrated a lack of DNA supply regulation by ordering DNA sequences of the small pox virus and having them delivered to his home (See http://www.guardian.co.uk/science/2006/jun/14/weaponstechnology.uk). The same journalist investigated three UK sequencing companies and found that one did not screen either customers or the sequences ordered. The second screened only customers, and the third screened customers and had carried out a pilot study on screening sequence orders. In addition, it has been suggested that the actual publishing of how the polio virus was synthesised, and

no longer confined to an elite group of scientists, as was the case for the first several decades of research using recombinant DNA. Now, anyone with a laptop computer can access public DNA sequence databases via the Internet, access free DNA design software, and place an order for synthesised DNA for delivery. Therefore there are valid reasons for taking the bio-security of synthetic biology seriously. ([188]) Given this inherent dual-use risk, designing ways to impede the malicious use of the technology, while at the same time *not* impeding, or even promoting, beneficial uses poses a number of ethical challenges.

Concerns over bio-terrorism have also prompted increased debate about whether or not 'dual-use' life science discoveries with implications for developing bio-weapons should be subject to a publishing ban. Much of this debate has focused on two particular studies: the genetic engineering of vaccine-resistant mousepox and the artificial synthesis of the polio virus. Proponents of a ban complain that publishing studies like these alerts would-be bio-terrorists to possibilities and provides them with explicit instructions for producing biological weapons. On the other hand, publishing such studies can yield benefits for medicine or bio-defence. Issues related to the freedom of science and censorship emerge, including the process of censorship decision-making applicable to the publishing of scientific results that may have a use for virulent pathogenic product production.

Due to the cost and analytical sophistication needed for synthesis, there are relatively few companies that synthesise long sequences of DNA. There have been suggestions that these companies screen all sequences for toxicity or infectivity before processing an order. That implies that databases of toxic or infective DNA sequences are available. These databases would of necessity fall within the ambit of the Database Directive ([189]). Regulation should ensure that all necessary information is readily available to these companies to permit the required searches. If the copyright protection provided for databases restricts access to the information necessary Article 6(2)(c) or Article 9(c) should be invoked to ensure that these companies are able to track possible dangerous sequences before synthesis. There is software available from CRAIC ([190]) termed 'BlackWatch' for the purpose of tracking DNA sequence synthesis which may be hazardous. The software is open-source (for the first generation). A new generation of the software is being developed in USA ([191]), able to address the 15 million orders a month worldwide that are expected by 2012 ([192]). There are many questions that need to be addressed so as to ensure that the system works, including; 1) Support for the development and maintenance of open source software; 2) Assistance for companies (particularly SMEs) to ensure involvement and compliance; 3) Mechanisms for reduction of cost to small companies involved in synthesising DNA; 4) Mechanisms for reporting to Competent Authorities where it is likely that the companies will not synthesise a particular sequence; 5) Mechanisms for ensuring privacy and identifying the chain of responsibility for placing particular sequences in the database(s) and identifying them as potentially harmful.

3.2.3. Justice

The EGE Opinion on ethics of agriculture technologies analysed the principle of justice. ([193]) It stated that cur-

the sequence and synthesis of the Spanish flu virus, could provide bioterrorists with the necessary information to engineer their own pathogenic organisms. Coupled with this is the availability of DNA synthesisers, which can be purchased from registered manufacturers or increasingly on second-hand auction sites such as eBay.

([188]) Alexander Kelle: Synthetic Biology & Biosecurity in Europe. 2009. M. Schmidt, A. Ganguli-Mitra, A. Kelle, H. deVriend (Eds.): Synthetic Biology. The Technoscience and its Societal Consequences, Springer 2009. See also: Synthetics: the Ethics of Synthetic Biology. In: IDEA League Summer School, August 2007, The Netherlands. http://www.ethicsandtechnology.eu/images/uploads/Ethics_of_synthetic_biology.pdf; H. deVriend: Constructing Life; Early social reflections on the emerging field of synthetic biology, The Hague. Rathenau Institute. Working Document 97 (2006); S. Miller and M. Selgelid: Ethical and philosophical consideration of the Dual-use dilemma in the biological sciences. Centre for Applied Philosophy and Public Ethics, Australian National University and Charles Sturt University, Canberra, Australia (2006). Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, Biotechnology Research in an Age of Bioterrorism, National Academies Press, 2004. National Science Advisory Board for Biosecurity, 'Addressing Biosecurity Concerns Related to the Synthesis of Select Agents,' December 2006. Report available at www.biosecurityboard.gov. Jonathan B. Tucker and Raymond A. Zilinskas, 'The Promise and Perils of Synthetic Biology,' The New Atlantis, Spring 2006.

([189]) Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases

([190]) https://biotech.craic.com/blackwatch/introduction.html

([191]) Bernauer, Hubert. 'Technical solutions for biosecurity in synthetic biology' (2008). http://www.synbiosafe.eu/uploads/pdf/iasb_report_biosecurity_syntheticbiology.pdf.

([192]) 'DOTS - DNA Order Tracking System.' http://www.mitre.org/news/digest/advanced_research/02_09/genes.html

([193]) http://ec.europa.eu/european_group_ethics/docs/opinion24_en.pdf.

rent discussions on the concept of justice emerged from the philosophical debate on the relationship between the State and citizens, particularly distributive justice (J. Rawls ([194]) and its critics) but also concerns the role of the State in protecting and advancing human rights. The principle of justice is therefore key to the ethics of synthetic biology. The global justice discourse affects issues of technology divide and common heritage, the question of inter-generational justice, ([195]) with implications for preserving the environment and natural resources for future generations (e.g., human intervention in the environment and biotic balances, intentional or unintentional release into the environment of synthetic products, bio-remedies, synthetic biology biofuels). The relationship between citizens' fundamental rights concerning the state of nature and the concept of a social contract affecting the actions of leaders against the desires of citizens (bio-security, bio-war, restriction in open access etc.) also needs to be addressed.

3.2.4. Intellectual Property

Synthetic biology provides a new set of tools for using biology, either for the purpose of pure research with an intention to understand the manner in which living systems have developed, including their interactions, or for producing new processes or products. An argument has developed as to whether all or some of the fruits of synthetic biology should be patentable, for the commercial benefit of those who have 'invented' the processes or products.

Many argue that patenting is an essential part of the protection of scientific endeavour. A recent paper on *'Inventing Biological Organisms: A Reader of Selected Articles'* states the case succinctly: 'The ability to patent biological inventions is central to protecting scientists' work… What can be patented, for how long, and the extent of global protection are critical issues. However, patenting biological organisms, particularly human genes and other human parts, is controversial. Economists question whether patenting is the quickest and best way to diffuse new knowledge throughout the marketplace. Some bioethicists question whether genetic information is the common heritage of mankind, making gene patenting inappropriate'. ([196]) Previous EGE publications deal in detail with the debate on gene patenting. ([197]) The concern has shifted to the role of the patent system as technology moves towards a 'knowledge economy'. It has always been assumed that there is an important balance to be struck between private and public interests in the manner in which the patent system is designed — limited rights for a limited time. This balance has shifted towards the private interest, particularly when examined from the perspective of the developing world. ([198])

The debate on the ethics of IPR is focusing on the question of which inventions should be able to be patented, and hence available directly for commercial exploitation, and which should not (if any). It has been argued that some discoveries or inventions should be considered as the common heritage of mankind. Following this line of reasoning, several experts on the ethics of patenting biological inventions have advocated that some discoveries or inventions should never

([194]) Rawls develops what he claims are principles of justice by using an entirely and deliberately artificial device which he calls the 'original position', in which everyone decides principles of justice from behind a 'veil of ignorance'. Rawls claims that all those in the original position would adopt a maximin strategy which would maximise the position of the least well-off. Rawls claims that parties in the original position would adopt two such principles, which would then govern the assignment of rights and duties and regulate the distribution of social and economic advantages across society (Rawls, 1971).

([195]) See Rawls (1971 and 1991), D. Parfit (1987), Partridge (1981) and Miller and Kumar (2007). See also Dobson, Andrew (ed.), *'Fairness and Futurity. Essays on Environmental Sustainability'*, Oxford University Press (1999); E. Agius, *'Towards a Relational Theory of Intergenerational Ethics'*, in Bijdragen 50 (1989) 293-313; Miller, Jon and Rahul Kumar (eds.), *'Reparations. Interdisciplinary Inquiries'* (2007), Oxford University Press; Partridge, Ernest (ed.), *'Responsibilities to Future Generations. Environmental Ethics'*, New York: Prometheus Books (1981); Ryberg, Jesper and Torbjön Tännsjö (eds.), *'The Repugnant Conclusion'*, Essays on Population Ethics, Dordrecht, Boston and London; Sikora, R.I. (2004) and Brian Barry (ed.), *'Obligations to Future Generations'*, Philadelphia: Temple University Press (1978). See http://plato.stanford.edu/entries/justice-intergenerational/#Bib.

([196]) California Research Bureau (1998) http://www.library.ca.gov/crb/98/reader/reader01.pdf.

([197]) A very detailed examination of the patent system, including an introduction to patent law in Europe and in the United States and an examination of many cases that involve patenting life forms, was produced for the EGE by Geertrui van Overwalle in 2002: EGE (2002) *Study on the patenting of inventions related to human stem cell research*. Luxembourg Office for Official Publications of the European Communities. ISBN 92-894-1987-3.

([198]) Walker, Simon. 2001. *The TRIPS Agreement, Sustainable Development and the Public Interest: Discussion Paper*. IUCN, Gland, Switzerland and Cambridge, UK and CIEL, Geneva, Switzerland ISBN 2-8317-0604-1.

result in commercialisation for profit. ([199]) These include processes the use of which offend human dignity, such as the production of chimeras from germ cells, totipotent cells from plants and animals, process for cloning human beings and modified germ-line cells.

This would imply that 'inventions' in biology in general and in synthetic biology in particular can be categorised as follows:

a. That which is common to all humankind, and should not be patentable or directly exploited for commercial gain;

b. That which, for a variety of reasons, should be placed in the public domain for all to use and exploit (the 'commons'). It may be that the process or product is so expensive to produce or require a vast range of expertise not available to any one organisation, or that the placing of the information in the public domain enables open standards that allow for the effective commercialisation and use of a number of products that use the technology or product;

c. That which may, at the inventor's discretion, be protected through an intellectual property rights system to encourage innovation.

The first category should include the human genome and large projects such as the hap-map project ([200]) that address discoveries in the human genome. This would include artificial chromosomes introduced into human cells and would be justified under Article 53(a) of the European Patent Convention (inventions for which commercial exploitation would be contrary to morality). The International Treaty on Plant Genetic Resources attempts to return some of that which was removed from the common heritage of mankind in the CBD to some crops (64) to permit free access to their genetic resources, arguing that '[n]o country is self-sufficient in plant genetic resources; all depend on genetic diversity in crops from other countries and regions. International cooperation and open exchange of genetic resources are therefore essential for food security'.

The second category covers pre-competitive inventions, where the cost would be too great for a single organisation to bear. It should take into account the link between private and public interest. Where the range of information is so great as to make it impossible for a single organisation to develop and use during the lifetime of a patent, the basic information should be placed in the public domain or made available at minimum cost to others to use. This would ensure that information is not withheld in a way that restricts innovation. As synthetic biology may involve the development of building blocks which could be assembled into a living organism, open standards should be developed to permit interaction between systems developed by the engineers.

The third category advocates that inventors should be mindful of the choices that they may be in a position to make. They could choose to patent the invention, or to place some or all of the information in the public domain, or use some form of open licence. Importantly, where a choice is made to patent, it should be remembered that, although the rules on patents are almost universal, the patents themselves are national, and an inventor may choose the jurisdictions in which protection is sought. It may be that, in order to encourage innovation in developing countries, inventors should be encouraged to choose not to patent their inventions in these countries. As the information regarding the invention (process or product) is disclosed in a patent application, an inventor may choose to use some sort of licence in countries where patent protection is not sought.

All these categories are relevant to the debate on IPR and synthetic biology products. It is clear that there is no general consensus on the ethics of patenting biological inventions. The patenting system (GATT) is interpreted differently in different countries; currently there are differences between the USA and the EU patent regime with regard to public morality, technical reproducibility and patents' utility. This also concerns issues related to the link between innovation and IPR. The debate has also been enriched by discussions concerning the patentability of the human genome and what should be eligible for patenting when common

([199]) Bovenberg JA (2006) *'Mining The Common Heritage of our Dna: Lessons learned from Grotius and Pardo'* Duke Law & Technology Review 8; Miller, A.R. and Davis, M.H., 2000. *Intellectual property: patents, trademarks, and copyright in a nutshell.* West Group, St. Paul; Juengst, E.T., 1998. *Should we treat the human germ-line as a global human resource?* In: Agius, E. and Busuttil, S. (eds.) *Germ-line intervention and our responsibilities to future generations.* Dordrecht, pp. 85-102.

([200]) See the HapMap website at http://www.hapmap.org/hapmappopulations.html.en. The HapMap is a catalogue of common genetic variants that occur in human beings. It describes what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world.

heritage considerations are concerned. Many international organisations hold that the human genome (and by extension other genomes) are 'the common heritage of mankind'. These include the Human Genome Organisation (HUGO) Ethics Committee (2000), ([201]) the Council on Responsible Genetics (CRG 2000), ([202]) the International Federation of Gynaecology and Obstetrics (1997), ([203]) UNESCO (1997), and the Council of Europe ([204]) (2001).

([201]) Human Genome Organisation Ethics Committee, 2000. *Genetic benefit sharing*. Science, 290 (5489), 49.

([202]) CRG, 2000. *The genetic bill of rights*. Council for Responsible Genetics CRG, Cambridge. [http://www.gene-watch.org/programs/bill-of-rights/bill-of-rights-text.html].

([203]) International Federation of Gynaecology and Obstetrics, 1997. *Patenting human genes*. http://www.figo.org/].

([204]) The Parliamentary Assembly of the Council of Europe (Council of Europe 2001) asserted that it was 'of the opinion that the results of this grandiose research effort — in which the United States has the lead over Europe — must be made available to all, genetic information being a common human heritage, as set out in Article 1 of the Universal Declaration on the Human Genome and Human Rights, adopted at UNESCO in Paris on 11 November 1997. The Assembly in particular refers in this context to the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine — Convention on Human Rights and Biomedicine (ETS No 164) as well as its own Recommendations 1425 (1999) on biotechnology and intellectual property and 1468 (2000) on biotechnologies', as well as that of UNESCO in its Universal Declaration on the Human Genome and Human Rights (1997). UNESCO's Declaration states that, 'The human genome underlies that fundamental unity of all members of the human family...in a symbolic sense, it (the human genome) is the heritage of humanity (...) The human genome in its natural state shall not give rise to financial gain.'

4. Recommendations

4.1. *Defining terminology and scope of the Opinion*

As already described in the first chapter of the Opinion, synthetic biology is a new research field that results from the convergence of different technological and scientific disciplines and allows a better understanding of biological systems, their complexity and emergent properties that derive from the interaction of complex pathways. At the same time it allows the production of bio-products which may have a direct use in a variety of sectors such as bio-remedies, bio-fuels, raw-materials or biomedical tools –vaccines for example–, or new bio-defence agents. The Group recognises that it is difficult to draw sharp lines between already established practices in biological research and the new approach of synthetic biology. Nevertheless, there is a gradual transition from modification to fabrication of biological systems, from engineering of simple to complex systems, and from adaptation of natural biological systems to engineering (or designing) of partially or totally artificial biological systems.

An internationally agreed definition of this research sector does not exist yet and this may create confusion with regard to scientific and regulatory frames to apply to different uses of synthetic biology. An internationally recognised definition of synthetic biology is therefore needed in particular if the research and applications of synthetic biology are to be regulated.

The Group´s understanding of synthetic biology ([205]), nevertheless, includes at least: 1) the design of minimal cells or organisms ([206]) (including minimal genomes), 2) the identification and use of biological 'parts' (the toolkit); 3) the construction of totally or partially artificial biological systems.

Specific concerns address its potential applications in the fields of biomedicine, biopharmaceuticals, chemical industry, environment and energy, production of smart materials and biomaterials particularly but not exclusively from the viewpoint of safety and security. ([207]) Beyond this, the debate is about aspects of justice, governance, science and society dialogue, intellectual property and philosophical discussions about life ([208]) (See Chapters 3.1 and 3.2). As for other new technologies, synthetic biology must respect the international frame on ethics and human rights (see Chapter 2.3 of this Opinion) and in particular the respect of human dignity, which is conceived as not only a fundamental right in itself but 'the real basis of fundamental rights' ([209]).

Other ethics principles that have to also be taken into account include, *inter alia*, the principle of *safety*; the principle of *sustainability*, the principle of justice, the principle of *precaution*, the principle of *freedom of research* as well as by the principle of *proportionality* ([210]).

4.2. *Safety*

In dealing with the ethical questions raised by synthetic biology a basic requirement is that both research and applications do not produce any specific harm to human health but also to the environment. In this respect safety is a pre-requisite to any use of synthetic biology. Many of the safety issues relevant to synthetic biology were already considered three decades ago at the meeting on recombinant DNA at the Asilomar Conference Centre in Pacific Grove, California, which opened a debate on the ethics of the newly emerging technologies based on DNA, focusing in particular on the safety of transmitting genes from one organism to another organism via a vector such as a virus or a plasmid. At present, legislation on bio-safety exists in the EU, including legislation to protect human and animal

([205]) See chapter 1.3 of the Opinion.

([206]) The term organism is here intended to include acellular, unicellular or multi-cellular biological entities that may be enhanced or modified.

([207]) See Andrew Balmer & Paul Martin: Synthetic Biology. Social and Ethical Challenges. May 2008. http://www.bbsrc.ac.uk/publications/corporate/synthetic_biology.pdf

([208]) See Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno: SYNBIOSAFE e-conference: online community discussion on the societal aspects of synthetic biology. In: Systems and Synthetic Biology (2008) September 16. Online: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf
Paul Rabinow & Gaymon Bennett: From Bio-Ethics to Human Practice. Working Paper # 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf

([209]) Declaration concerning the explanations relating to the Charter of Fundamental Rights

([210]) According to which (1) the goal or objective of the research must be important: (2) the methods used must be necessary to achieve the goals; and (3) there are no other less controversial or risky methods that could be used to achieve the same goal.

health and environment, or people exposed to biological agents and other hazardous agents. The question is whether the above mentioned frame responds entirely to the specific features of synthetic biology.

When addressed from a safety viewpoint synthetic biology opens a number of concerns, such as, *inter alia*: how to assess the safety of organisms that have a genome derived using recombinant DNA techniques and that allow the production of systems combining elements from multiple sources. How to evaluate such constructions for biological safety in organisms that may contain genes or proteins that have never existed together in a biological organism or that contain newly designed biological functions that do not exist in nature remains unclear.

A further concern relates to unknown risks to the environment and public health, determined by unexpected interactions between synthetic microorganisms and the environment or other organisms in it. Horizontal gene transfer and its potential impact to the balance of the ecosystems, or the interaction of synthetic microorganisms with naturally-occurring substances or unforeseen evolution of synthetic biology agents are all risks that may derive from the non contained use of synthetic biology agents or from inadvertent presence of the organisms in the environment.

Biosafety concerns regarding synthetic biology also affect risk assessment methods existing in the EU in relation to biology. The assessment methods for GMOs are based on a comparison of the altered organism with the natural organisms on which they are based, considering each individual trait introduced ([211]). Synthetic biology will produce organisms with multiple traits from multiple organisms, and therefore it may be difficult to predict their properties.

The biosafety of synthetic biology products is heavily debated between scientists and decision makers. Some scientists have even proposed that in absence of clear biosafety data all synthetic biology research protocols should take place in Biological Safety Level -P3 or P4 -laboratories with clear implications for the development of this scientific sector.

The Group is of the opinion that bio-safety considerations are pre-requisites for the promotion and implementation of an EU synthetic biology research program, both nationally and internationally.

Recommendation No 1: The Group recommends that any use of synthetic biology should be conditional on specific safety issues identified in this Opinion. Therefore the Group asks:

1) *The Commission to initiate a study on current risk assessment procedures in the EU. The study should (a) make a survey of relevant bio-safety procedures, (b) identify possible gaps in the current bio-safety regulation to effectively assess organisms and novel products developed through synthetic biology; (c) indicate the mechanism to fill the identified gaps.*

2) *The identified risk assessment procedure should then be carried out by the competent Authorities within the EU (e.g. EC, EMEA and EFSA) and National Authorities.*

3) *This should be conditional for financing of synthetic biology research and the marketing of synthetic biology products in the EU.*

Recommendation No 2: The Group proposes that, when the above biosafety rules are defined, the Commission starts an international debate with relevant counterparts to facilitate a standardised approach to bio-safety of synthetic biology for public and private funded trials. Instruments for the monitoring of the implementation of such provisions should be conceived as integral part of the bio-safety rules (including £liability issues).

Recommendation No 3: The Group advocates that a Code of Conduct for research on synthetic microorganisms should be prepared by the Commission. The Code should, for example, assure that synthetic biology organisms are manufactured in a way that they cannot autonomously survive if accidental release into the environment would take place.

4.2.1. Environmental applications

The Group is aware that synthetic biology has potential environmental applications. The Group acknowledges current synthetic biology research, for instance, to reduce environmental contaminants (bioremediation), such as heavy metals, pesticides and radioactive mate-

([211]) See risk assessment methods as discussed in the EGE Opinion on ethics of nanomedicine.

rial. The Group is aware of current research to produce synthetic biology agents able to degrade pesticides to reduce their environmental impact ([212]) or to produce biosensors for polluted water ([213]). The Group states that the goal of increasing environment protection and producing new detection tools is positive and may increase human welfare and environment protection. Specific concerns arise, however, from a bio-safety point of view when environmental applications of synthetic biology are envisaged and therefore adequate assessment of safety and environmental impact should be carried out before any environmental release is approved.

In the area of environmental applications, the fabrication of antipollution biological systems or organisms must be analyzed with respect to the protection of workers and citizens, freedom of consumers, and responsibility, including the responsibility for animals, plants, and the environment in general.

Recommendation No 4: The Group recommends that before an organism, fabricated or modified via synthetic biology, is released into the environment, ecological long term impact assessment studies must be carried out. Data resulting from such studies should then be evaluated taking into account the precautionary principle ([214]) and the measures foreseen in the EU legislation (Directive on the deliberate release into the environment of genetically modified organisms). In the absence of a favourable assessment the release of organisms fabricated or modified should not be authorised.

4.2.2. Energy and sustainable chemical industry

The Group is aware that synthetic biology could contribute to the development of a sustainable chemical industry in particular the production of synthetic biology microorganisms aimed to substitute agents and methods currently used by organic chemical industry for its production of raw materials.

As far use of synthetic biology for *energy purposes* the Group is also aware that synthetic biology research is currently aimed at engineering bacteria to produce organic compounds ([215]) aimed to substitute petrol as well as research seeking to engineer bacteria to produce the fuel hydrogen from different sources ([216]).

The Group acknowledges that these possibilities are made more significant by dwindling fossil fuel reserves, which currently provide the raw materials and by the impact on climate of the combustion of fossil fuels. The Group is however concerned about possible safety implications and therefore proposes the following:

Recommendation No 5: The Group proposes that the use of synthetic biology for alternative energy supply in EU Member States would be complementary to the EU renewable energy plan, and that international research trials (e.g. EU-USA) be promoted and co-financed to favour an integrated international approach.

Recommendation No 6: The Group recommends that competent authorities properly monitor the authorisation procedures for the production of synthetic biology-derived chemicals and materials, if not identical to equivalent substances, by taking into consideration (a) risk assessment factors and (b) safety of workers exposed to synthetic biology chemical agents and (c) environment protection.

As far use of synthetic biology for *chemical products and novel materials*, are concerned the Group is aware that chemical products not intended for food or feed derived from genetically modified organisms do not require specific labelling identifying them as genetically modified. The Group is aware that virtually all synthetic biology products that contain or are organisms or that are derived from such organisms in food or feed, must be labelled as being genetically modified. The Group is however concerned about possible uses of synthetic biology in the cosmetic and textile industry.

([212]) See http://pbd.lbl.gov/synthbio/aims.htm

([213]) Arsenic contamination of drinking water is a problem in developing parts of the world, such as Bangladesh. See: Aleksic J, Bizzari F, Cai Y et al. (2007) Development of a novel biosensor for the detection of arsenic in drinking water *Synthetic Biology*, IET 1: 87–90.

([214]) 2001/18/EC, 98/81/EC and regulatory freame in chapter 2.1 of the Opinion.

([215]) Such as fatty acids which are optimal for use as biodiesel or other energy rich compounds.

([216]) See also: LS9 (www.ls9.com), Amyris (www.amyris.com), OPX Biotecnologies (www.opxbiotechnologies.com), Solazyme (www.solazyme.com), Gevo (www.gevo.com)

Recommendation No 7: The Group asserts that the protection of consumers´ rights is a key factor to consider in EU market and stresses that labelling of specific synthetic biology products, such as cosmetics and textiles, should be explored.

4.2.3. Biomedicine and biopharmaceuticals production

Synthetic biology has potential in medical applications such as to improve and develop biosensors, drugs, therapies, devices and cells with new properties that may be used to improve human health or therapeutic methods. Applications of synthetic biology are expected in drug production, development of new vaccines, medical devices such as biosensors, diagnostics, virus synthesis for genetic therapies, and potential uses in cancer therapy.

The Group is aware that medical uses of synthetic biology at the moment are at a basic research stage and that clinical applications of new drugs and methods are still far from being available to patients.

As described in chapter two of this Opinion, the Group argues that medical applications of synthetic biology must not contravene the fundamental rights and ethics framework outlined earlier and be conditional on strict biosafety provisions. For currently envisaged products the existing regulatory framework is generally adequate to regulate the use of synthetic biology and must be implemented.

Recommendation No 8: The Group recommends that further to the application of scientific and legal frameworks, specific ethics considerations have also to be addressed by the competent Authorities (such as EMEA([217])) when drugs and medical products will result from synthetic biology protocols. Data on medical applications of synthetic biology carried out in EU MS or resulting from EU funding should be collected by relevant bodies in the countries where such trials take place and made available internationally.

([217]) As required by EU legislation Synthetic biology medical products will be assessed from a safety viewpoint. The relevant MS and EU (EMEA) Authorities should be sure that safety considerations expressed in this Opinion are taken prior authorisation procedures of both clinical and research trials and marketing procedures.

4.3. Biosecurity, prevention of bioterrorism and dual uses

The EGE is aware of the possible use or misuse of synthetic biology in relation to biosecurity as well as of current research in this specific sector carried out in the EU and USA. Synthetic biology may permit the development of new tools that could be useful for military purposes ranging from biomaterials to bioweapons. Ethical analysis must assess the balance between security and the need for transparency:

- the production and potential use of synthetic biology materials or systems in national security policies, including the production of bioweapons. These uses must be within current national and international regulatory frameworks. Transparency and release of information may impact on misuse for terrorist purposes – but open societies must find ways to deal with the difficult balance between citizens' right to information on the one hand, and the need to protect their security.

- the production and potential use of synthetic biology materials or systems for terrorist purposes, above all the production of biological systems that can have a massive destructive potential. Misuse of any kind of synthetic biology knowledge needs to be addressed.

- the production of synthetic organisms outside recognised institutions. Since synthetic biology materials and procedures are publicly available, biohacking is another scenario that requires governance with respect to security.

The EGE is also aware of the recent EC Communication adopted on June 24, 2009 ([218]), defining the new EU *Chemical, Biological, Radiological or Nuclear (CBRN)* policy. The Group considers this initiative valuable but not yet sufficient for an ethically sound and democratic approach to bio-security in the EU and beyond. The Group welcomes the embedding of ethics into the curricula of biosecurity scientists, including specific actions to better clarify the ethical dimension of synthetic biology uses for bio security.

In synthetic biology applications, however, information about the fabrication of synthetic viruses, for example,

([218]) COM(2009) 273 final; SEC(2009) 874; SEC(2009) 790; SEC(2009) 791

may lead to a new wave of bio-terrorism. There has not been much discussion about how this could be handled. Soldiers' and civilians' health must be secured, transparency maintained as far as possible, and research permitted only under strict monitoring. As described in chapter three of this Opinion, the Group argues that security and military applications of synthetic biology must not contravene the fundamental rights and ethics frameworks outlined in the opinion. The task of preventing terrorist and/or malicious uses of synthetic biology raises the moral dilemma of dual use for researchers as well as for democratic states. Some intended and unintended dual purposes can be foreseen but others not. One way of dealing with the dual use dilemma is through control mechanisms such as licensing and registering the tools used by synthetic biology.

Examples of actions that may be used to prevent unacceptable military or terrorist actions include: 1) a centralised database be developed at least at EU level, or preferably at international level where all DNA synthesisers would be registered by competent authorities; 2) departments or research groups dealing with biosecurity and biodefence use of synthetic biology should be licensed in the above registry; 3) criteria for the publication of data on highly pathogenic viruses or toxic agents be defined at Member State and EU level. ([219])

Moreover, ethical issues that arise because of the potential for dual use should be dealt with at the educational level. Fostering individual and institutional responsibility through ethics discussion on synthetic biology is a key issue.

Recommendation No 9: The Group recommends that the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction should incorporate provisions on the limitation or prohibition of research in synthetic biology.

Recommendation No 10: The Group asks the Commission to define, in consultation with the EGE, a comprehensive security and ethics framework for synthetic biology.

Recommendation No 11: The Group recommends that the European Commission 1) ensure that databases are available to all who use them; 2) Provides the legal systems for companies to report to Competent Authorities when asked to synthesise suspicious sequences whilst ensuring privacy; 3) Identifies the chain of responsibility for placing particular sequences in the database(s) and identifying them as potentially harmful.

4.4. Governance

The Group also advocates that if a technology is considered for use in the EU, its effects should be carefully studied and evaluated through an impact assessment that includes both the risks and benefits of the new technologies and the risks and benefits of the technologies replaced. This assessment should be in the context of the integrated approach to synthetic biology where environmental and social implications are taken into account. In addition to technical risk governance, a broader approach must be developed that is better able than present instruments to adjust to possible changes, in the environment, in societies, in market economics or in national policies. The ethics of synthetic biology should deal with a case-by-case study of the benefits and perils of this technology for specific ecological settings as well as with potential risks and benefits for the whole biosphere. ([220])

A responsible use of synthetic biology would imply using governance tools in order to encourage scientific advances and uses of research which may benefit human health; help save energy and reduce the negative effects of climate change and at the same time to safeguard it from misuse; i.e. bioterrorism and protect biosafety and bioesecurity. This is not an easy

([219]) Regulations are in place for genetically modified organisms which would include those fabricated using synthetic biology techniques in Europe that require registration and/or approval of the facilities where these organisms can be grown and studied. See also p.40 of this Opinion and Art. 7 of EC/98/81.

([220]) See Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno: SYNBIOSAFE e-conference: online community discussion on the societal aspects of synthetic biology. In: Systems and Synthetic Biology (2008) September 16. Online: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf
Paul Rabinow & Gaymon Bennett: From Bio-Ethics to Human Practice. Working Paper # 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf

task and poses a number of dilemmas for the EU to engage in.

a) General dilemmas; How can governance tools

   – encourage beneficial use and prevent misuse; when dual use is possible?

   – encourage transparency without creating risks of misuses?

   – secure against misuse without introducing unwanted censorship on publication etc. ?

b) Specific governance challenges: How can the EU use Governance tools to

- Take into account that synthetic biology includes a great number of areas with very different levels and intensity of regulations and identified possible gaps in securing biosafety and bioesecurity?

- Identify areas where soft-law will provide sufficient protection and areas where hard law is deemed necessarily (see recommendation 2 on biosafety rules and recommendation 9 on the Convention on biological weapons)?

- Encourage professional responsibilities for individual researches and institutions (including scientists who are not necessarily used to work with living organisms and the specific problems this entails) and to supplement the Code of conduct proposed in recommendations No 3?

- Play a role in the need for global governance on synthetic biology?

The Group expresses its concerns on the existing fragmented regulatory framework, which may not be sufficient to properly regulate current and emerging aspects of synthetic biology. It also stresses the need to explore a proper model of synthetic biology governance (soft law, codes of conducts etc.), also taking into consideration potential risks of delocalisation of research trials in countries where regulation may be less stringent than the one proposed in the EU.

Recommendation No 13: The Group urges the Commission to propose a robust governance framework for synthetic biology and put it in place in the EU. The Commission should review the legislation applicable to synthetic biology and assess its relevance to address the issues raised by synthetic biology. The above framework should address relevant stakeholders (scientists, industries, military agents, and political and administrative agents) and clearly indicate their responsibilities.

Recommendation No 14: The relevant science communities should be encouraged to establish ethical, preferably global, guidelines which may act as signposts and lead science institutions and individual researchers to assess the impact of their work including the consequences of misuse ([221]).

Recommendation No 15: EGE Proposes that the EU takes up the question of governance of synthetic biology in relevant global fora.

4.5. Intellectual property

4.5.1. Patenting and common heritage

The questions raised by the patenting of biological methods and materials have been a subject of heated debate for some time and it is now being discussed in different disciplines. The function of patents to stimulate research and its applications and to promote public disclosure of the basis of applications may be jeopardized by the massive number of applications of patents related to genetic material and biological methods. At the same time the appropriation of elements of biological organisms by specific industrial actors has also raised a number of ethical questions. Article 7 of the Patent Directive in relation to Biotechnological Inventions states 'The Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology.' This is the only Article of the Directive that has not been implemented in the rules implementing the Directive of the EPO or the patent offices of the Member States. It is difficult to implement as it specifies no action and is not addressed in any of the other Articles. There have often been complaints from Patent Offices that the morality clauses in European Patent Law are difficult to interpret (or even that they should be addressed by other legislation). The Group proposes that where there is a general issue raised by a particular patent application in the field of biotechnol-

([221]) See Unesco MOST Ethical guidelines for international comparative social science research.

ogy (including nanotechnology and synthetic biology) that the relevant Patent Offices ask the EGE for advice in the general area identified in the application.

As far as the patenting and common heritage issue is concerned, the Group acknowledges the complexity of the topic, as already indicated in Annex I of this Opinion. The Group stresses that general ethical issues involved in patent applications have to be addressed properly in the patent allocation system.

Recommendation No 16: The EGE proposes that debates on the most appropriate ways to ensure the public access to the results of synthetic biology is launched. These debates should include also what can be object of patent and what should be available through open access.

Recommendation No 17: The EU Patent Directive (98/44/EC) defines the EGE as the Body to assess ethics implications related to patents. The Group urges the European Patent Office and the National Patent Offices to take account of Article 7 of the Patent Directive and refer contentious ethical issues of a general relevance to the EGE for consideration. This is particularly important if a class of inventions that ought not to be directly exploited commercially ([222]) has to be defined.

4.5.2. Trade and global justice

The Group is aware of the global dimension of synthetic biology and its applications and considers economic development and growth of social welfare as a positive goal of the EU. Synthetic biology may contribute to the socio-economic prosperity of the EU and beyond. The Group welcomes this possibility; insofar principles of the EU Charter of fundamental rights and main EU fundamental values are not negatively affected by this technological sector and the trade of its products. The EGE therefore has concerns about the possible risks of a technology divide within the EU and between developed and less developed countries.

The EGE recommends the embedding of the EU fundamental values into the global trade of synthetic biology products. As in previous Opinions (such as Opinion 23 ([223]) and Opinion 24 ([224])), the Group underlines the need of introducing ethics considerations in the global trade and World Trade Organisations policy actions.

Actions to avoid a greater technological divide should then be taken. If trials involving synthetic biology products are being conducted in developing and emerging countries the same ethical standards as are required within the EU must be implemented ([225]). UN Millennium goals should be implemented.

Recommendation No 18: The EGE recommends that when synthetic biology is discussed at international level, including the WTO, the ethical issues associated to the technology should be addressed ([226]). This should be taken into account in the Doha round negotiations.

Recommendation No 19: The EGE urges that EU Biosafety standards for synthetic biology products as identified in recommendations N°1, 2 and 5 of this Opinion are adopted as minimal standards for EU import-export of synthetic biology products.

Recommendation No 20: The Group recommends specific EU actions to avoid new gaps between EU and developing and emerging countries, or within EU Members States, and to put into effect the recommendations expressed in this Opinion. Such actions should be introduced in bilateral and multilateral science programmes of the EU and in the EU policies concerning developing and emerging countries.

([222]) EC/98/44, Article 6.2 provides an indicative list of exclusion from patentability, namely '(a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; (c) uses of human embryos for industrial or commercial purposes; (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.' The Directive, Art 7, also states that 'The Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology.'

([223]) http://ec.europa.eu/european_group_ethics/activities/docs/opinion23_en.pdf

([224]) http://ec.europa.eu/european_group_ethics/docs/opinion24_en.pdf

([225]) http://ec.europa.eu/european_group_ethics/docs/avis17_en.pdf

([226]) See Chapters 2.2.b and 2.2.c of this Opinion.

4.6. Science and society dialogue

As elaborated in Chapter 3 of this Opinion, the ethics of synthetic biology is complex and the identified conceptual questions need an effective science and society dialogue.

The perception of synthetic biology is influenced by social, cultural and ethical considerations about manipulating life, economic implications for developed and developing regions, issues related to ownership and intellectual property, concerns about environmental degradation and potential military uses, and so on. Traditional and interactive media play an important role in shaping people's views on new and emerging technologies, including synthetic biology. Each of these issues deserves thorough consideration and public participation. This raises wider issues of trust and confidence building between the scientific community and the public, including the need to promote proper debate. It ultimately leads to issues of deliberative democracy, including questions about who draws the lines between what is allowed, acceptable, and what is not; and who overviews those who draw the lines.

Social scientists have suggested that upstream engagement could be productive for a development of science and technology consistent with societal expectations, concerns, and wishes. ([227]) Many scientists working in synthetic biology are already aware of the importance of public engagement, and to this end, they have engaged in activities such as debates, podcasts and blogs.

Public debate needs to be properly informed about the effective features and potentials of synthetic biology and this may raise difficulties of identifying, estimating and managing risks in an area where there are considerable uncertainties and knowledge gaps, and when the short-term and long-term risks may be different. Similar considerations apply to 'hype' benefits, where the public is confronted, with the assistance of media and science fiction writers, with unrealistic scenarios on synthetic biology products (for example, synthetic biology hype with regard to the curability of all diseases or bio-remedy to environmental pollution of prospects for energy crisis). Non-documented hopes or fears communicated to the public distort the public debate on synthetic biology.

Recommendation No 21: The Group asks the EU and EU Member States to take actions to promote public debates and engagement amongst the stakeholders in order to identify main societal concerns in the different areas covered by synthetic biology.

Recommendation No 22: The Group recommends that journalists, editors, including science editors, and other stakeholders promote responsible reporting on synthetic biology.

Recommendation No 23: In order to promote a comprehensive approach to new technologies by the media the Group asks the Commission to stimulate specific actions, such as, inter alia, creating fora, seminars and courses, addressing the implications of synthetic biology in the media.

4.7. Research

It has been observed for quite some time that basic research, the fundament of all different applications in a given field, has been pushed to the background in research funding programmes. Even though basic research is not to be sharply separated from applied research, the former needs public funding, and this should be the policy of the European Union.

A key novelty synthetic biology introduces in the scientific method of modern biology is the possibility not only to use deductive approaches from observed phenomena but synthesising heuristic tools that allow in themselves exploring basic biology phenomena. Basic research in synthetic biology is however not necessarily connected to market and industrial interests and is therefore dependent on public financing. The Group is concerned that this may lead to a lack of adequate funding of EU basic research in a near future, and that this may jeopardise the role the EU research may play in global governance of synthetic biology.

In parallel, the ethical debate on synthetic biology addresses issues related to the ethical legitimacy of manufacturing living organisms, similar to the debate on engineering life. Human intervention in nature, which includes the environment and other living organisms, also raises concerns over the 'naturalness' of intervention and 'manufacturing life'. ([228]) The Group therefore

([227]) http://www.bbsrc.ac.uk/organisation/policies/reviews/scientific_areas/0806_synthetic_biology.pdf

([228]) John Harris, 'Who's Afraid of a Synthetic Human?' The Times,

underlines the need of financing EU interdisciplinary research projects on the relation between humans and nature, particularly with regard to questions concerning the views towards life.

Recommendation No 24: The Group invites the Commission to support basic research in the fields of biology, chemistry, energy and materials science and engineering and applied research as identified in this Opinion. This should be reflected in the R&D EU research Framework Programmes budget. A similar invitation is addressed to EU member states in their national R&D programmes.

Recommendation No 25: The Group requests the EU to properly finance interdisciplinary research on the following aspects of synthetic biology:

- *risk assessment and safety;*
- *security uses of synthetic biology;*
- *ethical, legal and social implications*
- *governance;*
- *science and society (including media and the public).*

This should be reflected in the R&D EU research Framework Programmes budget. Similar request is addressed to EU MS in their national R&D programmes.

Recommendation No 26: The Group notes that synthetic biology could lead, in the future, to a paradigm shift in understanding concepts of life. It therefore calls on the Commission to initiate an open intercultural forum to address the issues, to include philosophical and religious input.

May 17, 2008. Colin Nickerson, 'A Quest to Create Life Out of Synthetics,' Boston Globe, April 2, 2008. Erik Parens, 'Making Cells Like Computers,' Boston Globe, February 18, 2008. Natalie Angier, 'Pursuing Synthetic Life, Dazzled by Reality,' New York Times, February 5, 2008.

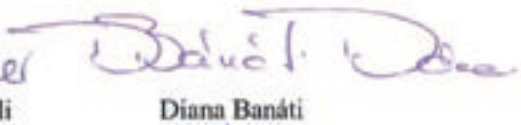
The European Group on Ethics in Science and New Technologies

The Chairperson: Göran Hermerén

The Members:

Emmanuel Agius

Francesco Busnelli



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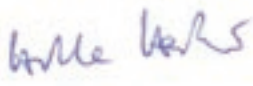

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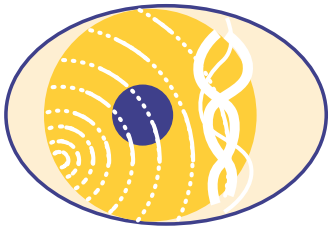


Groupe européen d'éthique
des sciences et des nouvelles
technologies auprès
de la Commission européenne

AVIS DU GROUPE EUROPÉEN
D'ÉTHIQUE DES SCIENCES
ET DES NOUVELLES TECHNOLOGIES
AUPRÈS DE LA COMMISSION EUROPÉENNE

Éthique de biologie synthétique

Référence: avis requis par le **président Barroso**
Rapporteurs: **Rafael Capurro**, **Julian Kinderlerer**,
Paula Martinho da Silva et **Pere Puigdomenech Rosell**

Seul le texte original en anglais est authentique.

N° 25

4. Recommandations

4.1. *Définir la terminologie et la portée de l'avis*

Comme déjà décrit dans le premier chapitre de l'avis, la biologie synthétique représente un nouveau domaine de recherche qui résulte de la convergence de différentes disciplines technologiques et scientifiques et qui ouvre la voie à une meilleure compréhension des systèmes biologiques, de leur complexité et des propriétés émergentes qui découlent de l'interaction entre des approches complexes. Parallèlement, elle permet la production de bioproduits directement utilisables dans divers domaines, tels que les produits de biorémédiation, les biocarburants, les matières premières ou les outils biomédicaux (vaccins, par exemple), ou de nouveaux agents de défense biologique. Le GEE reconnaît qu'il est difficile de tracer une limite précise entre des pratiques déjà établies dans la recherche biologique et la nouvelle approche de la biologie synthétique. Néanmoins, il existe une transition progressive entre la modification et la fabrication de systèmes biologiques, entre l'élaboration de systèmes simples et l'élaboration de systèmes complexes, ainsi qu'entre l'adaptation de systèmes biologiques naturels et l'élaboration (ou la conception) de systèmes biologiques partiellement ou totalement artificiels.

Il n'existe pas encore de définition internationalement acceptée de ce domaine de recherche. Cette situation pourrait provoquer une certaine confusion, s'agissant des cadres scientifiques et réglementaires à appliquer aux différentes utilisations de la biologie synthétique. Il est dès lors nécessaire qu'une définition de la biologie synthétique soit reconnue internationalement, en particulier si la recherche et les applications dans ce domaine doivent être réglementées.

Néanmoins, le GEE considère que la notion de «biologie synthétique» ([1]), recouvre au moins: 1) la conception de cellules ou d'organismes minimaux ([2]) (y compris de génomes minimaux); 2) l'identification et l'utilisation de «parties» biologiques (la boîte à outils); 3) la construction de systèmes biologiques partiellement ou totalement artificiels.

([1]) Cf. chapitre 1.3. du présent avis.

([2]) Le terme d'«organisme» recouvre ici des entités biologiques acellulaires, unicellulaires ou multicellulaires qu'il est possible de modifier ou d'améliorer.

Ses applications potentielles dans les domaines de la biomédecine, des biomédicaments, de l'industrie chimique, de l'environnement et de l'énergie, de la production de matériaux intelligents et de biomatériaux donnent lieu à des préoccupations spécifiques notamment, mais pas exclusivement, du point de vue de la sécurité et de la sûreté ([3]). En outre, le débat porte sur des aspects juridiques, de gouvernance, de dialogue entre la science et la société, de propriété intellectuelle et de discussions philosophiques sur le vivant ([4]) (cf. chapitres 3.1. et 3.2. du présent avis). Tout comme les autres nouvelles technologies, la biologie synthétique doit respecter le cadre de référence international en matière d'éthique et de droits de l'homme (cf. chapitre 2.3. du présent avis); elle doit notamment respecter la dignité humaine, qui «n'est pas seulement un droit fondamental en soi, mais constitue la base même des droits fondamentaux» ([5]).

Parmi les autres principes éthiques à prendre en considération figurent, notamment, les principes de *sécurité*, de *durabilité*, de *justice*, de *précaution*, de *liberté de la recherche* et de *proportionnalité* ([6]).

4.2. *Sécurité*

S'agissant des questions éthiques soulevées par la biologie synthétique, il est fondamental d'exiger que la recherche et les applications dans ce domaine ne nuisent ni à la santé humaine ni à l'environnement. À cet égard, la sécurité constitue une condition préalable à toute utilisation de la biologie synthétique.

([3]) Cf. Andrew Balmer & Paul Martin, Synthetic Biology. Social and Ethical Challenges, mai 2008, http://www.bbsrc.ac.uk/publications/corporate/synthetic_biology.pdf.

([4]) Cf. Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno, «SYNBIOSAFE e-conference: online community discussion on the societal aspects of synthetic biology», in: Systems and Synthetic Biology (16 septembre 2008). Accessible en ligne à l'adresse suivante: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf
Paul Rabinow & Gaymon Bennett, From Bio-Ethics to Human Practice, Working Paper no 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf.

([5]) Déclaration concernant les explications relatives à la Charte des droits fondamentaux.

([6]) D'après lequel (1) le but ou l'objectif de la recherche doit être important; (2) les méthodes utilisées doivent être nécessaires en vue d'atteindre ces objectifs; et (3) il n'existe pas d'autres méthodes moins controversées ou moins risquées qui pourraient être utilisées en vue d'atteindre ces objectifs.

Nombre de questions relatives à la sécurité en matière de biologie synthétique ont déjà été abordées il y a trois décennies lors de la réunion sur l'ADN recombinant au centre de conférence Asilomar de Pacific Grove, en Californie, qui avait ouvert un débat sur l'éthique des technologies émergentes de l'époque basées sur l'ADN, axé principalement sur la sécurité de la transmission de gènes d'un organisme à un autre par un vecteur tel qu'un virus ou un plasmide. L'UE dispose aujourd'hui d'une législation en matière de biosécurité, y compris d'une législation visant à protéger la santé humaine et animale ainsi que l'environnement, ou les personnes exposées à des agents biologiques ou à d'autres agents dangereux. La question est de savoir si le cadre susmentionné répond entièrement aux particularités de la biologie synthétique.

Lorsqu'on l'aborde du point de vue de la sécurité, la biologie synthétique soulève un certain nombre de questions dont celle, notamment, de l'évaluation de la sécurité des organismes dont le génome est le produit de techniques utilisant de l'ADN recombinant et qui permettent de produire des systèmes combinant des éléments provenant de sources multiples. Il subsiste des incertitudes quant à la façon d'évaluer ces constructions d'un point de vue de la biosécurité d'organismes pouvant contenir des gènes ou des protéines qui n'ont jamais coexisté dans un organisme biologique ou contenant des fonctions biologiques nouvelles qui n'existent pas dans la nature.

Une autre question concerne les risques inconnus pour l'environnement et la santé publique découlant des interactions inattendues entre les microorganismes synthétiques et l'environnement ou d'autres organismes. Le transfert de gènes horizontal et son incidence possible sur l'équilibre des écosystèmes, l'interaction de microorganismes synthétiques avec des substances naturelles ou encore l'évolution imprévue d'agents de biologie de synthèse représentent toute une série de risques pouvant découler d'une utilisation non contrôlée de ces agents biologiques de synthèse ou d'une présence imprévue de ces organismes dans l'environnement.

Les questions de biosécurité concernant la biologie synthétique touchent également les méthodes d'évaluation des risques qui existent dans l'UE dans le domaine de la biologie. Les méthodes d'évaluation des OGM sont fondées sur la comparaison de l'organisme modifié avec les organismes naturels dont il dérive, en considérant chaque trait individuel introduit ([7]). La biologie synthétique produira des organismes possédant de multiples traits provenant de multiples organismes. Il pourrait dès lors être difficile de prédire leurs propriétés.

La biosécurité des produits issus de la biologie synthétique fait l'objet d'intenses débats entre les scientifiques et les décideurs. Certains scientifiques ont même proposé qu'en l'absence de données claires en matière de biosécurité, tous les protocoles de recherche en biologie synthétique aient lieu dans des laboratoires de niveau P3 ou P4 en matière de biosécurité, ce qui aurait des implications précises en ce qui concerne le développement de ce domaine scientifique.

Le GEE est d'avis que les considérations sur la biosécurité constituent une condition indispensable à la promotion et à la mise en œuvre d'un programme européen de recherche en matière de biologie synthétique, à la fois sur le plan national et international.

Recommandation n° 1: Le GEE recommande que toute utilisation de la biologie synthétique soit subordonnée aux questions spécifiques de sécurité définies dans le présent avis. Dès lors, le GEE demande:

1) *que la Commission lance une étude sur les procédures actuelles d'évaluation des risques au sein de l'UE. Cette étude devrait a) faire une enquête sur les procédures pertinentes en matière de biosécurité, b) déceler les lacunes éventuelles dans la réglementation actuelle sur la biosécurité afin d'évaluer efficacement les organismes et les produits nouveaux créés au moyen de la biologie synthétique, c) indiquer le mécanisme permettant de combler les lacunes décelées;*

2) *que la procédure d'évaluation des risques ainsi déterminée soit ensuite mise en œuvre par les autorités compétentes au sein de l'UE (par exemple la CE, l'EMEA et l'EFSA) et par les autorités nationales;*

3) *que le financement de la recherche en biologie synthétique et la commercialisation de produits issus de la biologie synthétique dans l'UE soient subordonnés à ces conditions.*

([7]) Cf. les méthodes d'évaluation des risques telles que débattues dans l'avis du GEE sur les aspects éthiques de la nanomédecine.

Recommandation n° 2: Le GEE propose qu'une fois la réglementation susmentionnée en matière de biosécurité définie, la Commission lance un débat international avec les parties concernées afin de favoriser une approche standardisée de la biosécurité en matière de biologie synthétique pour les tests financés par des fonds publics et privés. Les instruments de suivi de la mise en application de ces dispositions devraient être considérés comme faisant partie intégrante de la réglementation en matière de biosécurité (y compris des questions de fiabilité).

Recommandation n° 3: Le GEE invite la Commission à préparer un code de conduite pour la recherche sur les microorganismes synthétiques. Ce code devrait, par exemple, garantir que les organismes de biologie synthétique soient fabriqués de telle façon qu'ils ne puissent survivre de manière autonome s'ils étaient libérés accidentellement dans l'environnement.

4.2.1. Applications environnementales

Le GEE est conscient du fait que la biologie synthétique peut également avoir des applications environnementales. Il reconnaît le rôle joué par la recherche actuelle en matière de biologie synthétique, notamment pour réduire les polluants présents dans l'environnement (bioréhabilitation) tels que les métaux lourds, les pesticides et les matériaux radioactifs. Il a connaissance des recherches actuelles visant à produire des agents de biologie synthétique capables de dégrader des pesticides afin de réduire leur impact environnemental ([8]) ou visant à produire des biocapteurs pour les eaux polluées ([9]). Il déclare que l'objectif d'amélioration de la protection de l'environnement et de fabrication de nouveaux outils de détection est un objectif positif qui peut contribuer au bien-être humain et à la protection de l'environnement. Cependant, des questions spécifiques surgissent, du point de vue de la biosécurité, lorsque des applications environnementales de biologie synthétique sont envisagées. Dès lors, une évaluation appropriée en matière de sécurité et d'impact environnemental devrait être réalisée avant toute approbation préalable à une dissémination en milieu ouvert.

Dans le domaine des applications environnementales, la fabrication de systèmes ou d'organismes biologiques antipollution doit être examinée en tenant compte des aspects de protection des travailleurs et des citoyens, de liberté des consommateurs, et de responsabilité, y compris celle due aux animaux, aux plantes et à l'environnement en général.

Recommandation n° 4: Le GEE recommande que, préalablement à la dissémination dans l'environnement d'un organisme fabriqué ou modifié par l'intermédiaire de la biologie synthétique, des études d'évaluation d'impact à long terme soient réalisées. Les données dégagées par ces études devraient ensuite être évaluées en tenant compte du principe de précaution ([10]) et des mesures prévues dans la législation européenne (directive relative à la dissémination volontaire d'organismes génétiquement modifiés dans l'environnement). En l'absence d'évaluation favorable, la dissémination d'organismes fabriqués ou modifiés ne devrait pas être autorisée.

4.2.2. Énergie et industrie chimique durable

Le GEE est conscient du fait que la biologie synthétique pourrait contribuer au développement d'une industrie chimique durable, en particulier à la production de microorganismes de biologie synthétique visant à remplacer les agents et les méthodes actuellement utilisées par l'industrie chimique organique pour sa production de matières premières.

S'agissant de l'utilisation de la biologie synthétique à des *fins énergétiques*, le GEE a également connaissance du fait que la recherche en matière de biologie synthétique vise actuellement à concevoir des bactéries destinées à produire des composés organiques ([11]) amenés à remplacer le pétrole ou à produire de l'hydrogène à partir de différentes sources ([12]).

([8]) Cf. http://pbd.lbl.gov/synthbio/aims.htm.

([9]) La contamination de l'eau potable à l'arsenic est un véritable problème dans certains pays en développement comme le Bangladesh. Cf. Aleksic J., Bizzari F., Cai Y. et al. (2007), «Development of a novel biosensor for the detection of arsenic in drinking water», *Synthetic Biology*, IET 1, p. 87–90.

([10]) Directive 2001/18/CE, directive 98/81/CE et cadre réglementaire au chapitre 2.1. de l'avis.

([11]) Tels que des acides gras parfaitement adaptés à l'utilisation en tant que biodiesel ou d'autres composés à forte teneur énergétique.

([12]) Cf. aussi: LS9 (www.ls9.com), Amyris (www.amyris.com), OPX Biotechnologies (www.opxbiotechnologies.com), Solazyme (www.solazyme.com), Gevo (www.gevo.com).

Le GEE reconnaît que ces applications gagneront en importance compte tenu de la diminution des réserves de carburant fossile et de l'impact climatique de la combustion des carburants fossiles. Toutefois, il se préoccupe des implications possibles en matière de sécurité et propose dès lors ce qui suit:

Recommandation n° 5: Le GEE propose que l'utilisation de la biologie synthétique en tant que source d'énergie de substitution pour les États membres de l'UE soit complémentaire au plan d'action de l'UE en matière d'énergie renouvelable, et que les essais de recherche au niveau international (UE - États-Unis, par exemple) soient promus et cofinancés afin de favoriser une stratégie internationale intégrée.

Recommandation n° 6: Le GEE recommande que les autorités compétentes suivent de manière appropriée les procédures d'autorisation de la production de matériaux et de produits chimiques dérivés de la biologie synthétique, si cette production n'est pas identique à des substances équivalentes, en prenant en considération a) les facteurs d'évaluation des risques, b) la sécurité des travailleurs exposés aux agents chimiques provenant de la biologie synthétique et c) la protection de l'environnement.

S'agissant de l'utilisation de la biologie synthétique pour les *produits chimiques* et *les matériaux nouveaux*, le GEE est conscient du fait que les produits chimiques non destinés aux denrées alimentaires ou aux aliments pour animaux qui sont dérivés d'organismes génétiquement modifiés ne demandent pas un étiquetage spécifique les identifiant comme génétiquement modifiés. Le GEE est conscient du fait que la quasi-totalité des produits de la biologie synthétique entrant dans la composition de denrées alimentaires ou d'aliments pour animaux qui contiennent ou sont des organismes modifiés ou dérivent de ces organismes devraient être étiquetés comme génétiquement modifiés. Toutefois, le GEE exprime ses préoccupations à propos d'utilisations possibles de la biologie synthétique dans l'industrie cosmétique et textile.

Recommandation n° 7: Le GEE affirme que la protection des droits des consommateurs est un élément crucial à prendre en considération en ce qui concerne le marché intérieur de l'UE et insiste sur le fait que l'étiquetage de produits spécifiques issus de la biologie synthétique, tels les cosmétiques et les textiles, devrait être exploré.

4.2.3. Biomédecine et production biopharmaceutique

La biologie synthétique ouvre de nouvelles perspectives en matière d'applications médicales, telles que la conception et l'amélioration de biocapteurs, de médicaments, de thérapies, d'appareils et de cellules disposant de propriétés nouvelles qui pourraient être utilisées pour améliorer la santé humaine ou les méthodes thérapeutiques. Des applications de la biologie synthétique sont prévues dans les domaines suivants: production de médicaments, mise au point de nouveaux vaccins, appareils médicaux tels que biocapteurs, diagnostics, synthèse de virus pour les thérapies génétiques et utilisations potentielles dans la thérapie anticancéreuse.

Le GEE est conscient du fait que les utilisations médicales de la biologie synthétique en sont pour le moment au stade de la recherche fondamentale et que les applications cliniques de nouveaux médicaments et de nouvelles méthodes sont encore loin d'être disponibles pour les patients.

Comme décrit au chapitre deux du présent avis, le GEE indique que les applications médicales de la biologie synthétique ne peuvent pas enfreindre le cadre des droits fondamentaux et de l'éthique précédemment établi et doivent être soumises à des dispositions strictes en matière de biosécurité. Pour les produits actuellement envisagés, le cadre réglementaire existant régit dans l'ensemble de manière appropriée l'utilisation de la biologie synthétique et doit être appliqué.

Recommandation n° 8: Le GEE recommande que, outre l'application de cadres scientifiques et juridiques, des considérations éthiques spécifiques soient également prises en compte par les autorités compétentes (telles que l'EMEA([13])) lorsque paraîtront des médicaments et des produits médicaux résultant de protocoles fondés sur la biologie synthétique. Les données concernant les applications médicales de la biologie synthétique mises en pratique dans les États membres de l'UE ou résultant de financements de l'UE devraient être collectées par des organes compétents dans les pays

([13]) Comme l'exige la législation européenne, les produits médicaux provenant de la biologie synthétique seront évalués du point de vue de la sécurité. Les autorités compétentes des États membres et de l'UE (EMEA) devraient s'assurer que les considérations en matière de sécurité exprimées dans le présent avis soient prises en compte avant toute procédure d'autorisation d'essais cliniques et de recherche et toute procédure de commercialisation.

où ces essais ont lieu et devraient être rendues disponibles au niveau international.

4.3. Biosécurité, prévention du bioterrorisme et doubles usages

S'agissant de biosécurité, le GEE est conscient des utilisations et abus possibles de la biologie synthétique ainsi que de la recherche actuelle dans l'UE et aux États-Unis dans ce secteur spécifique. La biologie synthétique peut permettre la conception de nouveaux outils pouvant être utilisés à des fins militaires, qu'il s'agisse de biomatériaux ou d'armes biologiques. L'analyse éthique doit mettre en balance l'objectif de sécurité et le besoin de transparence:

- la production et l'utilisation possible de matériaux ou de systèmes provenant de la biologie synthétique dans les politiques nationales de sécurité, y compris la production d'armes biologiques. Ces utilisations doivent avoir lieu dans le respect des cadres réglementaires nationaux et internationaux actuels. La transparence et la diffusion d'informations peuvent favoriser les abus à des fins terroristes, mais une société ouverte doit trouver des façons de gérer le difficile équilibre entre le droit à l'information des citoyens et la nécessité d'assurer leur sécurité;

- la production et l'utilisation possible de matériaux ou de systèmes provenant de la biologie synthétique à des fins terroristes, en particulier la production de systèmes biologiques qui présentent un fort potentiel de destruction. Il convient de s'attaquer à tout usage impropre des connaissances en biologie synthétique;

- la production d'organismes synthétique en dehors des institutions reconnues. Étant donné que les matériaux et les procédures en matière de biologie synthétique sont à la disposition du grand public, la génétique libre constitue un autre scénario exigeant une gouvernance en matière de sécurité.

Le GEE prend également note de la récente communication adoptée par la Commission européenne le 24 juin 2009 ([14]), qui définit la nouvelle politique de l'UE dans le domaine chimique, biologique, radiologique ou nucléaire (CBRN). S'il considère cette initiative comme louable, elle n'est toutefois selon lui pas encore suffisante dans l'optique d'une approche saine et démocratique, d'un point de vue éthique, de la biosécurité au sein de l'UE et au delà. Le GEE se félicite de l'intégration des préoccupations éthiques dans la formation des scientifiques spécialisés dans la biosécurité, y compris d'actions spécifiques visant à clarifier la dimension éthique des utilisations de la biologie synthétique en matière de biosécurité.

S'agissant des applications de biologie synthétique, toutefois, des informations concernant la fabrication de virus de synthèse, par exemple, pourraient provoquer une nouvelle vague de bioterrorisme. Rares ont été les débats sur la manière de gérer ce risque. Il convient de protéger la santé des civils et des militaires, de garantir une transparence aussi poussée que possible et de permettre la recherche uniquement dans le cadre d'un encadrement strict. Comme décrit au chapitre trois du présent avis, le GEE soutient que les applications de la biologie synthétique à des fins militaires et de sécurité ne doivent pas enfreindre le cadre de l'éthique et des droits fondamentaux établi dans le présent avis. La tâche de prévention d'usages terroristes et/ou malveillants de la biologie synthétique place les chercheurs comme les États démocratiques devant le dilemme moral du double usage. La dualité de certains objectifs, intentionnelle ou non, peut être prévue, mais pas dans tous les cas. Une façon de traiter le dilemme du double usage passe par les mécanismes de contrôle tels que le brevetage et l'enregistrement des outils utilisés par la biologie synthétique.

Parmi les exemples de mesures envisageables pour prévenir toute action militaire ou terroriste inacceptable figurent: 1) l'établissement, au niveau européen au moins, mais de préférence au niveau international, d'une base de données centralisée dans laquelle les autorités compétentes enregistreraient tous les synthétiseurs d'ADN; 2) l'inscription dans le registre susmentionné des départements ou groupes de recherche travaillant sur l'utilisation de la biologie synthétique dans les domaines de la biosécurité ou de la biodéfense; 3) la définition, au niveau des États membres et de l'UE, de critères de publication des données concernant les virus ou les agents toxiques hautement pathogènes ([15])

([14]) COM(2009) 273 final; SEC(2009) 874; SEC(2009) 790; SEC(2009) 791

([15]) En matière d'organismes génétiquement modifiés, y compris ceux produits grâce aux techniques de la biologie synthétique, des réglementations sont en vigueur en Europe, qui exigent un enregistrement et/ou une approbation des

Il convient en outre d'envisager les questions éthiques soulevées par le risque de double usage sous un angle pédagogique. Il est crucial de responsabiliser les individus et les institutions en suscitant le débat sur l'éthique de la biologie synthétique.

Recommandation n° 9: Le GEE recommande d'intégrer des dispositions sur la limitation ou l'interdiction de la recherche en biologie synthétique dans la convention sur l'interdiction de la mise au point, de la fabrication et du stockage des armes bactériologiques (biologiques) ou à toxines et sur leur destruction.

Recommandation n° 10: Le GEE demande à la Commission de définir, en concertation avec lui, un cadre éthique et de sécurité complet en matière de biologie synthétique.

Recommandation n° 11: Le GEE recommande que la Commission européenne

1) *garantisse que les bases de données sont accessibles à tous leurs utilisateurs;*

2) *fournisse aux entreprises les systèmes juridiques leur permettant de faire rapport aux autorités compétentes lorsque ces entreprises sont chargées de synthétiser des séquences suspectes, tout en garantissant la confidentialité; 3) détermine la chaîne des responsabilités pour l'intégration de séquences particulières dans la (les) base(s) de données et leur identification comme potentiellement nocives.*

4.4. Gouvernance

Le GEE préconise également que lorsqu'il est prévu d'utiliser une technologie dans l'UE, il convient d'en étudier soigneusement ses effets et de les soumettre à une évaluation d'impact qui inclue à la fois les risques et les profits des technologies nouvelles et ceux des technologies remplacées. Cette évaluation devrait prendre place dans le contexte de l'approche intégrée de la biologie synthétique qui tient compte des implications tant environnementales que sociales. Outre la gouvernance du risque technologique, il convient de mettre en place une stratégie plus large et mieux à même, par rapport aux instruments actuels, de s'adapter aux changements qui pourraient affecter l'environnement, les sociétés, les économies de marché ou les politiques nationales. L'éthique de la biologie synthétique devrait étudier au cas par cas les bénéfices et les dangers de cette technologie pour certains milieux écologiques ainsi que les risques et les bénéfices éventuels pour l'ensemble de la biosphère. ([16])

Une utilisation responsable de la biologie synthétique devrait impliquer l'utilisation d'outils de gouvernance visant à encourager les avancées scientifiques et les applications de la recherche qui pourraient être bénéfiques à la santé humaine, ainsi qu'à contribuer aux économies d'énergie et à la réduction des effets négatifs du changement climatique tout en prévenant les abus de la biologie synthétique, à savoir le bioterrorisme, et en préservant la biosécurité et la biosûreté. Il ne s'agit pas d'une sinécure et cette tâche pose un certain nombre de questions auxquelles l'UE doit répondre.

a) Questions d'ordre général: comment les outils de gouvernance peuvent-ils

– encourager l'utilisation à des fins bénéfiques et prévenir les abus? Quand y a-t-il risque de double usage?

– encourager la transparence sans créer les conditions favorables aux abus?

– protéger contre les abus sans introduire une censure non souhaitée des publications et autres?

b) Défis spécifiques de gouvernance: comment l'UE peut-elle utiliser les outils de gouvernance afin de

• tenir compte du fait que la biologie synthétique consiste en un grand nombre de domaines comprenant des niveaux et une densité de réglementation très variés et déceler les lacunes éventuelles dans la préservation de la biosécurité et de la biosûreté?

infrastructures où ces organismes peuvent être cultivés et étudiés. Cf. également la page 40 du présent avis et l'article 7 de la directive 98/81/CE du Conseil.

([16]) Cf. Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno, «SYNBIOSAFE e-conference: online community discussion on the societal aspects of synthetic biology», in: Systems and Synthetic Biology (16 septembre 2008). Accessible en ligne à l'adresse suivante: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf
Paul Rabinow & Gaymon Bennett, From Bio-Ethics to Human Practice. Working Paper no 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf.

- déterminer les domaines où des normes juridiques non contraignantes offriront une protection suffisante et ceux où une législation contraignante est jugée nécessaire (cf. recommandation n° 2 sur la réglementation en matière de biosécurité et la recommandation n° 9 sur la convention sur les armes biologiques)?

- encourager les responsabilités professionnelles pour les chercheurs individuels et les institutions (y compris les scientifiques qui ne sont pas nécessairement habitués à travailler avec des organismes vivants et les problèmes spécifiques que cela implique) et compléter le code de conduite proposé dans la recommandation n° 3?

- jouer un rôle dans la recherche nécessaire d'une gouvernance mondiale en matière de biologie synthétique?

Le GEE exprime ses préoccupations quant à l'actuel cadre réglementaire fragmenté, qui pourrait ne pas être suffisant pour réglementer de manière appropriée les aspects actuels et à venir de la biologie synthétique. Il insiste également sur la nécessité d'examiner la mise en place d'un modèle approprié de gouvernance en matière de biologie synthétique (normes juridiques non contraignantes, codes de conduite, etc.), en tenant compte aussi des risques de délocalisation des essais de recherche dans des pays où la réglementation pourrait être moins contraignante que celle en vigueur dans l'UE.

Recommandation n° 13: Le GEE recommande vivement à la Commission de proposer un solide cadre de gouvernance pour la biologie synthétique et de le mettre en place au niveau de l'UE. La Commission devrait réviser la législation applicable à la biologie synthétique et évaluer sa pertinence par rapport aux questions soulevées par la biologie synthétique. Le cadre susmentionné devrait prendre en compte les parties prenantes concernées (scientifiques, industries, agents militaires, politiques et administratifs) et indiquer clairement leurs responsabilités.

Recommandation n° 14: Les communautés scientifiques concernées devraient être encouragées à établir des lignes directrices éthiques, de préférence au niveau mondial, qui pourraient faire office de points de repère et inciter les institutions scientifiques et les chercheurs individuels à évaluer l'incidence de leur travail, y compris les conséquences d'abus éventuels ([17]).

Recommandation n° 15: Le GEE propose que l'UE soulève la question de la gouvernance de la biologie synthétique au sein de forums mondiaux consacrés à ce sujet.

4.5. Propriété intellectuelle

4.5.1. Brevetage et patrimoine commun

Les questions soulevées par le brevetage des méthodes et des matériaux biologiques font l'objet de vifs débats depuis quelque temps et sont maintenant à l'ordre du jour de discussions dans différentes disciplines. Le fait que les brevets remplissent une fonction de stimulation de la recherche et de ses applications concrètes ainsi qu'une fonction de promotion de la diffusion au grand public de la base des applications peut être remis en question par l'énorme quantité de demandes de brevets relatifs au matériel génétique et aux méthodes biologiques. Parallèlement, l'appropriation d'éléments d'organismes biologiques par des acteurs industriels spécifiques a également soulevé un certain nombre de questions éthiques. L'article 7 de la directive sur les brevets concernant les inventions biotechnologiques dispose que «le groupe européen d'éthique des sciences et des nouvelles technologies de la Commission évalue tous les aspects éthiques liés à la biotechnologie». C'est le seul article de la directive qui n'ait pas été appliqué dans la réglementation mettant en œuvre cette directive de l'Office européen des brevets ou des offices des brevets des différents États membres. Il est difficile à appliquer étant donné qu'il ne précise aucune action et qu'aucun autre article ne reprend sa teneur. Les différents offices nationaux des brevets se sont souvent plaints de ce que les clauses morales du droit européen des brevets sont difficiles à interpréter (allant même jusqu'à proposer qu'elles soient abordées par une autre législation). Le GEE propose que, lorsqu'une demande de brevet soulève une question d'ordre général dans le domaine de la biotechnologie (y compris la nanotechnologie et la biologie synthétique), les offices des brevets concernés demandent l'avis du GEE dans le domaine général concerné par le brevet déposé.

([17]) Cf. les principes éthiques du programme MOST de l'Unesco pour une recherche internationale et comparative des sciences sociales.

S'agissant de la question du brevetage et du patrimoine commun, le GEE reconnaît la complexité du sujet, comme le signale déjà l'annexe I du présent avis. Le GEE souligne que les questions éthiques générales soulevées par les demandes de brevet doivent être traitées de manière adéquate dans le cadre du système de délivrance des brevets.

Recommandation n° 16: Le GEE propose que soient lancés des débats sur les façons les plus appropriées de garantir l'accès du public aux résultats de la biologie synthétique. Ces débats devraient également porter sur ce qui peut faire l'objet d'un brevet et sur ce qui devrait relever du domaine public.

Recommandation n° 17: Conformément à la directive européenne sur les brevets (98/44/CE), l'organe chargé d'évaluer les implications éthiques des brevets est le GEE. Ce dernier recommande vivement à l'Office européen des brevets et aux offices des brevets des différents États membres de tenir compte de l'article 7 de la directive sur les brevets et de rapporter les questions éthiques controversées d'ordre général au GEE afin que celui-ci les examine. Ce point est particulièrement important lorsqu'il s'agit de définir une classe d'inventions qui ne devrait pas être directement exploitée commercialement ([18]).

4.5.2. Commerce et justice mondiale

Le GEE est conscient de la dimension mondiale de la biologie synthétique et de ses applications et considère le développement économique et la croissance du bien-être social comme un objectif positif de l'UE. La biologie synthétique peut contribuer à la prospérité socio-économique de l'UE et au-delà. Le GEE se félicite de cette possibilité, pour autant que ce secteur technologique et le commerce de ses produits ne portent pas atteinte aux principes de la Charte européenne des droits fondamentaux ni aux principales valeurs fondamentales de l'UE. C'est pourquoi le GEE se préoccupe des risques possibles d'une fracture technologique au sein de l'UE et entre les pays développés et moins développés.

Le GEE recommande l'intégration des valeurs fondamentales de l'UE dans le commerce mondial des produits issus de la biologie synthétique. Tout comme dans ses avis précédents (tels que les avis 23 ([19]) et 24 ([20])), il souligne la nécessité d'introduire des considérations éthiques dans le commerce mondial et dans les actions de l'Organisation mondiale du commerce.

Il conviendrait dès lors de prendre des mesures visant à éviter l'accentuation de la fracture technologique. Si des essais impliquant des produits issus de la biologie synthétique sont menés dans les pays en développement et émergents, il convient d'appliquer les mêmes normes éthiques que celles en vigueur au sein de l'UE ([21]). Les objectifs du millénaire pour le développement des Nations unies devraient être mis en œuvre.

Recommandation n° 18: Le GEE recommande que lorsque la biologie synthétique fera l'objet de discussions au niveau international, y compris au sein de l'OMC, les questions éthiques associées à cette technologie ([22]) soient abordées. Ce point devrait être pris en considération lors des négociations du cycle de Doha.

Recommandation n° 19: Le GEE recommande vivement que les normes européennes de biosécurité pour les produits issus de la biologie synthétique, telles que définies dans les recommandations n° 1, 2 et 5 du présent avis, soient adoptées au titre de normes minimales pour les importations et exportations européennes de produits issus de la biologie synthétique.

Recommandation n° 20: Le GEE recommande que l'UE prenne des mesures spécifiques afin d'éviter de nouvelles fractures entre l'UE et les pays en développement et émergents, ou au sein des États membres de l'UE,

([18]) L'article 6, paragraphe 2, de la directive 98/44/CE fournit une liste indicative des procédés exclus du brevetage, à savoir: «a) les procédés de clonage des êtres humains; b) les procédés de modification de l'identité génétique germinale de l'être humain; c) les utilisations d'embryons humains à des fins industrielles ou commerciales; d) les procédés de modification de l'identité génétique des animaux de nature à provoquer chez eux des souffrances sans utilité médicale substantielle pour l'homme ou l'animal, ainsi que les animaux issus de tels procédés.» L'article 7 dispose également que «le groupe européen d'éthique des sciences et des nouvelles technologies de la Commission évalue tous les aspects éthiques liés à la biotechnologie.»

([19]) http://ec.europa.eu/european_group_ethics/activities/docs/opinion23_en.pdf

([20]) http://ec.europa.eu/european_group_ethics/docs/opinion24_en.pdf

([21]) http://ec.europa.eu/european_group_ethics/docs/avis17_en.pdf

([22]) Cf. chapitres 2.2.b et 2.2.c du présent avis.

et afin de mettre en application les recommandations formulées dans le présent avis. De telles mesures devraient être introduites dans les programmes scientifiques bilatéraux et multilatéraux de l'UE et dans les politiques de l'UE concernant les pays en développement et émergents.

4.6. Dialogue entre la science et la société civile

Comme développé dans le chapitre 3 du présent avis, la problématique éthique de la biologie synthétique est complexe et les questions conceptuelles mises au jour appellent à un dialogue efficace entre la science et la société civile.

La perception de la biologie synthétique est influencée par des considérations sociales, culturelles et éthiques portant sur la manipulation de la vie, les implications économiques pour les régions développées et en développement, les questions relatives à la propriété et à la propriété intellectuelle, les préoccupations à propos de la dégradation de l'environnement et des risques d'utilisations militaires, etc. Les médias traditionnels et interactifs jouent un rôle important dans la représentation que les gens se font des technologies nouvelles et émergentes, y compris de la biologie synthétique. Chacune de ces questions mérite une considération et une participation publique approfondies. Ce point soulève plus largement la question de la confiance à établir entre la communauté scientifique et le grand public, y compris la nécessité de promouvoir un débat approprié. Enfin, cet aspect conduit à aborder des questions relatives à la démocratie délibérative, y compris la question de savoir qui trace les limites entre ce qui est permis, acceptable, et ce qui ne l'est pas, et qui contrôle ceux qui tracent ces limites.

Les spécialistes des sciences sociales ont suggéré qu'un engagement en amont pourrait favoriser un développement scientifique et technologique qui soit cohérent avec les attentes, les préoccupations et les souhaits de la société ([23]). De nombreux scientifiques travaillant dans le domaine de la biologie synthétique sont déjà conscients de l'importance de l'engagement public et, dans cette optique, se sont impliqués dans des activités telles que des débats, des balados et des blogs.

([23]) http://www.bbsrc.ac.uk/organisation/policies/reviews/scientific_areas/0806_synthetic_biology.pdf

Le débat public doit être alimenté par des informations correctes sur les caractéristiques effectives et les potentialités de la biologie synthétique, ce qui pourrait soulever des difficultés de définition, d'évaluation et de gestion des risques dans un domaine où les incertitudes et les lacunes des connaissances sont considérables et où les risques à court et long terme peuvent être différents. Des considérations similaires s'appliquent aux conséquences des «battages» auxquels le public est confronté, à travers les médias et les écrivains de science-fiction qui élaborent des scénarios irréalistes à propos de produits issus de la biologie synthétique (par exemple, le battage au sujet de la possibilité de guérir toutes les maladies ou de la bioréhabilitation pour lutter contre la pollution de l'environnement, ou encore des perspectives dans le cadre de la crise énergétique). La diffusion au grand public d'espoirs ou de craintes nourris par des informations non documentées fausse le débat public sur la biologie synthétique.

Recommandation n° 21: Le GEE demande à l'UE et à ses États membres de prendre des mesures pour promouvoir les débats publics entre parties prenantes ainsi que leur participation afin de cerner les principales préoccupations de la société dans les différents domaines concernés par la biologie synthétique.

Recommandation n° 22: Le GEE recommande que les journalistes, les éditeurs, y compris les éditeurs de publications scientifiques, et les autres parties prenantes promeuvent une couverture responsable des sujets touchant à la biologie synthétique.

Recommandation n° 23: Afin de promouvoir une approche exhaustive des nouvelles technologies par les médias, le GEE demande à la Commission de favoriser des actions spécifiques telles que, par exemple, la création de forums, de séminaires et de cours abordant les implications de la biologie synthétique dans les médias.

4.7. Recherche

Depuis un certain temps, on observe que la recherche fondamentale, à la base de toutes les différentes applications dans un domaine donné, a été reléguée au second plan dans les programmes de financement de la recherche. Même si la recherche fondamentale ne doit pas être rigoureusement séparée de la recherche appliquée, elle a besoin d'un financement public qui devrait s'inscrire au cœur de la politique de l'UE.

La biologie synthétique a introduit dans la méthode scientifique de la biologie moderne un élément nouveau capital: la possibilité non seulement de se servir de démarches déductives fondées sur des phénomènes observés, mais aussi de synthétiser des outils heuristiques permettant en eux-mêmes d'explorer des phénomènes biologiques de base. Cependant, la recherche fondamentale en biologie synthétique n'est pas nécessairement liée directement aux intérêts commerciaux et industriels et dépend dès lors des financements publics. Le GEE s'inquiète de ce que cette absence de lien direct n'entraîne un manque de financement adéquat de la recherche fondamentale dans un proche avenir et que cela ne compromette le rôle que la recherche européenne pourrait jouer dans la gouvernance mondiale de la biologie synthétique.

Parallèlement, le débat éthique à propos de la biologie synthétique aborde des questions relatives à la légitimité éthique de la fabrication d'organismes vivants, tout comme pour le débat sur l'ingénierie du vivant. L'intervention de l'homme dans la nature, qui comprend l'environnement et d'autres organismes vivants, soulève également des questions à propos du «caractère naturel» de cette intervention et de la «fabrication du vivant» ([24]). Le GEE souligne dès lors la nécessité de financer au niveau de l'UE des projets de recherche interdisciplinaire sur la relation entre les humains et la nature, en particulier par rapport aux questions concernant le vivant.

Recommandation n° 24: Le GEE invite la Commission à soutenir la recherche fondamentale dans les domaines de la biologie, de la chimie, de l'énergie et de la science et de l'ingénierie des matériaux, ainsi que la recherche appliquée, telles que définies dans le présent avis. Ce soutien devrait se refléter dans le budget alloué aux programmes-cadres de recherche et de développement de l'UE. Une invitation semblable est adressée aux États membres de l'UE à propos de leurs programmes de recherche et de développement nationaux.

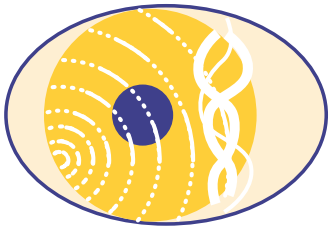
Recommandation n° 25: Le GEE demande à l'UE de financer de manière appropriée la recherche interdisciplinaire portant sur les aspects suivants de la biologie synthétique:

- *évaluation des risques et sécurité,*
- *utilisations de la biologie synthétique à des fins de sécurité,*
- *implications éthiques, juridiques et sociales,*
- *gouvernance;*
- *science et société (y compris les médias et le public).*

Ce soutien devrait se refléter dans le budget alloué aux programmes-cadres de recherche et de développement de l'UE. Une invitation semblable est adressée aux États membres de l'UE à propos de leurs programmes de recherche et de développement nationaux.

Recommandation n° 26: Le GEE note que la biologie synthétique pourrait entraîner, à l'avenir, un changement de paradigme dans la compréhension du vivant. C'est pourquoi il invite la Commission à mettre sur pied un forum interculturel et ouvert où ces questions pourront être abordées et qui accordera également une place aux aspects philosophiques et religieux.

([24]) John Harris, «Who's Afraid of a Synthetic Human?», *The Times*, 17 mai 2008. Colin Nickerson, «A Quest to Create Life Out of Synthetics», *Boston Globe*, 2 avril 2008. Erik Parens, «Making Cells Like Computers», *Boston Globe*, 18 février 2008. Natalie Angier, «Pursuing Synthetic Life, Dazzled by Reality», *New York Times*, 5 février 2008.



Europäische Gruppe
für Ethik in Naturwissenschaften
und neuen Technologien
bei der Europäischen Kommission

STELLUNGNAHME DER EUROPÄISCHEN
GRUPPE FÜR ETHIK
IN NATURWISSENSCHAFTEN
UND NEUEN TECHNOLOGIEN
BEI DER EUROPÄISCHEN KOMMISSION

Ethik der synthetischen Biologie

Bezug: Ersuchen von **Präsident Barroso**

Berichterstatter: **Rafael Capurro**, **Julian Kinderlerer**, **Paula Martinho da Silva** und **Pere Puigdomenech Rosell**

Nur der Originaltext auf Englisch ist authentisch.

Nr.
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4. Empfehlungen

4.1. Definition der Terminologie und Umfang der Stellungnahme

Wie bereits im ersten Abschnitt der Stellungnahme beschrieben, ist synthetische Biologie ein neues Forschungsfeld, das sich daraus ergibt, dass hier verschiedene technologische und wissenschaftliche Disziplinen zusammenlaufen und das für ein besseres Verständnis der biologischen Systeme, ihrer Vielschichtigkeit und der sich neu herausbildenden Eigenschaften sorgt, die sich aus der Wechselwirkung komplexer Wege ergeben. Zugleich bietet die synthetische Biologie die Möglichkeit der Herstellung von biologischen Erzeugnissen, die unmittelbar in einer Vielzahl von Sektoren wie Bio-Medikamente, Biokraftstoffe, Rohstoffe oder biomedizinische Werkzeuge, wie etwa Impfstoffe oder auch neue biologische Abwehrstoffe, zum Einsatz gelangen. Die Gruppe erkennt an, dass es schwierig ist, bereits eingeführte Praktiken in der biologischen Forschung und den neuen, der synthetischen Biologie zugrunde liegenden Ansatz genau gegeneinander abzugrenzen. Nichtsdestoweniger lässt sich ein schrittweiser Übergang von der Veränderung biologischer Systeme hin zu ihrer Entwicklung feststellen, von der Entwicklung einfacher Systeme hin zur Konstruktion komplexer Systeme und von der Anpassung natürlicher biologischer Systeme hin zur Auslegung bzw. Konstruktion von teilweise oder komplett künstlichen biologischen Systemen.

Bislang gibt es noch keine international vereinbarte Definition dieses Forschungsbereichs, was im Hinblick auf den wissenschaftlichen Rahmen und das Regelwerk für die unterschiedliche Nutzung der synthetischen Biologie Verwirrung stiften könnte. Eine international anerkannte Definition der synthetischen Biologie ist daher insbesondere dann erforderlich, wenn die Forschung und die Anwendungen in diesem Bereich einer Regelung bedürfen.

Der Begriff „synthetische Biologie" umfasst nach dem Verständnis der Gruppe ([1]) mindestens folgende Aspekte: 1.) das Design von Minimalzellen bzw. -organismen ([2]) (einschließlich Minimalgenome), 2.) die Beschreibung und Verwendung von „bioparts" (Werkzeugkasten) und 3.) die Konstruktion von teilweise oder komplett künstlichen biologischen Systemen.

Ein spezielles Anliegen sind die potenziellen Anwendungen in den Bereichen Biomedizin, Biopharmaka, chemische Industrie, Umwelt und Energie, die Erzeugung von intelligenten Materialien und von Biomaterialien, und zwar insbesondere (wenngleich nicht ausschließlich) unter dem Aspekt der Sicherheit (*safety*) und des Ausschlusses eines möglichen Missbrauchs (*security*). ([3]) Darüber hinaus erstreckt sich die Debatte auf Aspekte der Gerechtigkeit, der „Governance", der Wissenschaft, des gesellschaftlichen Dialogs und des geistigen Eigentums sowie auf philosophische Diskussionen über das Leben ([4]) (siehe Abschnitte 3.1 und 3.2). Im Hinblick auf weitere neue Technologien muss die synthetische Biologie im Einklang mit dem internationalen Rahmen für Ethik und Menschenrechte (siehe Abschnitt 2.3 dieser Stellungnahme) und insbesondere mit dem Gebot der Achtung der Würde des Menschen stehen, die nicht nur als Grundrecht an sich verstanden wird, sondern „das eigentliche Fundament der Grundrechte" bildet ([5]).

Weitere ethische Grundsätze, die in diesem Zusammenhang berücksichtigt werden müssen, sind unter anderem der *Sicherheitsgrundsatz*, der Grundsatz der *Nachhaltigkeit*, das Prinzip der *Gerechtigkeit*, das *Vorsorgeprinzip*, das Prinzip *der Freiheit der Forschung* sowie der Grundsatz der *Verhältnismäßigkeit* ([6]).

([1]) Siehe Abschnitt 1.3 der Stellungnahme.

([2]) Unter dem Begriff „Organismus" werden in diesem Zusammenhang azellulare, einzellige oder mehrzellige biologische Einheiten verstanden, die verstärkt oder verändert werden können.

([3]) Siehe Andrew Balmer & Paul Martin: Synthetic Biology. Social and Ethical Challenges. Mai 2008. http://www.bbsrc.ac.uk/publications/corporate/synthetic_biology.pdf .

([4]) Siehe Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno: SYNBIOSAFE e-conference: online community discussion on the societal aspects der synthetischen Biologie. In: Systems and Synthetic Biology 16. September (2008). Online: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf.
Paul Rabinow & Gaymon Bennett: From Bio-Ethics to Human Practice. Working Paper # 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf.

([5]) Erklärung zu den Erläuterungen zur Charta der Grundrechte.

([6]) Demzufolge (1) müssen Ziel oder Zweck der Forschung von Belang sein; (2) müssen die angewandten Methoden für die Erreichung der Zielvorgaben erforderlich sein; und (3) gibt es keine anderen, weniger umstrittenen oder gefährlichen Methoden, die zur Erreichung desselben Ziels angewandt werden könnten.

4.2. Sicherheit

Im Umgang mit ethischen Fragen, die von der synthetischen Biologie aufgeworfen werden, lautet ein grundsätzliches Postulat, dass in der Forschung ebenso wie im Hinblick auf die Anwendungsmöglichkeiten die menschliche Gesundheit ebenso wenig gefährdet werden darf wie die Umwelt. Diesbezüglich ist Sicherheit eine Grundvoraussetzung für die Nutzung der synthetischen Biologie in jedweder Hinsicht. Viele sicherheitsrelevante Fragen in Bezug auf die synthetische Biologie wurden bereits vor dreißig Jahren auf der Sitzung zum Thema rekombinante DNA im Asilomar Conference Centre in Pacific Grove, Kalifornien, diskutiert, was eine Debatte über die ethischen Aspekte der neu entstehenden Technologien auf der Grundlage von DNA auslöste, in deren Mittelpunkt insbesondere die Sicherheit des Transfers von Genen von einem Organismus zu einem anderen über einen Vektor wie etwa ein Virus oder ein Plasmid stand. Derzeit gibt es in der EU Rechtsvorschriften zur biologischen Sicherheit einschließlich von Rechtsvorschriften zum Schutz der Gesundheit von Mensch und Tier oder von Menschen, die biologischen Stoffen und anderen Gefahrstoffen ausgesetzt sind. Die Frage lautet, ob der vorstehend beschriebene Rahmen den besonderen Merkmalen der synthetischen Biologie tatsächlich uneingeschränkt gerecht wird.

Betrachtet man die Frage unter sicherheitsrelevanten Aspekten, so ergeben sich aus der synthetischen Biologie eine Reihe von Fragen, unter anderem, wie die Sicherheit von Organismen bewertet werden kann, die ein Genom beinhalten, das anhand von rekombinanten DNA-Verfahren gewonnen wurde, und die Erzeugung von Systemen ermöglichen, bei denen Bestandteile aus einer Vielzahl von Quellen miteinander kombiniert werden. Wie solche Konstruktionen für die biologische Sicherheit von Organismen bewertet werden sollen, die möglicherweise Gene oder Proteine enthalten, die noch niemals zusammen in einem biologischen Organismus existiert haben, oder die neu konstruierte biologische Funktionen umfassen, die in der Natur gar nicht vorkommen, ist nach wie vor unklar.

Anlass zur Besorgnis bieten aber auch die unbekannten Risiken für die Umwelt und die öffentliche Gesundheit, die durch unerwartete Wechselwirkungen zwischen synthetischen Mikroorganismen und der Umwelt oder anderen in der Umwelt vorkommenden Organismen ausgelöst werden. Ein horizontaler Gentransfer und dessen potenzielle Auswirkungen auf das Gleichgewicht der Ökosysteme oder auch die Wechselwirkung zwischen synthetischen Mikroorganismen und in der Natur vorkommenden Stoffen oder auch die unvorhergesehene Entwicklung synthetischer biologischer Substanzen sind allesamt Risiken, die sich aus einer unkontrollierten Nutzung von Stoffen der synthetischen Biologie oder aus dem unbeabsichtigten Vorkommen von Organismen in der Umwelt ergeben können.

Die Bedenken im Zusammenhang mit der Biosicherheit wirken sich auch auf die Methoden der Risikobewertung aus, die in der EU im Zusammenhang mit der Biologie entwickelt wurden. Die Methoden zur Bewertung genetisch veränderter Organismen (GVO) beruhen auf einem Vergleich des veränderten Organismus mit den natürlichen Organismen, die ihnen als „Vorbilder" dienen, wobei jedes einzelne der eingebrachten Merkmale genau geprüft wird ([7]). Die synthetische Biologie wird Organismen hervorbringen, die sich durch eine Vielfalt von Merkmalen von vielen verschiedenen Organismen auszeichnen und deren Eigenschaften sich daher nur schwer vorhersagen lassen.

Die Biosicherheit von Erzeugnissen der synthetischen Biologie ist ein Thema, das von Wissenschaftlern und Entscheidungsträgern heftig diskutiert wird. Einige Wissenschaftler haben sogar vorgeschlagen, alle Forschungsprotokolle der synthetischen Biologie von Labors der Biosicherheitsstufe P3 oder P4 erstellen zu lassen, solange keine eindeutigen Daten zur Biosicherheit vorliegen, was mit klaren Folgen für die weitere Entwicklung dieses Gebiets der Wissenschaft verbunden ist.

Die Gruppe ist der Auffassung, dass Überlegungen zur Biosicherheit unabdingbare Voraussetzungen für die Förderung und Umsetzung eines EU-Forschungsprogramms im Bereich der synthetischen Biologie auf nationaler wie internationaler Ebene sind.

Empfehlung Nr. 1: Die Gruppe empfiehlt, dass der Einsatz der synthetischen Biologie von bestimmten Sicherheitsfragen abhängig gemacht wird, die in dieser Stellungnahme näher ausgeführt werden. Daher ersucht die Gruppe

([7]) Siehe Methoden zur Risikobewertung, die in der Stellungnahme der Europäischen Gruppe für Ethik der Naturwissenschaften und der Neuen Technologien (EGE) zu ethischen Aspekten der Nanomedizin diskutiert werden.

1) die Kommission, eine Studie zu den derzeit bestehenden Verfahren zur Risikobewertung in der EU zu veranlassen. Die Studie sollte (a) eine Erhebung wichtiger Biosicherheitsverfahren durchführen, (b) mögliche Lücken in der derzeit geltenden Verordnung über Biosicherheit für eine effiziente Bewertung von im Rahmen der synthetischen Biologie entwickelten Organismen und neuartigen Produkten aufdecken; (c) die Mechanismen zur Schließung der aufgedeckten Lücken aufzeigen.

2) Das beschriebene Verfahren zur Risikobewertung sollte anschließend von den zuständigen Behörden in der EU (z. B. Europäische Kommission, EMEA und EFSA) und den nationalen Behörden durchgeführt werden.

3) Die Finanzierung der Forschung im Bereich der synthetischen Biologie und die Vermarktung von Produkten der synthetischen Biologie in der EU sollten an diese Bedingung geknüpft werden.

Empfehlung Nr. 2: Die Gruppe schlägt vor, dass die Kommission nach der Definition der vorstehend genannten Vorschriften für die Biosicherheit eine internationale Debatte mit den entsprechenden Ansprechpartnern anstößt, damit ein einheitliches Konzept im Bereich der Biosicherheit der synthetischen Biologie für öffentlich und privat finanzierte Versuche gefördert wird. Instrumente zur Überwachung der Umsetzung dieser Vorschriften sollten als fester Bestandteil der Vorschriften zur Biosicherheit konzipiert werden (einschließlich von Haftungsfragen).

Empfehlung Nr. 3: Die Gruppe setzt sich dafür ein, dass die Kommission einen Verhaltenskodex für die Forschung im Bereich synthetischer Mikroorganismen erstellt. Dieser Kodex sollte beispielsweise gewährleisten, dass Organismen der synthetischen Biologie so hergestellt werden, dass sie im Fall einer unbeabsichtigten Freisetzung in die Natur nicht selbständig überleben können.

4.2.1. Anwendungsmöglichkeiten im Bereich Umweltschutz

Die Gruppe ist sich dessen bewusst, dass es für die synthetische Biologie auch potenzielle Anwendungsmöglichkeiten im Bereich Umweltschutz gibt. Die Gruppe erkennt an, dass die derzeitige Forschung im Bereich der synthetischen Biologie beispielsweise zum Abbau von Umweltschadstoffen (biologische Sanierung) beitragen kann, etwa von Schwermetallen, Pestiziden und radioaktiven Stoffen. Die Gruppe ist sich dessen bewusst, dass die derzeitige Forschung Stoffe der synthetischen Biologie herstellen kann, die in der Lage sind, Pestizide abzubauen, um die dadurch verursachte Umweltbelastung zu verringern ([8]), oder auch Biosensoren für verunreinigtes Wasser ([9]). Die Gruppe erklärt, dass die stetige Verbesserung des Umweltschutzes und die Herstellung neuer Werkzeuge zur Erkennung von Umweltbelastungen ein positives Ziel sind und zur Steigerung des Wohlergehens der Menschen und zur Verbesserung des Umweltschutzes beitragen können. Besondere Bedenken ergeben sich jedoch im Hinblick auf die Biosicherheit, wenn Anwendungen der synthetischen Biologie im Bereich Umweltschutz geplant sind und daher zunächst die Sicherheit und Umweltverträglichkeit angemessen bewertet werden müssen, bevor eine Genehmigung zur Freisetzung der Stoffe in die Umwelt erteilt wird.

Bei den Anwendungsmöglichkeiten im Bereich Umweltschutz muss die Erzeugung umweltschonender biologischer Systeme bzw. Organismen im Hinblick auf den Schutz von Arbeitnehmern und Bürgern, die Freiheit der Verbraucher und die Verantwortung einschließlich der Verantwortung für Tiere, Pflanzen und die Umwelt im Allgemeinen analysiert werden.

Empfehlung Nr. 4: Die Gruppe empfiehlt, dass vor der Freisetzung eines im Rahmen der synthetischen Biologie hergestellten oder modifizierten Organismus in die Umwelt Langzeitstudien zur Umweltverträglichkeit durchgeführt werden müssen. Die Daten aus diesen Studien sollten dann unter Berücksichtigung des Vorsorgeprinzips ([10]) und der in der EU-Rechtsprechung vorgesehenen Maßnahmen (Richtlinie über die absichtliche Freisetzung genetisch veränderter Organismen in die Umwelt) bewertet werden. Fällt die Bewertung negativ aus, sollte keine Genehmigung zur Freisetzung von hergestellten oder modifizierten Organismen erteilt werden.

([8]) Siehe http://pbd.lbl.gov/synthbio/aims.htm.

([9]) In den sich entwickelnden Teilen der Welt wie z. B. Bangladesch stellt die Kontamination des Trinkwassers durch Arsen ein großes Problem dar. Siehe: Aleksic J, Bizzari F, Cai Y *et al.* (2007) Development of a novel biosensor for the detection of arsenic in drinking water *Synthetic Biology*, IET 1: 87–90.

([10]) 2001/18/EG, 98/81/EG und Regelungsrahmen in Abschnitt 2.1 der Stellungnahme.

4.2.2. *Energie und nachhaltige chemische Industrie*

Die Gruppe ist sich dessen bewusst, dass die synthetische Biologie einen Beitrag zur Entwicklung einer nachhaltigen chemischen Industrie leisten könnte, vornehmlich zur Herstellung von Mikroorganismen im Rahmen der synthetischen Biologie mit dem Ziel, Wirkstoffe und Methoden zu ersetzen, die derzeit von der organischen chemischen Industrie für die Herstellung von Rohstoffen eingesetzt werden.

Was die Anwendungsmöglichkeiten der synthetischen Biologie zu *Energiezwecken* anbetrifft, ist sich die Gruppe ebenfalls bewusst, dass das Ziel der Forschung auf dem Gebiet der synthetischen Biologie darin besteht, Bakterien zu entwickeln, die organische Verbindunge ([11]) zur Substitution von Erdöl produzieren, und die Konstruktion von Bakterien zu erforschen, die den Brennstoff Wasserstoff aus alternativen Quellen herstellen ([12]).

Die Gruppe erkennt an, dass diese Möglichkeiten durch die immer knapper werdenden fossilen Energiereserven, die derzeit die Rohstoffe liefern, und durch die Auswirkungen der Verbrennung fossiler Kraftstoffe auf das Klima zunehmend an Bedeutung gewinnen. Die Gruppe hat allerdings Bedenken bezüglich der möglichen Auswirkungen für die Sicherheit und unterbreitet daher folgende Vorschläge:

Empfehlung Nr. 5: Die Gruppe schlägt den Einsatz der synthetischen Biologie für die alternative Energieversorgung in den Mitgliedstaaten ergänzend zum EU-Plan zum Ausbau erneuerbarer Energien und die Förderung und Kofinanzierung internationaler Forschungsversuche (z. B. EU-USA) im Hinblick auf die Förderung eines integrierten internationalen Konzepts vor.

Empfehlung Nr. 6: Die Gruppe empfiehlt, dass die zuständigen Behörden die Genehmigungsverfahren für die Herstellung von Chemikalien und Stoffen aus der synthetischen Biologie, sofern diese nicht mit entsprechenden Stoffen identisch sind, streng überwachen und dabei (a) Faktoren der Risikobewertung und (b) der Sicherheit der Arbeitnehmer, die den im Rahmen der synthetischen Biologie erzeugten Chemikalien ausgesetzt sind, sowie (c) dem Umweltschutz Rechnung tragen.

Was den Einsatz der synthetischen Biologie für *chemische Produkte und neuartige Materialien* anbetrifft, so ist sich die Gruppe dessen bewusst, dass chemische Produkte auf Basis genetisch veränderter Organismen, die nicht als Lebens- oder Futtermittel gedacht sind, nicht speziell als genetisch verändert gekennzeichnet zu werden brauchen. Die Gruppe ist sich dessen bewusst, dass praktisch alle Produkte der synthetischen Biologie, die Organismen enthalten oder Organismen sind oder aus solchen Organismen in Lebens- oder Futtermitteln stammen, als genetisch verändert gekennzeichnet werden müssen. Die Gruppe hat allerdings Bedenken in Bezug auf mögliche Anwendungen der synthetischen Biologie in der Kosmetik- und Textilindustrie.

Empfehlung Nr. 7: Die Gruppe macht geltend, dass der Verbraucherschutz ein Schlüsselfaktor auf dem EU-Markt ist, dem Rechnung getragen werden muss, und betont, dass die Kennzeichnung spezifischer Produkte der synthetischen Biologie, wie Kosmetika und Textilien, untersucht werden sollte.

4.2.3. *Biomedizinische und biopharmazeutische Herstellung*

Die synthetische Biologie bietet auch potenzielle Anwendungsmöglichkeiten in der Medizin, etwa zur Verbesserung und Entwicklung von Biosensoren, Medikamenten, Therapien, Geräten und Zellen mit neuen Eigenschaften, die zur Verbesserung der menschlichen Gesundheit oder therapeutischer Modelle genutzt werden können. Es wird erwartet, dass die synthetische Biologie auch in den Bereichen Arzneimittelherstellung, Entwicklung neuer Impfstoffe, medizinischer Geräte wie Biosensoren, Diagnostika, die Synthese von Viren für Gentherapien sowie potenziell auch im Bereich der Krebstherapien Anwendung findet.

Die Gruppe ist sich bewusst, dass sich die Anwendung der synthetischen Biologie im medizinischen Bereich derzeit noch im Stadium der Grundlagenforschung befindet und dass klinische Anwendungen neuer Medikamente und Methoden noch lange nicht für Patienten zur Verfügung stehen.

([11]) Wie z. B. Fettsäuren, die sich optimal für den Einsatz als Biodiesel eignen, oder andere energiereiche Verbindungen.

([12]) Siehe auch: LS9 (www.ls9.com), Amyris (www.amyris.com), OPX Biotecnologies (www.opxbiotechnologies.com), Solazyme (www.solazyme.com), Gevo (www.gevo.com).

Wie in Abschnitt 2 dieser Stellungnahme beschrieben, macht die Gruppe geltend, dass medizinische Anwendungen der synthetischen Biologie nicht gegen die Grundrechte und den an früherer Stelle bereits genannten Rahmen für Ethik verstoßen dürfen und an die Einhaltung strenger Vorschriften im Bereich der Biosicherheit geknüpft werden müssen. Für die derzeit geplanten Produkte ist der bereits bestehende Regelungsrahmen für eine Regulierung der Nutzung der synthetischen Biologie im Allgemeinen angemessen und muss umgesetzt werden.

Empfehlung Nr. 8: Die Gruppe empfiehlt, dass die zuständigen Behörden (z. B. die EMEA ([13])) neben der Anwendung wissenschaftlicher und rechtlicher Rahmen im Fall von aus den Protokollen der synthetischen Biologie hervorgegangenen Medikamenten und medizinischen Erzeugnissen spezifische ethische Überlegungen anstellen. Daten über medizinische Anwendungen der synthetischen Biologie in den EU-Mitgliedstaaten bzw. Daten aus EU-Finanzierungen sollten von den zuständigen Einrichtungen in den Ländern erhoben werden, in denen Versuche stattfinden, und international zugänglich gemacht werden.

4.3. Biosicherheit, Prävention von Bioterrorismus und Doppelverwendung

Die EGE ist sich der möglichen Nutzung bzw. des möglichen Missbrauchs der synthetischen Biologie in Bezug auf die Biosicherheit und die derzeitige Forschung in diesem speziellen Bereich, die in der EU und den USA betrieben wird, bewusst. Die synthetische Biologie kann die Entwicklung neuer Werkzeuge ermöglichen, die für militärische Zwecke von Biomaterialien bis hin zu biologischen Waffen reichen können. Bei einer Analyse der ethischen Aspekte muss auch für ein ausgewogenes Verhältnis zwischen der Sicherheit und der notwendigen Transparenz gesorgt werden:

- Die Herstellung und potenzielle Verwendung von Materialien oder Systemen der synthetischen Biologie im Rahmen der nationalen Sicherheitspolitik einschließlich der Herstellung von biologischen Waffen. Solche Anwendungsmöglichkeiten müssen im Einklang mit den derzeitigen nationalen und internationalen Regelungsrahmen stehen. Transparenz und die Herausgabe von Informationen können zu Missbrauch zu terroristischen Zwecken führen – doch offene Gesellschaften müssen Mittel und Wege finden, um mit diesem nur schwer zu erzielenden Gleichgewicht zwischen dem Recht der Bürger auf Unterrichtung einerseits und dem notwendigen Schutz ihrer Sicherheit andererseits umzugehen.

- Die Herstellung und potenzielle Nutzung von Materialien oder Systemen der synthetischen Biologie für terroristische Zwecke, an erster Stelle die Herstellung biologischer Systeme, die ein großes zerstörerisches Potenzial aufweisen können. Der Missbrauch jeder Art von Kenntnissen der synthetischen Biologie muss bekämpft werden.

- Die Herstellung synthetischer Organismen außerhalb der anerkannten Einrichtungen. Da Stoffe und Verfahren der synthetischen Biologie öffentlich zugänglich sind, ist Biohacking ein weiteres Szenario, das im Hinblick auf die Sicherheit kontrolliert und gesteuert werden muss.

Die EGE ist sich auch der erst vor kurzem, d. h. am 24. Juni 2009 angenommenen Mitteilung der Kommission ([14]), bewusst, in der die neue EU-Politik im Bereich der *chemischen, biologischen, radiologischen oder nuklearen Stoffe oder Wirkstoffe* (CBRN) definiert wird. Nach Auffassung der Gruppe ist diese Initiative zwar wertvoll, jedoch für einen ethisch vertretbaren und demokratischen Ansatz im Bereich der Biosicherheit in der EU und darüber hinaus noch nicht ausreichend. Die Gruppe begrüßt die Verankerung ethischer Aspekte in die Studienpläne von Wissenschaftlern im Bereich der Biosicherheit einschließlich spezifischer Maßnahmen, die die ethische Dimension der Anwendungsmöglichkeiten der synthetischen Biologie für die Biosicherheit besser erläutern können.

Bei Anwendungen der synthetischen Biologie könnten Informationen beispielsweise über die Herstellung

([13]) Nach Maßgabe der EU-Rechtsvorschriften werden medizinische Produkte der synthetischen Biologie unter sicherheitsrelevanten Aspekten bewertet. Die hierfür zuständigen Behörden in den Mitgliedstaaten und auf EU-Ebene (EMEA) sollten sicher sein, dass die in dieser Stellungnahme dargelegten Überlegungen zu sicherheitsrelevanten Aspekten auch tatsächlich angestellt werden, bevor sie die Genehmigung für klinische Versuchsverfahren und Forschungsversuche sowie für Marketingverfahren erteilen.

([14]) KOM(2009) 273 endgültig; SEK(2009) 874; SEK(2009) 790; SEK(2009) 791.

synthetischer Viren eine neue Welle des Bioterrorismus auslösen. Wie mit diesem Problem umzugehen ist, wurde bislang noch nicht eingehend diskutiert. Die Gesundheit von Soldaten und Zivilisten muss geschützt, Transparenz sollte möglichst aufrechterhalten, und Forschung kann nur bei einer strengen Überwachung zugelassen werden. Wie in Abschnitt 3 dieser Stellungnahme näher ausgeführt, macht die Gruppe geltend, dass die Sicherheit und die militärischen Anwendungen der synthetischen Biologie nicht gegen die Grundrechte und den in dieser Stellungnahme dargelegten Rahmen für Ethik verstoßen dürfen. Die Aufgabe, terroristische und/oder böswillige Anwendungen der synthetischen Biologie zu verhindern, ist für Forscher und demokratische Staaten gleichermaßen mit dem moralischen Dilemma der Doppelverwendung verbunden. Manche beabsichtigten und unbeabsichtigten Doppelverwendungen lassen sich vorhersehen, andere wiederum nicht. Eine Möglichkeit, mit dem Dilemma der Doppelverwendung besser umzugehen, besteht darin, auf Kontrollmechanismen zurückzugreifen, etwa die Zulassung und Registrierung der im Rahmen der synthetischen Biologie eingesetzten Werkzeuge.

Als Beispiel für mögliche Maßnahmen zur Verhinderung nicht hinnehmbarer militärischer Aktionen oder Terrorakte können u. a. Folgende angeführt werden: 1) eine zentrale Datenbank, die zumindest auf EU-Ebene oder nach Möglichkeit sogar auf internationaler Ebene eingerichtet wird, in der alle DNA-Synthesizer von den zuständigen Behörden registriert werden; 2) Forschungsabteilungen oder Forschergruppen, die die synthetische Biologie im Bereich der Biosicherheit und Bioverteidigung anwenden, sollten in dem genannten Register erfasst werden; 3) auf Ebene der Mitgliedstaaten und der EU sollten Kriterien für die Veröffentlichung von Daten über hochgradig pathogene Viren oder toxische Stoffe definiert werden. ([15])

Darüber hinaus gibt es aber auch ethische Bedenken, weil das Potenzial der Doppelverwendung auch im Rahmen der Ausbildung behandelt werden sollte. Die Förderung des Verantwortungsbewusstseins von Menschen und Institutionen im Rahmen einer Diskussion über die ethischen Aspekte der synthetischen Biologie ist eine Frage von zentraler Bedeutung.

Empfehlung Nr. 9: Die Gruppe empfiehlt, dass das Übereinkommen über das Verbot der Entwicklung, Herstellung und Lagerung bakteriologischer (biologischer) Waffen und von Toxinwaffen sowie über die Vernichtung solcher Waffen auch Bestimmungen zur Beschränkung bzw. zum Verbot der Forschung im Bereich der synthetischen Biologie enthalten sollte.

Empfehlung Nr. 10: Die Gruppe ersucht die Kommission, im Einvernehmen mit der EGE einen umfassenden Rahmen für Ethik und Sicherheit im Bereich der synthetischen Biologie festzulegen.

Empfehlung Nr. 11: Die Gruppe empfiehlt, dass die Europäische Kommission 1) dafür Sorge trägt, dass allen Nutzern Datenbanken zur Verfügung stehen; 2) den Unternehmen Rechtssysteme bereitstellt, damit sie den zuständigen Behörden Bericht erstatten, sobald sie gebeten werden, verdächtige Sequenzen unter gleichzeitiger Einhaltung des Datenschutzes zu synthetisieren; 3) die Kette der Zuständigkeiten ermittelt, wenn es darum geht, bestimmte Sequenzen in die Datenbank(en) einzugeben und sie als potenziell schädlich einzustufen.

4.4. Regulierung („Governance“)

Die Gruppe tritt außerdem dafür ein, dass die Auswirkungen einer Technologie, deren mögliche Anwendung in der EU in Betracht gezogen wird, anhand einer Folgenabschätzung sorgfältig untersucht und bewertet werden. Diese Folgenabschätzung sollte sich sowohl auf die Risiken als auch die Vorteile der neuen Technologien und die Risiken und Vorteile der dadurch ersetzten Technologien erstrecken. Sie sollte im Rahmen des integrierten Ansatzes für den Bereich der synthetischen Biologie erfolgen, der Umwelt- und sozialen Auswirkungen Rechnung trägt. Neben einer technischen Risikosteuerung muss ein breiter angelegter Ansatz entwickelt werden, der besser als die derzeit verfügbaren Instrumente in der Lage ist, sich an mögliche Veränderungen in der Umwelt, in der Gesellschaft, in der Marktwirtschaft oder in der nationalen Politik anzupassen. Die Ethik der synthetischen Biologie sollte sich mit einer Untersuchung der Vorzüge und Risiken dieser Technologie bei bestimmten ökologischen Konstellationen von Fall zu Fall sowie mit potenziel-

([15]) Für genetisch veränderte Organismen einschließlich von Organismen, die mithilfe der Verfahren der synthetischen Biologie hergestellt werden, gibt es Verordnungen in Europa, die eine Registrierung und/oder Genehmigung der Einrichtungen vorschreiben, in denen diese Organismen gezüchtet und untersucht werden dürfen. Siehe hierzu auch S. 40 dieser Stellungnahme sowie Art. 7 98/81/EG.

len Risiken und Vorteilen für die gesamte Biosphäre befassen ([16]).

Ein verantwortungsvoller Umgang mit der synthetischen Biologie würde auch den Einsatz von Regulierungswerkzeugen voraussetzen, um den wissenschaftlichen Fortschritt sowie Anwendungsmöglichkeiten der Forschung zu fördern, die der menschlichen Gesundheit zugute kommen können; ein solcher verantwortungsbewusster Umgang würde helfen, Energie zu sparen und die negativen Auswirkungen des Klimawandels zu verringern und zugleich vor Missbrauch, d. h. Bioterrorismus, schützen sowie zur Biosicherheit beitragen. Diese Aufgabe ist keinesfalls einfach und stellt die EU vor eine ganze Reihe von Dilemmata.

a) Allgemeine Dilemmata: Wie können Regulierungswerkzeuge

– einen nutzbringenden Einsatz fördern und Missbrauch verhindern, wenn eine Doppelverwendung möglich ist?

– Transparenz fördern, ohne das Risiko eines Missbrauchs einzugehen?

– vor Missbrauch schützen, ohne zu einer ungewollten Zensur bei der Veröffentlichung usw. zu führen?

b) Spezifische Herausforderungen an die Regulierung: Wie kann die EU Regulierungswerkzeuge einsetzen, um

- der Tatsache Rechnung zu tragen, dass die synthetische Biologie eine Vielzahl von Bereichen umfasst, die in völlig unterschiedlichem Maß und in unterschiedlicher Ausprägung reguliert sind und in denen mögliche Lücken klaffen, was die Gewährleistung der Biosicherheit und den Ausschluss eines möglichen Missbrauchs anbetrifft?

- Bereiche zu ermitteln, in denen das nicht zwingende Recht („soft law“) für ausreichenden Schutz sorgt, und Bereiche, in denen ein normativ festgelegtes Recht („hard law“) für notwendig erachtet wird (siehe Empfehlung 2 zu den Vorschriften für die Biosicherheit und Empfehlung 9 zum Übereinkommen über biologische Waffen)?

- einzelne Forscher und Einrichtungen (einschließlich von Wissenschaftlern, die nicht unbedingt mit lebenden Organismen arbeiten und mit den damit verbundenen spezifischen Probleme konfrontiert sind) anzuhalten, professionell Verantwortung zu übernehmen und den in Empfehlung Nr. 3 vorgeschlagenen Verhaltenskodex zu ergänzen?

- im Hinblick auf die notwendige weltweite Regulierung im Bereich der synthetischen Biologie eine Rolle zu spielen?

Die Gruppe äußert Bedenken hinsichtlich des bestehenden bruchstückhaften Regelungsrahmens, der möglicherweise für eine entsprechende Regulierung der derzeitigen und sich neu herausbildenden Aspekte der synthetischen Biologie nicht ausreichend ist. Außerdem hebt sie die Notwendigkeit hervor, ein geeignetes Modell der Governance im Bereich der synthetischen Biologie zu untersuchen (nicht zwingendes Recht, Verhaltenskodizes usw.), wobei auch potenziellen Risiken der Auslagerung von Forschungsversuchen in Länder Rechnung zu tragen ist, in denen sich die Regulierung im Vergleich zum Vorschlag für die EU möglicherweise weniger streng gestaltet.

Empfehlung Nr. 13: Die Gruppe ersucht die Kommmission dringend, einen soliden Rahmen für die Regulierung im Bereich der synthetischen Biologie vorzuschlagen und diesen in der EU einzurichten. Die Kommission sollte die für die synthetische Biologie anwendbaren Rechtsvorschriften einer Überprüfung unterziehen und prüfen, ob diese auch geeignet sind, Antworten auf die durch die synthetische Biologie aufgeworfenen Fragen zu geben. Der vorstehend dargelegte Rahmen sollte sich an die entsprechenden Interessengruppen (Wissenschaftler, Industrie, Vertreter des Militärs sowie Vertreter von Politik und Verwaltung) wenden und deren Verantwortungsbereiche und Aufgaben klar darlegen.

Empfehlung Nr. 14: Die entsprechenden Wissenschaftsgemeinden sollten dazu angehalten werden, ethische Leitlinien, vorzugsweise weltweit, einzuführen, die als

([16]) Siehe Markus Schmidt, Helge Togersen, Agomoni Ganguli-Mitra, Alexander Kelle, Anna Deplazes, Nikola Biller-Andorno: SYNBIOSAFE e-conference: online community discussion on the societal aspects der synthetischen Biologie. In: Systems and Synthetic Biology, 16. September (2008). Online: http://www.zora.uzh.ch/3947/2/Schmidt_m_torg.V.pdf .
Paul Rabinow & Gaymon Bennett: From Bio-Ethics to Human Practice. Working Paper # 11, 2007 http://anthropos-lab.net/wp/publications/2007/08/workingpaperno11.pdf .

„Wegweiser" fungieren und wissenschaftliche Einrichtungen und einzelne Forscher dazu bringen sollen, die Auswirkungen ihrer Arbeit einschließlich der Folgen eines Missbrauchs ([17]) zu bewerten.

Empfehlung Nr. 15: Die EGE schlägt vor, dass die EU die Frage der Governance im Bereich der synthetischen Biologie auf den entsprechenden globalen Foren anspricht.

4.5. Geistiges Eigentum

4.5.1. Patentierung und gemeinsames Erbe

Die im Zusammenhang mit der Patentierung biologischer Methoden und Stoffe aufgeworfenen Fragen waren eine gewisse Zeit lang Gegenstand heftiger Debatten und werden jetzt in verschiedenen Disziplinen erörtert. Die Funktion von Patenten, Anreize für die Forschung und deren Anwendungen zu bieten und eine Veröffentlichung der Grundlage dieser Anwendungen zu fördern, könnte durch die enorm hohe Zahl von Patentanmeldungen in Verbindung mit genetischem Material und biologischen Methoden aufs Spiel gesetzt werden. Zugleich hat die Verwendung von Bestandteilen biologischer Organismen durch bestimmte industrielle Akteure auch dazu geführt, dass zunehmend Fragen nach den ethischen Aspekten gestellt werden. In Artikel 7 der Richtlinie über die Patentierung biotechnologischer Erfindungen heißt es: „Die Europäische Gruppe für Ethik der Naturwissenschaften und Neuen Technologien der Kommission bewertet alle ethischen Aspekte im Zusammenhang mit der Biotechnologie". Dies ist der einzige Artikel in dieser Richtlinie, der nicht in Durchführungsbestimmungen zur Richtlinie des EPA bzw. der Patentämter in den Mitgliedstaten umgesetzt wurde. Er ist deshalb so schwierig umzusetzen, weil darin keine konkreten Maßnahmen beschrieben sind und auch in keinem der anderen Artikel darauf eingegangen wird. Die Patentämter klagen häufig darüber, dass sich die Auslegung der Bestimmungen des Europäischen Patentrechts zu den guten Sitten schwierig gestaltet (oder diese Bestimmungen sogar im Rahmen anderer Rechtsvorschriften aufgegriffen werden sollten). Die Gruppe schlägt vor, dass dann, wenn im Rahmen einer bestimmten Patentanmeldung im Bereich der Biotechnologie (einschließlich Nanontechnologie und synthetische Biologie) eine allgemeine Frage aufgeworfen wird, die entsprechenden Patentämter die EGE in dem in der Anmeldung bezeichneten allgemeinen Bereich um Rat ersuchen sollen.

Im Hinblick auf die Frage der Patentierung und des gemeinsamen Erbes erkennt die Gruppe an, dass es sich hierbei um ein vielschichtiges Thema handelt, wie bereits in Anhang I dieser Stellungnahme ausgeführt wurde. Die Gruppe hebt hervor, dass allgemeine ethische Fragen im Zusammenhang mit Patentanmeldungen entsprechend im Rahmen des Systems der Patenterteilung geklärt werden sollten.

Empfehlung Nr. 16: Die EGE schlägt vor, dass Debatten über die am besten geeigneten Möglichkeiten angestoßen werden, um den Zugang der Öffentlichkeit zu den Ergebnissen der synthetischen Biologie zu gewährleisten. Diese Debatten sollten sich auch auf die Frage erstrecken, was Gegenstand des Patents sein kann und was im Rahmen eines offenen Zugangs zur Verfügung gestellt werden sollte.

Empfehlung Nr. 17: Die EU-Patentrichtlinie (98/44/EG) definiert die EGE als das Gremium, das die ethischen Auswirkungen in Verbindung mit Patenten einer Bewertung unterzieht. Die Gruppe ersucht das Europäische Patentamt und die nationalen Patentämter dringend, Artikel 7 der Patentrichtlinie Rechnung zu tragen und kontroverse ethische Fragen von allgemeiner Bedeutung der EGE zur Prüfung vorzulegen. Dies ist dann besonders wichtig, wenn eine Gruppe von Erfindungen definiert werden muss, die nicht unmittelbar gewerblich verwertet werden sollten ([18]).

([17]) Siehe Unesco MOST Ethische Leitlinien für eine international vergleichbare sozialwissenschaftliche Forschung.

([18]) Artikel 6 Absatz 2 der Richtlinie 98/44/EG enthält eine Liste von Beispielen, die von der Patentierbarkeit ausgenommen sind, und zwar „(a) Verfahren zum Klonen von menschlichen Lebewesen; (b) Verfahren zur Veränderung der genetischen Identität der Keimbahn des menschlichen Lebewesens; (c) die Verwendung von menschlichen Embryonen zu industriellen oder kommerziellen Zwecken; (d) Verfahren zur Veränderung der genetischen Identität von Tieren, die geeignet sind, Leiden dieser Tiere ohne wesentlichen medizinischen Nutzen für den Menschen oder das Tier zu verursachen, sowie die mit Hilfe solcher Verfahren erzeugten Tiere." In Artikel 7 der Richtlinie heißt es weiter: „Die Europäische Gruppe für Ethik der Naturwissenschaften und der Neuen Technologien der Kommission bewertet alle ethischen Aspekte im Zusammenhang mit der Biotechnologie."

4.5.2. Handel und globale Gerechtigkeit

Die Gruppe ist sich der globalen Dimension der synthetischen Biologie und ihrer Anwendungsmöglichkeiten bewusst und sieht die wirtschaftliche Entwicklung und die Zunahme der sozialen Wohlfahrt als ein positives Ziel der EU an. Die synthetische Biologie kann zum sozioökonomischen Wohlstand der EU und darüber hinaus beitragen. Die Gruppe begrüßt diese Möglichkeit, soweit die Grundsätze der EU-Charta der Grundrechte und die wichtigsten Grundwerte der EU von diesem Technologiesektor und vom Handel mit seinen Produkten nicht negativ beeinflusst werden. Daher hat die EGE Bedenken hinsichtlich der möglichen Risiken einer technologischen Kluft innerhalb der EU sowie zwischen entwickelten und weniger entwickelten Ländern.

Die EGE empfiehlt, die Grundwerte der EU in den globalen Handel mit Produkten der synthetischen Biologie einzubinden. Wie in früheren Stellungnahmen (z. B. Stellungnahme 23 ([19]) und Stellungnahme 24 ([20])) betont die Gruppe die Notwendigkeit, ethische Betrachtungen in den globalen Handel und in die politischen Aktionen der Welthandelsorganisation einzubinden.

Im Anschluss daran sollten Maßnahmen ergriffen werden, um eine technologische Kluft größeren Ausmaßes zu verhindern. Wenn in Entwicklungs- und Schwellenländern Versuche mit Produkten der synthetischen Biologie durchgeführt werden, müssen dieselben ethischen Standards wie in der EU angewandt werden ([21]). Die Millenniumsziele der Vereinten Nationen sollten umgesetzt werden.

Empfehlung Nr. 18: Die EGE empfiehlt, dass bei Diskussionen über die synthetische Biologie auf internationaler Ebene einschließlich der WTO auch ethische Fragen in Verbindung mit der Technologie angesprochen werden sollten ([22]). Dies sollte bei der Doha-Verhandlungsrunde berücksichtigt werden.

Empfehlung Nr. 19: Die EGE bittet dringend darum, dass die EU-Standards im Bereich Biosicherheit für Produkte der synthetischen Biologie, die in den Empfehlungen Nr. 1, 2 und 5 dieser Stellungnahme beschrieben sind, als Mindeststandards für Aus- und Einfuhren von Produkten der synthetischen Biologie aus der EU bzw. in die EU übernommen werden.

Empfehlung Nr. 20: Die Gruppe empfiehlt der EU, spezifische Maßnahmen zu ergreifen, um zu verhindern, dass neue Lücken zwischen der EU und den Entwicklungs- und Schwellenländern bzw. innerhalb der EU-Mitgliedstaten aufklaffen, und die in dieser Stellungnahme ausgesprochenen Empfehlungen zu verwirklichen. Maßnahmen dieser Art sollten in den bilateralen und multilateralen Wissenschaftsprogramme der EU und in der EU-Politik für Entwicklungs- und Schwellenländer verankert werden.

4.6. Wissenschaftlicher und gesellschaftlicher Dialog

Wie in Abschnitt 3 dieser Stellungnahme ausführlich dargelegt, sind die ethischen Aspekte der synthetischen Biologie komplex, und die aufgeworfenen konzeptuellen Fragen müssen im Rahmen eines wirksamen wissenschaftlichen und gesellschaftlichen Dialogs erörtert werden.

Die Art der Wahrnehmung der synthetischen Biologie wird von sozialen, kulturellen und ethischen Erwägungen über die Manipulation von Leben, von den wirtschaftlichen Auswirkungen auf entwickelte und in Entwicklung befindliche Regionen, von Fragen in Verbindung mit Eigentum und geistigem Eigentum, von Bedenken hinsichtlich einer Zerstörung der Umwelt und potenzieller militärischer Anwendungen usw. beeinflusst. Die herkömmlichen und interaktiven Medien spielen eine wichtig Rolle, wenn es darum geht, die Meinungen der Menschen zu neuen und aufstrebenden Technologien einschließlich der synthetischen Biologie zu prägen. Jede dieser Fragen bedarf einer gründlichen Betrachtung und der Beteiligung der Öffentlichkeit. Damit werden weiter gefasste Fragen der Vertrauensbildung zwischen der Wissenschaftsgemeinschaft und der Öffentlichkeit einschließlich der Notwendigkeit, eine angemessene Debatte zu fördern, aufgeworfen. Und schließlich führt dies zu Fragen der beratenden Demokratie einschließlich von Fragen wie zum Beispiel, wer die Trennlinien zieht zwischen dem, was erlaubt und akzeptabel ist und was nicht; und wer überblickt, wer diese Trennlinien zieht.

([19]) http://ec.europa.eu/european_group_ethics/activities/docs/opinion23_en.pdf

([20]) http://ec.europa.eu/european_group_ethics/docs/opinion24_en.pdf

([21]) http://ec.europa.eu/european_group_ethics/docs/avis17_de.pdf.

([22]) Siehe Abschnitte 2.2.b und 2.2.c dieser Stellungnahme.

Sozialwissenschaftler haben vorgeschlagen, dass eine Verpflichtung im Vorfeld der wissenschaftlichen und technologischen Entwicklung im Einklang mit gesellschaftlichen Erwartungen, Bedenken und Wünschen förderlich sein könnte. ([23]) Viele Wissenschaftler, die im Bereich der synthetischen Biologie tätig sind, sind sich bereits der Bedeutung einer öffentlichen Verpflichtung bewusst und haben sich zu diesem Zweck an Aktivitäten wie Debatten, Podcasts und Blogs beteiligt.

In die öffentliche Debatte müssen sachdienliche und angemessene Informationen über die tatsächlichen Merkmale und Potenziale der synthetischen Biologie eingebracht werden, was Schwierigkeiten bei der Ermittlung, Einschätzung und Steuerung von Risiken in einem Bereich mit sich bringen könnte, der von erheblicher Unsicherheit und von großen Wissenslücken geprägt ist, vor allem, wenn damit kurz- und langfristig unterschiedliche Risiken verbunden sind. Ähnliche Überlegungen sind in Bezug auf die Vorteile angebracht, die in den Medien hochgejubelt werden, wobei die Öffentlichkeit auch durch die Beiträge von Medien- und Science-Fiction-Autoren mit unrealistischen Szenarien zu Produkten der synthetischen Biologie konfrontiert wird (zum Beispiel der Medienrummel um die synthetische Biologie im Hinblick auf die Heilbarkeit aller Krankheiten, auf biologische Abhilfemaßnahmen zur Bekämpfung der Umweltverschmutzung oder auf die Wahrscheinlichkeit einer Energiekrise). Hoffnungen oder Befürchtungen, die der Öffentlichkeit ohne entsprechende Nachweise kommuniziert werden, verzerren die öffentliche Debatte über die synthetische Biologie.

Empfehlung Nr. 21: Die Gruppe ersucht die EU und die EU-Mitgliedstaaten, Maßnahmen zur Förderung öffentlicher Debatten und zur Verpflichtung der Interessengruppen zu ergreifen, um die wichtigsten gesellschaftlichen Anliegen in den einzelnen Bereichen, auf die sich die synthetische Biologie bezieht, aufzuzeigen.

Empfehlung Nr. 22: Die Gruppe empfiehlt, dass Journalisten, Redakteure einschließlich Wissenschaftsredakteure und andere Akteure eine verantwortungsvolle Berichterstattung über die synthetische Biologie fördern.

Empfehlung Nr. 23: Zur Förderung eines umfassenden Ansatzes im Bereich der neuen Technologien durch die Medien bittet die Gruppe die Kommission, spezifische Maßnahmen zu initiieren, u. a. die Einrichtung und Durchführung von Foren, Seminaren und Kursen, die sich mit den Auswirkungen der synthetischen Biologie in den Medien befassen.

4.7. Forschung

Seit geraumer Zeit ist zu beobachten, dass die Grundlagenforschung, die das Fundament aller Anwendungen in einem bestimmten Forschungsfeld darstellt, in Programmen der Forschungsförderung in den Hintergrund gedrängt wird. Auch wenn sich die Grundlagenforschung nicht scharf von der angewandten Forschung abgrenzen lässt, ist Erstere auf öffentliche Gelder angewiesen, und dies sollte auch die Politik der Europäischen Union sein.

Ein äußerst wichtiges Novum, das mit der synthetischen Biologie in die wissenschaftliche Methodik der modernen Biologie eingebracht wird, ist die Möglichkeit, nicht nur deduktive Methoden bei beobachteten Phänomenen anzuwenden, sondern auch heuristische Werkzeuge zu synthetisieren, die an sich schon die Untersuchung grundlegender Phänomene der Biologie ermöglichen. Die Grundlagenforschung im Bereich der synthetischen Biologie ist jedoch nicht unbedingt an Interessen des Marktes und der Industrie gekoppelt und ist daher auf öffentliche Gelder angewiesen. Die Gruppe ist besorgt, dass dies in naher Zukunft zu einem Mangel an angemessener Finanzierung der Grundlagenforschung in der EU führen und die Rolle der EU-Forschung im Zusammenhang mit der weltweiten Regulierung der synthetischen Biologie gefährden könnte.

Parallel dazu befasst sich die ethische Debatte über die synthetische Biologie mit Themen in Verbindung mit der ethischen Legitimität der Herstellung lebender Organismen, ähnlich wie die Debatte über die Manipulation des Lebens. Das Eingreifen des Menschen in die Natur einschließlich der Umwelt und anderer lebender Organismen wirft Fragen zur „Natürlichkeit“ des

([23]) http://www.bbsrc.ac.uk/organisation/policies/reviews/scientific_areas/0806_synthetic_biology.pdf.

Eingreifens und zur „Herstellung von Leben“ auf ([24]) Daher unterstreicht die Gruppe die Notwendigkeit, interdisziplinäre EU-Forschungsprojekte über die Beziehung zwischen Mensch und Natur zu finanzieren, insbesondere in Bezug auf Fragen nach den Vorstellungen vom Leben.

Empfehlung Nr. 24: Die Gruppe bittet die Kommission, die Grundlagenforschung in den Bereichen Biologie, Chemie, Energie, Materialwissenschaften und Werkstofftechnik sowie die angewandte Forschung im Sinne dieser Stellungnahme zu fördern. Dies sollte sich im Budget für die EU-Forschungsrahmenprogramme niederschlagen. Ein ähnlicher Antrag wird an die EU-Mitgliedstaaten in Bezug auf ihre nationalen FuE-Programme gerichtet.

Empfehlung Nr. 25: Die Gruppe ersucht die EU, die interdisziplinäre Forschung zu folgenden Aspekten der synthetischen Biologie in angemessenem Rahmen zu finanzieren:

- *Risikobewertung und Sicherheit;*
- *Anwendungen der synthetischen Biologie im Bereich Sicherheit;*
- *ethische, rechtliche und soziale Auswirkungen*
- *Governance;*
- *Wissenschaft und Gesellschaft (einschließlich Medien und Öffentlichkeit).*

Dies sollte sich im Budget der EU-Forschungsrahmenprogramme niederschlagen. Ein ähnlicher Antrag wird an die EU-Mitgliedstaaten in Bezug auf ihre nationalen FuE-Programme gerichtet.

Empfehlung Nr. 26: Die Gruppe nimmt zur Kenntnis, dass die synthetische Biologie in Zukunft zu einem Paradigmenwechsel im Zusammenhang mit den Vorstellungen vom Leben führen könnte. Sie ersucht daher die Kommission, ein offenes interkulturelles Forum zu initiieren, das sich mit diesen Fragen befasst, einschließlich philosophischer und religiöser Beiträge.

([24]) John Harris, „Who's Afraid of a Synthetic Human?“ The Times, 17. Mai 2008. Colin Nickerson, „A Quest to Create Life Out of Synthetics,“ Boston Globe, 2. April 2008. Erik Parens, „Making Cells Like Computers,“ Boston Globe, 18. Februar 2008. Natalie Angier, „Pursuing Synthetic Life, Dazzled by Reality,“ New York Times, 5. Februar 2008.

Annex I: The Patent System, Biotechnology and Synthetic Biology

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1. INTRODUCTION

A very detailed examination of the patent system, including an introduction to patent law in Europe and in the United States and an examination of many cases that involve the patenting of life forms, was produced for the EGE by Geertrui van Overwalle in 2002 ([1]). There is therefore no attempt to provide the detailed examination of the patent system in this current paper.

2. INNOVATION

'The last half of the 19th century and the first years of the 20th century saw the development of technologies that would create the basis of wealth generation by means of major new industries – principally petrochemical, automotive, aviation and electronics. These developments helped create the modern world.' ([2]). During the latter part of the 20th Century and the beginning of this century electronics and biotechnology have been leading the revolution in providing ever-increasing sophistication to our lives. Amongst the new technologies are those involving the manipulation (and commercialization) of biology. The range of applications to which new uses of biology are becoming available is extensive, reaching far beyond the provision of medicines, food and fibre. Synthetic biology provides a new set of tools for using biology, and may either be for the purpose of pure research with an intention to understand the manner in which living systems have developed including their interactions, or for producing new processes or products. An argument has developed as to whether all or some of the fruits of synthetic biology should be patentable, for the commercial benefit of those that 'invent' the processes or products.

The 'bioeconomy' is primarily growing in developed countries. The United States originated 40.6% of biotechnology patents in 2005, with the European Union at 25.1% and Japan at 17%. Brazil, China, India, Indonesia, the Russian Federation and South Africa combined provided 2.7% of the total patents in biotechnology ([3]). Developing countries may not have the infrastructure to support the use of modern technologies and hence lack the capacity to innovate in areas (like biotechnology) where infrastructure is essential. The same problem exists for nanotechnology (US 41.8, EU 25.4, Japan 16.7).

It is believed that for the 'bioeconomy' to grow, Intellectual Property, primarily in the form of patents, will play an important role – this includes the manner in which they are recognised, traded and managed. IP will have an impact on where the bioeconomy will flourish, the form it takes and to whom the principal benefits will accrue. ([4])

([1]) EGE (2002) Study on the patenting of inventions related to human stem cell research. Luxembourg Office for Official Publications of the European Communities. ISBN 92-894-1987-3

([2]) The Royal Academy of Engineering (May 2009) 'Synthetic Biology: scope, applications and implications' ISBN: 1-903496-44-6

([3]) OECD (2008) Compendium of Patent Statistics

([4]) Herder M and Gold ER 'Intellectual Property Issues in Biotechnology: Health and Industry' Report prepared for the OECD International Futures project on the Bioeconomy to 2030: Designing a Policy Agenda (OECD, 2008)

Many argue that patenting is an essential part of the protection of scientific endeavour. A recent paper on 'Inventing Biological Organisms: A Reader of Selected Articles' states the case succinctly: 'The ability to patent biological inventions is central to protecting scientists' work… What can be patented, for how long, and the extent of global protection are critical issues. However, patenting biological organisms, particularly human genes and other human parts, is controversial. Economists question whether patenting is the quickest and best way to diffuse new knowledge throughout the marketplace. Some bioethicists question whether genetic information is the common heritage of mankind, making gene patenting inappropriate' ([5]). The debate about gene patenting has been dealt with in detail in the previous EGE paper (footnote 1). The concern has shifted to the role of the patent system as technology moves towards a 'knowledge economy'. It has always been assumed that there is an important balance between private and public interests in the manner in which the patent system has been designed – limited rights for a limited time. This balance has shifted towards the private interest, particularly when examined from the perspective of the developing world. ([6])

There is an assumption within governments and judicial reasoning that IP rights (Patent rights in particular) 'are crucial if not absolutely necessary to foster innovation' ([7]) 'Should some biological inventions be kept in the public domain and not be patentable? Would this slow or speed the development of socially important products? Conversely, does patenting new biotechnology products (agricultural seeds that are resistant to pesticides, for example) accelerate the development of products that have high social utility?' Gold has argued that the evidence for assumptions about patents having a positive effect on innovation is relatively weak. ([8])

Gold explains:

'More recent work has… cast doubt on this conclusion. The international economics literature considers cross-country differences in patent systems and the implications of these differences for economic behavior. The link between patents and innovation in the multi-country (open economy) is less clear.

Even within a closed economy, patents on initial innovations may deter later discoveries that build on patented innovations. There are also structural reasons to believe that one can never know, in fact, whether patents actually encourage or discourage innovation. First, […] while patent law takes a 'one-size-fits-all' approach to innovation, the markets for different products and knowledge assets differ significantly from one another. Second, the empirical study of the effects of patents on innovation suffers from the lack of control. Given that innovation is driven by many factors (including access to capital, access to skilled managers, first mover advantage, curiosity, *etc.*), cross-jurisdictional comparisons are difficult. Since countries rarely radically change their patent systems without changing fundamental aspects of their economies, single jurisdiction controls are usually lacking. Several studies that examine changes within a single jurisdiction – the semi-conductor industry in the US between the 1970s and 1980s and the strengthening of the Japanese patent system in the 1980s – indicate that patents either reduced innovation or had no effect. Third, […] industry rarely relies solely on a single patent to secure its inventions. Normally, firms use a

([5]) California Research Bureau (1998) http://www.library.ca.gov/crb/98/reader/reader01.pdf

([6]) Walker, Simon. 2001. The TRIPS Agreement, Sustainable Development and the Public Interest: Discussion Paper. IUCN, Gland, Switzerland and Cambridge, UK and CIEL, Geneva, Switzerland ISBN 2-8317-0604-1

([7]) Herder M and Gold ER 'Intellectual Property Issues in Biotechnology: Health and Industry' Report prepared for the OECD International Futures project on the Bioeconomy to 2030: Designing a Policy Agenda (OECD, 2008) page 5

([8]) E. Richard Gold et al., 'The Unexamined Assumptions of Intellectual Property: Adopting an evaluative Approach to Patenting Biotechnological Innovation' (2004) 18 Public Affairs Quarterly 299

combination of patents, trade secrets, and even trademarks to protect their innovations. In addition, firms also use other mechanisms such as complementary asset management (by forming alliances) and innovation lead-time to gain advantage over competitors.

All of these intellectual property management mechanisms make it difficult, if not impossible, to isolate the effect of patents on innovation.' ([9]) The vast majority of drugs produced (and patented) by the pharmaceutical companies never reach commercialization, as they fail during the various processes, including trials on patients, to meet the criteria for an effective drug. These patents would then count as not 'used' although they may be kept to ensure that when other companies produce similar products they can be relied on to block anything that might be competitively efficacious.

A distinction between pure science, not for commercial gain and technology has become blurred during the last 20 years. The goal of biological research during the first part of the 20th century was primarily to understand the mechanisms of biology; products were spin-off results of the research. Pressure from government and industry during the latter part of the 20th century moved the goal of research towards a conscious search for commercial products from the information available from biological research. Very often commercialization now occurs before a full understanding of the biology has been achieved. On 27 April 2009 President Obama spoke at a meeting of the National Academy of Science in New York. He addressed the relationship between primary basic research and technology:

> 'The fact is an investigation into a particular physical, chemical, or biological process might not pay off for a year, or a decade, or at all. And when it does, the rewards are often broadly shared, enjoyed by those who bore its costs but also by those who did not.
>
> And that's why the private sector generally under-invests in basic science, and why the public sector must invest in this kind of research – because while the risks may be large, so are the rewards for our economy and our society.'

This paper does not attempt to address the rationale for using the patent system to allow the bio-economy to grow, rather it asks the question what discoveries and inventions should be capable of being patented, and hence available directly for commercial exploitation, and which of these should not be (if any). It has been argued that some discoveries or inventions should be considered as the common heritage of mankind, and this argument is developed and considered later in this paper. Perhaps common heritage is not a necessary concept, rather that these would be in the common ownership – to the benefit of all. There is a general appreciation in Europe that there are some discoveries or inventions that should never result in commercialisation for profit. For example, processes the use of which offend human dignity such as the production of chimeras from germ-cells, or totipotent cells from plants and animals; process for cloning a human being, modified germ-line cells etc. Article 6, paragraph 2 of Directive 98/44/EC on the legal protection of biotechnological inventions provides a non-exclusive list of those products and processes considered to be not patentable due to their commercial exploitation being contrary to morality or *ordre public*. This may provide a conceptual framework for other inventions that may be unpatentable, but there are no criteria provided.

Article 7 of the Directive provides '[t]he Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology.' It gives no advice on how to implement the Article, which is the only one not implemented by any of the European Patent Offices in their rules.

([9]) ibid

It may be that 'inventions' in biology in general and in synthetic biology in particular should be placed in one of three categories:

a. That which is common to all humankind, and should not be patentable or directly exploited for commercial gain.

b. That which, for a variety of reasons, should be placed in the public domain for all to use and exploit (the 'commons'). It may be that the process or product is so expensive to produce or require a vast range of expertise not available to any one organisation, or that the placing of the information in the public domain enables open standards that allow for the effective commercialisation and use of a number of products that use the technology or product.

c. That which may, at the inventor's discretion, be protected through an intellectual property rights system to encourage innovation.

3. THE PATENT SYSTEM

Most nations of the world are party to the World Trade Organisation. As part of their agreement to join the organisation, they agreed and in general ratified all the component treaties of the General Agreements on Tariffs and Trade (GATT). The last successful round of trade negotiations culminated in all ratifying Member States endorsing all agreements in the WTO package under the so-called 'single undertaking'. No opting out of individual treaties (over 17 in total) was allowed as they were to be ratified all at once. One of these is the TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights). TRIPS provides for each country to institute a minimum set of laws protecting intellectual property, so that where inventors so wish they may protect that which they have created or invented in any jurisdiction. Countries may not discriminate between domestic and international 'creations'. ([10])

It is patently obvious that a business has a competitive advantage if it develops, maintains and exploits its assets appropriately. These have to include its intellectual property where it has an advantage over its competitors if it has information which it has not shared (secrecy) or where it has asserted rights that permit it to assure that others cannot use or copy without permission. A relatively new concept is that the portfolio of intellectual property constitutes a currency that is negotiable for use in (commercial or research?) interactions with others. Patents may then be used as such, without the intention to use them in advancing technology.

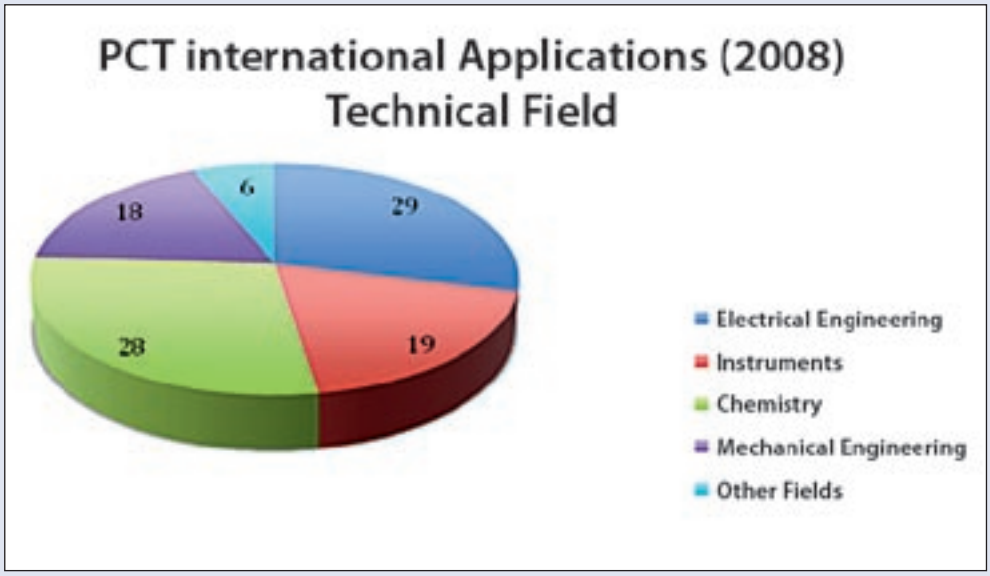
A patent is a limited 'negative' national right given to an inventor for a short period of time (usually 20 years from date of filing) in exchange for a publication of a full specification that allows anyone reading the patent to replicate the invention. In practice descriptions are often published a (relatively) long time after application, and due to careful patent drafting can be difficult to replicate. The patent specifies a set of claims by the inventor that permits the exclusion of others from making, using, offering for sale, selling, or importing that which is claimed, but only in the jurisdiction to which it applies. This relatively old system has worked extremely well for inventions in many fields in engineering, including modern electric and electronic engineering. The patent system is thought to be extremely important in the pharmaceutical industry, where the companies argue that it has enabled the expensive innovation of modern drugs and devices. Gold quotes studies conducted by Levin et al. and Cohen et al. over the last twenty years to have shown that

([10]) TRIPS Article 27.1 provides that '…patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.'

R&D managers in pharmaceutical companies attributed significantly more importance to patent rights relative to their counterparts in other sectors. ([11]), ([12])

In the last few years there appears to have been a "patent gold gush,' in which 'inventions long thought unpatentable —everything from gene sequences of unknown function to one-step purchasing over the Internet— are now being claimed as property.' These developments are of particular concern because they tend to allow patents on subject matter that is both further 'upstream' in the innovation process and further afield from traditional industrial products and processes than has ever before been the case. ([13]) Does this expansion of the patent system encourage or discourage innovation and is the incentive really necessary to achieve innovation? The Canadian Supreme Court, in deciding against permitting the patenting of an altered mouse, stated succinctly that 'The massive private sector investment in biotechnological research is exactly the sort of research and innovation that the Patent Act was intended to promote. Healthcare is the major beneficiary of biotechnology. At the same time, vast amounts of money must be found to finance biomedical research. The Patent Act embodies the public policy that those who directly benefit from an invention should be asked, through the patent system, to pay for it, at least in part.' ([14])

The diagram below indicates the range of patent applications in all fields in 2008 at WIPO (Patent Cooperation Treaty applications) ([15]). It indicates that traditional applications still predominate, although applications for pharmaceuticals and biotechnology are increasing. The largest proportions of PCT applications related to the medical technology (12%), computer technology (8.5%) and pharmaceuticals (7.9%) sectors. Between 2003 and 2005 medicine and biotechnology accounted for 14.8% of nanotechnology filings. ([16])



([11]) Richard D. Levin et al., 'Appropriating the Returns from Industrial Research and Development' (1987) Brookings Papers on Economic Activity 783

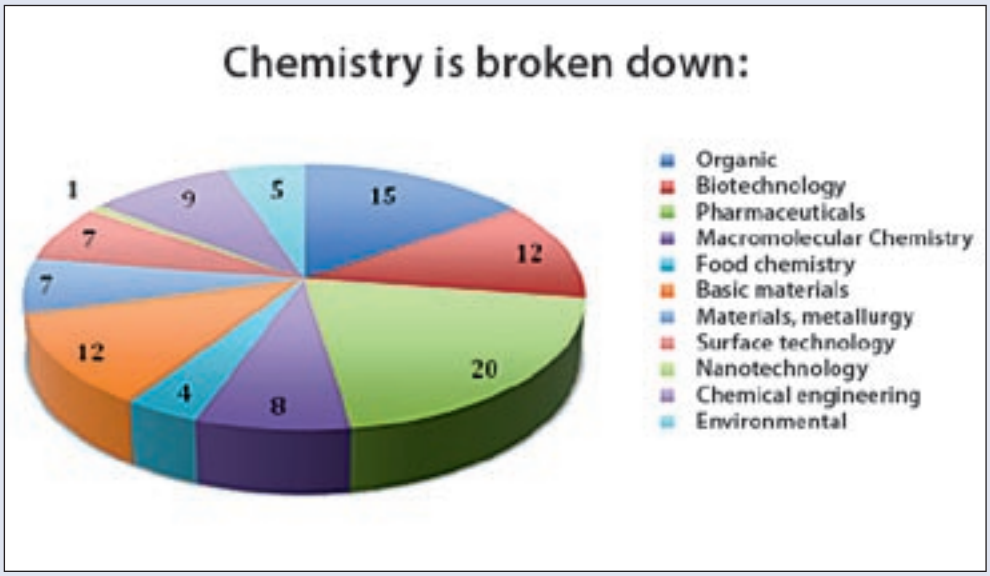
([12]) W. Cohen et al., 'Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector' Working Paper (Pittsburgh: Carnegie-Mellon University 1997).

([13]) McManis C 'Re-Engineering Patent Law: The Challenge of New Technologies' Washington University Journal of Law and Policy http://law.wustl.edu/journal/2/p1mcmanis.pdf

([14]) Harvard College v. Canada (Commissioner of Patents), [2002] 4 S.C.R. 45, 2002 SCC 76

([15]) WIPO - The International Patent System in 2008 http://www.wipo.int/pct/en/activity/pct_2008.html

([16]) OECD Compendium of Patent Statistics 2008



The numbers in the diagram are the percentage of the total for each sector. The numbers in the chemistry segment can be broken down further:

There is, however, a question as to whether the system is efficient in 2 areas:

a. Modern technologies, specifically biotechnologies, personalised medicine and biologics where a specification that allows specific claims to be made may be difficult.

b. The ability to replicate an invention from its specification requires a basic infrastructure to be in place in the country in which a copy is to be used for further innovation. The system therefore favours economies that are advanced enough to replicate an invention and hence allow for innovation. The US patent office alludes to this as follows:

> 'The patentee is not required to disclose all possible uses, but promoting the subsequent discovery of other uses is one of the benefits of the patent system. When patents for genes are treated the same as for other chemicals, progress is promoted because the original inventor has the possibility to recoup research costs, because others are motivated to invent around the original patent, and because a new chemical is made available as a basis for future research. Other inventors who develop new and non-obvious methods of using the patented compound have the opportunity to patent those methods.'

In most jurisdictions, as defined in the TRIPS Agreement patents may only be granted if they meet specific criteria. They must be new, involve an inventive step and be of industrial application.

i. 'An invention shall be considered to be new if it does not form part of the state of the art' ([17]), which includes that which has been communicated to the 'public' by oral or written means.

([17]) European Patent Convention, Article 54

ii. 'An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.' ([18]) There has been controversy over whether uses for genes are not obvious to scientists 'skilled in the art'. The meaning of invention may be different in different jurisdictions. For example, the distinction between inventions and discoveries is not entirely clear. In the United States an inventor may patent a discovery if the invention satisfies the statutory requirements. The US Constitution (Article 1 (8)) provides for Congress to have the obligation 'To promote the Progress of Science and useful Arts by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries' 35USC 101 provides for patents for those who 'invent or discover'.

iii. 'An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.' ([19]) If a patent application specifies only the DNA or RNA structure without specifying a utility for a particular sequence, the claimed invention is not patentable in the US or under the European Patent Convention. Under US law, if an invention discloses a 'specific substantial and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable.' ([20]) US Patent law stipulates that 'a patent must be granted when at least one specific, substantial and credible utility has been disclosed, and the application satisfies the other statutory requirements.' Similar rulings have been made in Europe.

iv. 'Biotechnological inventions' in Europe are inventions which concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used. ([21]) They are patentable if they are

   (a) biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature;

   (b) plants or animals if the technical feasibility of the invention is not confined to a particular plant or animal variety;

   (c) a microbiological or other technical process, or a product obtained by means of such a process other than a plant or animal variety. ([22])

v. 'Synthetic DNA preparations are eligible for patents in the US because their purified state is different from the naturally occurring compound.'[20] In an early patent for adrenaline, the court explained that compounds isolated from nature are patentable: 'even if it were merely an extracted product without change, there is no rule that such products are not patentable'. (is there therefore (in the US) no conceptual difference between a synthesized purified DNA preparation and one found in the state of nature and which is subsequently purified? Are they hence interchangeable as end products for the purpose of patenting etc, and should we therefore not go any further in distinguishing between them in terms of origin of initial creation?) The same condition applies in Europe.

([18]) European Patent Convention, Article 56

([19]) European Patent Convention, Article 57

([20]) USPTO (2001) Utility Examination Guidelines Federal Register (2001) Vol 66 Page 1093.

([21]) European Patent Convention, Rule 26(2)

([22]) European Patent Convention, Rule 27

vi. A patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature.

vii. The US has no clauses that require a decision on whether a product or process is not patentable when its commercial exploitation may be contrary to morality or *ordre public*. European patent law does have these clauses, and the biotechnology directive ([23]) specifies a non-exclusive list of inventions that are not patentable:

a. processes for cloning human beings;

b. processes for modifying the germ line genetic identity of human beings;

c. uses of human embryos for industrial or commercial purposes

d. processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

4. GENOMES & PATENTS

An enormous amount of data has been generated in determining the sequences of the genomes of living systems. At the time of collection of the data for the human genome project the US National Institutes of Health claimed ownership of the data, triggering many to attempt to patent DNA sequences (initially even where a use could not have been known). Many scientists were concerned with this approach – not only because of a lack of utility of the naked DNA sequences in question. ([24])

Many international organizations asserted that the human genome (and by extension other genomes) are 'the common heritage of mankind'. These include the Human Genome Organization (HUGO) Ethics Committee (2000) ([25]), the Council on Responsible Genetics (CRG 2000)([26]), and the International Federation of Gynaecology and Obstetrics (1997)([27]). The Parliamentary Assembly of the Council of Europe (Council of Europe 2001) asserted that it was 'of the opinion that the results of this grandiose research effort – in which the United States has the lead over Europe – must be made available to all, genetic information being a common human heritage, as set out in Article 1 of the Universal Declaration on the Human Genome and Human Rights, adopted at UNESCO in Paris on 11 November 1997. The Assembly in particular refers in this context to the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine – Convention on Human Rights and Biomedicine (ETS No. 164) as well as its own Recommendations 1425 (1999) on biotechnology and intellectual property and 1468 (2000) on biotechnologies', ([28]) as well

([23]) DIRECTIVE 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions

([24]) HUGO Statement on the Patenting of DNA Sequences and Rebecca S. Eisenberg & Robert P. Merges, *Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial CDNA Sequences*, 23 AIPLA Q.J. 1 (1995)

([25]) Human Genome Organization Ethics Committee, 2000. Genetic benefit sharing. Science, 290 (5489), 49.

([26]) CRG, 2000. The genetic bill of rights. Council for Responsible Genetics CRG, Cambridge. [http://www.gene-watch.org/programs/bill-of-rights/bill-of-rights-text.html]

([27]) International Federation of Gynecology and Obstetrics, 1997. *Patenting human genes*. http://www.figo.org/]

([28]) Council of Europe, 2001. *Recommendation 1512: Protection of the human genome*. [http://assembly.coe.int/Documents/AdoptedText/ta01/EREC1512.htm]

as that of UNESCO in its Universal Declaration on the Human Genome and Human Rights ([29]). UNESCO's Declaration states that, 'The human genome underlies that fundamental unity of all members of the human family...in a symbolic sense, it (the human genome) is the heritage of humanity...The human genome in its natural state shall not give rise to financial gain.'

What exactly is the 'common heritage of mankind'? Bartha Knoppers has described it as that which 'argues against private appropriation in favor of sharing, administration in the common interest, benefits and burdens equitably distributed, equitable access, peaceful use and preservation for future generations' ([30])

When the US Patent Office considered its guidelines for utility patents in 2001 it addressed the question of whether there should be patents on genes 'as the nature of the human genome is at the core of what it means to be human, and no person should be able to own/control something so basic.' They decided that 'patents do not confer ownership of genes, genetic information or sequences. The patent system promotes progress by securing a complete disclosure of an invention to the public, in exchange for the inventor's legal right to exclude other people from making, using, offering for sale, selling, or importing the composition for a limited time. That is, a patent owner can stop infringing activity by others for a limited time.'[20]

Jasper Bovenberg has argued that we should not simply focus on the criteria for patentability when examining whether the claim of ownership should be entertained. In focussing on utility, novelty, non-obviousness and even the requirement to ensure disclosure of a patented object, we detract from the question of whether or not such sequences should be patentable at all. ([31])

The United Nations has endorsed the UNESCO Universal Declaration 'stating, in a symbolic sense, that the human genome is the heritage of humanity. The Declaration stipulates that the human genome, in its natural state, shall not give rise to financial gains and that an international framework be established to make the benefits of research on the genome available to all.' ([32])

Bovenberg argues that the prohibition on financial gain is that the common heritage principle bars private appropriation. In addition, there is a need to apply this concept in practice. He addresses the first through the medium of the arguments of Grotius in relation to the legal status of the sea. Is the genome the property of an individual, *res nullius*, the property of nobody, *res communis* – common property, or *res publicae* – public property. In his arguments Grotius traced the origin of these terms, and hence the use to which each of these could be put. Grotius reached two conclusions from these definitions of property. '[F]irst, that which cannot be occupied, or which never has been occupied, cannot be the property of anyone, because all property has arisen from occupation.' Second, 'all that which has been so constituted by nature that although serving some one person it still suffices for the common use of all other persons, is today and ought in perpetuity to remain in the same condition as when it was first created by nature.' Based on these conclusions, Grotius then listed many objects that by nature were open

([29]) UNESCO, 1997. Universal declaration on the human genome and human rights., Geneva. [http://www.unesco.org/shs/human_rights/hrbc.htm]

([30]) quoted in De Jonge, B and Korthals M (2006), 'vicissitudes of benefit sharing of crop genetic resources: Downstream and upstream' Developing World Bioethics 6 144-157

([31]) Bovenberg JA (2006) 'Mining The Common Heritage of our Dna: Lessons learned from Grotius and Pardo' Duke Law & Technology Review 8

([32]) Universal Declaration on the Human Genome and Human Rights, UNESCO Gen. Conf. Res. 29 C/Res.16, reprinted in Records of the General Conference, UNESCO, 29th Sess., 29 C/Resolution 19, at 41 (1997) (adopted by the UN General Assembly, G.A. res. 152, U.N. GAOR, 53rd Sess., U.N. Doc. A/RES/53/152 (1999)

to the use of all; the water, the sun, the air and the waves. All of these were not susceptible to occupation, and their common use was destined for all. ([33]) This argument is not sufficient, however, for although the 'sea' is *res omnium communes*, that which is in the sea, including minerals and fish, can be owned by an individual. This argument, when applied to the genome, provides that the genome itself is common property but derived inventions or discoveries could in theory be owned. In relation to synthetic biology, it is conceivable that the genome and much of that which is used to produce a synthetic product is common to all, but the product itself could be owned, and therefore patentable. The use of genes to produce pharmaceuticals or probes for disease remains a commercial activity, therefore patentable if the criteria are met.

Grotius' argument about the sea and its contents could conceivably be extended to ownership of all that falls within the high and low water marks. Many countries provide for common ownership of land within these borders, with rights similar to those on common land.

Resnik ([34]) has argued very differently. In his article, *The human genome: common resource but not common heritage*, he states that '[T]hose who oppose proprietary control of DNA have voiced a variety of objections to the patenting of DNA sequences, including the claim that patenting DNA violates human dignity, the assertion that patenting DNA violates the sacredness of nature, and the hypothesis that patenting DNA will have adverse effects on the progress of science, medicine and agriculture'. The article quoted does not address these issues directly, but rather the idea that the human genome is the common heritage of mankind – to which Resnik takes exception. The article reminds the reader that 'The common-heritage idea has influenced ethical and policy debates concerning the commercialization of the human genome' for some time, and that this needs to be considered carefully. He argues that the 'main ethical and policy rationale for granting patents is utilitarian: patents promote scientific and technological progress by giving financial incentives to inventors, investors and entrepreneurs' The argument is reiterated that '[u]nder a theory known as the patent 'bargain', the government grants an inventor a private right in exchange for public disclosure of information in the patent application.' ([35])

Resnik's primary argument is that

'A moment's reflection on the nature of DNA is sufficient to show that there are some significant problems with regarding the human genome as mankind's common heritage. The first problem is that there is not a single, identifiable thing (or set of things) that constitute(s) the human genome. There is a significant amount of genetic variation among members of the species *Homo sapiens*. Although human beings share most of their DNA, there are thousands of single-nucleotide polymorphisms (SNPs), which vary from person to person (Venter et al. 2001). Human beings also exhibit a great deal of variation in haplotypes (or patterns of sequence variation). The second problem is that there is not a single, identifiable set of people who inherit the human genome. Human beings share 98.5% of the DNA with chimpanzees, 95% with other primates, a great percentage of their DNA with other species, including fruit flies and yeast (Venter et al. 2001). So, only 1.5% of the human genome is actually 'our' common heritage; the

([33]) Bovenberg JA (2006) 'Mining The Common Heritage of our DNA: Lessons learned from Grotius and Pardo' Duke Law & Technology Review 8 paragraph 12

([34]) http://library.wur.nl/frontis/ethics/13_resnik.pdf

([35]) Miller, A.R. and Davis, M.H., 2000. Intellectual property: patents, trademarks, and copyright in a nutshell. West Group, St. Paul.

other 98.5% of the genome is the heritage of other species. ([36]) Should we say that the human genome is also the common heritage of the chimpanzees, the primates, all mammals, or even yeast? Does it make sense to say that non-human species can have property interests? ([37]) The third problem is that we cannot identify the persons or set of persons who have bequeathed our DNA to us. Did our ancestors ever intend to bequeath their DNA to all of humanity? These three problems show that is does not make much sense to regard the human genome as literally our common heritage. The common heritage idea may have symbolic importance, but it is an empirical fiction.' ([38]) In essence Resnik argues 'the human genome is not literally our common heritage. ([39]) If the human genome were literally our common heritage, the patenting of human DNA would be morally unacceptable because it would require the consent of every human being, a practical impossibility. ([40]) Even though the human genome is not literally our common heritage, it is still a very important common resource, and we have moral duties of stewardship and justice vis-à-vis the human genome. Our duties of stewardship include duties to refrain from harming the human genome but not duties to benefit the genome actively, because the idea of 'benefiting' or 'improving' the genome has clear eugenics implication. Our duties of justice imply obligations to share benefits fairly in genetics research and development. …. Finally, global benefit sharing may occur as products and services developed by companies become less expensive and more widely available. Short-term problems with access to genetic technology can be justified on the grounds that the system that allows such inequities, i.e. the patent system, promotes the interests of all members of society, especially the worst-off members, in the long run.' This argument runs counter to Lincoln's Gettysburg address, where he declared that "government of the people, by the people, for the people' is the essence of US democracy, yet there is no requirement for a referendum on every issue voted on by congress or decided by the President of the USA. Another counter-argument could be that as stewardship of the human genome does not necessarily involve active intentional improvement (other than through deliberate or capricious selective gene breeding, i.e., in the pairing and matching of sexual partners), it shall be made clear that the human genome can only be subject to the

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([36]) Substantively, it would appear that Resnik is questioning that there is such a thing as the human genome at all. If in agreement, one would need to ask then what it is that teams of scientists all over the world have spent billions of dollars and years sequencing; was the project misguided from the start, or is knowing the basis of human chemical life composition not an important research question? As President Clinton said at the conclusion and publication of the public sequencing effort in June 2000: 'Today we are learning the language in which God created life', of course it is understood that he meant human life.

([37]) The debate in fact might be broader than that. Again, given the huge sums and money and most often the collaborative research effort put toward sequencing the genome of living organisms, including that of humans, should there not be a social return regardless? Is the ownership/property discursive paradigm the most appropriate analytical and practical tool for the promotion of further innovation to increase knowledge on our species and ensure its survival onto an unseen future?

([38]) Juengst, E.T., 1998. Should we treat the human germ-line as a global human resource? In: Agius, E. and Busuttil, S. eds. Germ-line intervention and our responsibilities to future generations. Kluwer Academic Press, Dordrecht, 85-102.

([39]) A contrary view might suggest that there would seem to be some aspects in which the human genome can be understood as that which is common to humanity proper, or which forms part of its chemical (DNA) constitutive essence in parts, and including re-arrangement in a distinct chromosomal number—barring some viable anomalies. This enforces the boundaries of species. If what we take to constitute humanity in essence therefore is commonly inherited from progenitors to offspring in an unalterable chain of procreation (i.e., that no human child born of nature can fall off the species if his/her parents are 'human' from the start with respect to their genome), than it would not be far-fetched to posit that whatever the outcome of genetic permutation of sexual reproduction in the phenotypic variety of humans, there is safety in the knowledge that the genome of constitutive humans is therefore the essential non-excludable common heritage of these. No one will lose membership in a lifetime.

([40]) There are socially negotiated, acceptable and perhaps political, shortcut mechanisms for getting consent on other types of research involving human subjects, and for the disposition of research results; why not for research on the human genome and the use of its outcomes?

realm of mutational innovation which can be both fortuitous or debilitative to human health and condition, and ultimately to the human genome itself. What's more, there is no agreed global mechanism in place to ensure that the outcomes of research on the human genome are distributed equitably amongst all those who bear the essential minimum human genome sequence, i.e. Homo sapiens.

These arguments permit a return to the original questions, but in a slightly different form.

Is it only objects like the human genome that should be non-patentable as they are part of our common heritage? All the references to common ownership or heritage relate to human material; can this be extended to non-human products or processes that use material other than human tissue? The International undertaking on plant genetic resources, agreed in 1983, was based on the *'universally accepted principle that plant genetic resources are a heritage of mankind and consequently should be available without restriction'*. This was modified in 1991 when the Food and Agriculture Organisation passed resolution 3/91 that asserted that the concept of 'heritage of mankind' is subject to the sovereign rights of nations over their genetic resources ([41]) When the Convention on Biological Diversity was agreed in 1992, much of that which had been considered to be in common ownership was recognised (or reaffirmed) as within the sovereign rights of States. Article 15 addresses access to genetic resources and identifies these as sovereign rights. Decisions on their exploitation depend solely on the need to assure biological diversity, and do not presume their 'integrity' as a common resource. (would such an argument for the human genome be too premature or unrealistic given the Human Hap-Map project sequencing an ethnic diversity of genome sequences for differences etc?).

The United States Patent Office and the European Patent Office, after long deliberation have agreed that a mouse created for a particular purpose is patentable; the Canadian Supreme Court, in a divided judgement, found that under their patent law the mouse (the 'Harvard Oncomouse') could not be patented. The invention was titled transgenic animals, although it referred primarily to a mouse produced through the injection and incorporation of an oncogene into the embryo. The purpose was to provide for research into cancer. The court held that under Canadian Patent Law, a 'higher life form is not patentable because it is not a 'manufacture' or 'composition of matter' within the meaning of 'invention''. The court stated firmly that it was irrelevant whether the court believed that higher life forms such as the oncomouse ought to be patentable, the only question being addressed related to the wording of the Patent Act and whether the words 'manufacture' and 'composition of matter', within the context of the Patent Act, are sufficiently broad to include higher life forms. An important question discussed by the court related to whether it is defensible to permit the patenting of lower life forms, including bacteria whilst denying patentability to higher forms, such as a mouse. Among the arguments for a distinction is that the specific exception for plants and animals in trade agreements demonstrates that a distinction between higher and lower life forms is widely accepted as valid.

In Europe the Patent Office granted the Patent, stating: 'In the case at hand three different interests are involved and require balancing: there is a basic interest of mankind to remedy widespread and dangerous diseases, on the other hand the environment has to be protected against the uncontrolled dissemination of unwanted genes and, moreover, cruelty to animals has to be avoided. The latter two aspects may well justify regarding an invention as immoral and therefore unacceptable unless the advantages, i.e. the benefit to mankind, outweigh the negative aspects.' ([42])

([41]) FAO (2000) Multilateral Trade Negotiations on agriculture a resource manual http://www.fao.org/docrep/003/x7355e/X7355e06.htm

([42]) (Grant of European patent No. 0 169 762 (Onco-mouse/Harvard) (1992), OJ EPO 1992, 588, at pp. 591-92)

Case law in Europe, therefore, provides little evidence of any ability to decline granting of patents relating to higher life forms where other criteria are met; the only grounds would be where it is considered contrary to morality to exploit the 'invention' commercially.

An argument could be made that the information in the genome of any life form is so vast that it is in the public interest that the sequence should be placed in the public domain in order to ensure that innovation occurs. A patent would disallow others from using the information contained in the patented material for up to 20 years, and it may be that the holder is incapable of deriving the maximum benefit from the material in that time.

Hence the categories identified earlier may be confirmed as follows:

a. **That which is common to all humankind, and should not be patentable or directly exploited for commercial gain.**
   This should include the human genome and large projects such as the hap-map project ([43]) that address discoveries in the human genome. This would include artificial chromosomes introduced into human cells and would be justified under article 53(a) of the European Patent Convention (inventions for which the commercial exploitation would be contrary to morality). The International treaty on Plant Genetic Resources attempts to return some of that which was removed from the common heritage of mankind in the CBD to some crops (64) to permit free access to their genetic resources, arguing that '[n]o country is self-sufficient in plant genetic resources; all depend on genetic diversity in crops from other countries and regions. International cooperation and open exchange of genetic resources are therefore essential for food security'.

b. **That which, for a variety of reasons, should be placed in the public domain for all to use and exploit (the 'commons'). It may be that the process or product is so expensive to produce or require a vast range of expertise not available to any one organisation, or that the placing of the information in the public domain enables open standards that allow for the effective commercialisation and use of a number of products that use the technology or product.**
   This exclusion should address pre-competitive inventions, where the cost would be too great for a single organisation to bear. In addition, consideration of the compact between the private and public interest should be brought to bear. Where the range of information is so great as to make it impossible for a single organisation to develop and use during the lifetime of a patent, the basic information should be placed in the public domain or made available at minimum cost to others to use. This would ensure that information is not held so as to restrict innovation.

   As synthetic biology may involve the development of building blocks which could be assembled into a living organism, the development of open-standards that permit interaction between systems developed by the engineers needs to be explored.

c. **That which may, at the inventor's discretion, be protected through an intellectual property rights system to encourage innovation.**
   Inventors should be mindful of the choices that they may be able to make. They could choose to patent the invention, or could choose to place some or all of the information in the public domain or using some form of open licence. Importantly, where a choice is

([43]) See the HapMap website at http://www.hapmap.org/hapmappopulations.html.en. The HapMap is a catalog of common genetic variants that occur in human beings. It describes what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world.

made to patent, it should be remembered that although the rules relating to patents are almost universal, the patents themselves are national, and an inventor could choose the jurisdictions in which protection is sought. It may be that in order to encourage innovation in developing countries, inventors should be encouraged to choose not to patent their inventions in these countries. As the information regarding the invention (process or product) is disclosed in a patent application, an inventor could choose to use some sort of licence in countries where patent protection is not sought.

Patenting in biotechnology would have to serve some goal of utility (as a sub-category of equity served in purpose) in the distribution of the benefits, and perhaps also necessarily of the costs, of advanced research in biotechnology. Excluding one area of research from commercial ownership through the patent system does not mean that the benefits need necessarily have no return. Returns can bear social value for forming infrastructure for further development in research capacity or in real actual economic terms in the long run.

A second problem arises when dealing with Synthetic Biology – concern that unscrupulous individuals may attempt to use published information to synthesise dangerous DNA sequences. Due to the cost and analytical sophistication needed for synthesis, there are relatively few companies that synthesise long sequences of DNA. There have been suggestions that these companies screen all sequences for toxicity or infectivity before processing an order. That implies that databases of toxic or infective DNA sequences are available. These databases would of necessity fall within the ambit of the Database Directive ([44]). Regulation should ensure that all necessary information is readily available to these companies to permit the required searches. If the copyright protection provided for databases restricts access to the information necessary Article 6(2)(c) ([45]) or Article 9(c) ([46]) should be invoked to ensure that these companies are able to track possible dangerous sequences before synthesis.

([44]) Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases

([45]) Article 6: Exceptions to restricted acts
2. Member States shall have the option of providing for limitations on the rights set out in Article 5 in the following cases:
(c) where there is use for the purposes of public security of for the purposes of an administrative or judicial procedure;

([46]) Article 9 : Exceptions to the sui generis right
Member States may stipulate that lawful users of a database which is made available to the public in whatever manner may, without the authorization of its maker, extract or re-utilize a substantial part of its contents:
(c) in the case of extraction and/or re-utilization for the purposes of public security or an administrative or judicial procedure.

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European Commission

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« The Ethics of Synthetic Biology and Emerging Technologies»

« New Directions »

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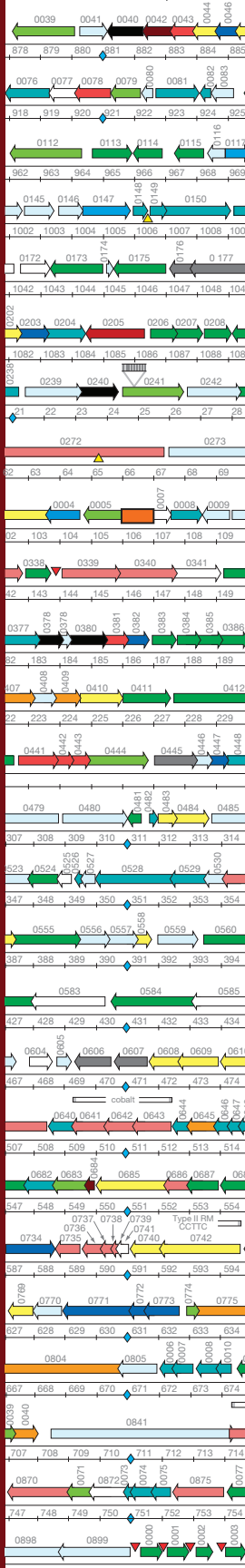
NEW DIRECTIONS

The Ethics of Synthetic Biology and Emerging Technologies



Presidential Commission for the Study of Bioethical Issues

December 2010

NEW DIRECTIONS

The Ethics of Synthetic Biology and Emerging Technologies

Presidential Commission
for the Study of Bioethical Issues

Washington, D.C.
December 2010

www.bioethics.gov

ABOUT THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

The Presidential Commission for the Study of Bioethical Issues (PCSBI) is an advisory panel of the nation's leaders in medicine, science, ethics, religion, law, and engineering. PCSBI advises the President on bioethical issues arising from advances in biomedicine and related areas of science and technology. The Commission seeks to identify and promote policies and practices that ensure scientific research, health care delivery, and technological innovation are conducted in a socially and ethically responsible manner.

For more information about PCSBI, please see www.bioethics.gov.

On the front cover: Portion of the genome map of *M. mycoides* JCVI-syn1.0. From Gibson, D.G., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 329(5987):52-56.

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PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

President Barack Obama
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Mr. President:

We are pleased to present to you this report, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*. In response to your request of May 20, 2010, this first report of the Presidential Commission for the Study of Bioethical Issues (PCSBI) examines the implications of the emerging science of synthetic biology, including the announcement in May of the successful creation of a self-replicating bacterial cell with a completely synthetically-replicated genome. It offers recommendations to ensure that America reaps the benefits of this developing field within appropriate ethical boundaries.

PCSBI approached this task through inclusive and deliberative engagement with ethicists, scientists, engineers, and individuals in faith, business, and non-profit communities. We held three public meetings, both in and outside of Washington, D.C., created an open forum for dialogue, and heard many diverse voices.

The Commission found that synthetic biology offers extraordinary promise to create new products for clean energy, pollution control, and medicine, to revolutionize chemical production and manufacturing, and to create new economic opportunities. With this promise comes a duty to attend carefully to potential risks, be responsible stewards, and consider thoughtfully the implications for humans, other species, nature, and the environment.

PCSBI concluded that synthetic biology is capable of significant but limited achievements posing limited risks. Future developments may raise further objections, but the Commission found no reason to endorse additional federal regulations or a moratorium on work in this field at this time. Instead, the Commission urges monitoring and dialogue between the private and public sectors to achieve open communication and cooperation.

The Commission recommends that the government, through a coordinated process or body within the Executive Office of the President, lead an ongoing review of developments, risks, opportunities, and oversight as this field grows. This review should be in consultation with relevant scientific, academic, international, and public communities, and whenever possible its results should be made public. We also recommend that reasonable risk assessment should precede any field release of synthetic organisms. We suggest support for public engagement, education, and dialogue to ensure public trust and avoid unnecessary limitations on science and social progress.

You gave the Commission a rare and exceptional opportunity to be proactive and forward looking in this first study. The Commission is grateful for the opportunity to serve you and the nation in this way. We would be happy to brief you if you have any questions about our recommendations.

Sincerely,

Amy Gutmann, Ph.D.
Chair

James Wagner, Ph.D.
Vice-Chair

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THE WHITE HOUSE

WASHINGTON

May 20, 2010

Dr. Amy Gutmann
President and Christopher H. Browne
Distinguished Professor of Political Science
University of Pennsylvania
1 College Hall, Room 100
Philadelphia, Pennsylvania 19104-6380

Dear Dr. Gutmann,

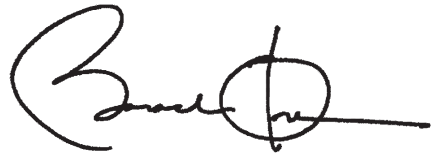
As you know, scientists have announced a milestone in the emerging field of cellular and genetic research known as synthetic biology. While scientists have used DNA to develop genetically modified cells for many years, for the first time, all of the natural genetic material in a bacterial cell has been replaced with a synthetic set of genes. This development raises the prospect of important benefits, such as the ability to accelerate vaccine development. At the same time, it raises genuine concerns, and so we must consider carefully the implications of this research.

I therefore request that the Presidential Commission for the Study of Bioethical Issues undertake, as its first order of business, a study of the implications of this scientific milestone, as well as other advances that may lie ahead in this field of research. In its study, the Commission should consider the potential medical, environmental, security, and other benefits of this field of research, as well as any potential health, security or other risks. Further, the Commission should develop recommendations about any actions the Federal government should take to ensure that America reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks. My Science and Technology Advisor, Dr. John P. Holdren, will be in communication with you about the scope and progress of your study.

I ask that the Commission complete its study within six months and provide me with a report with its findings, as well as any recommendations and suggestions for future study that the Commission deems appropriate. Given the importance of this issue, I request that the Commission consult with a range of constituencies, including scientific and medical communities, faith communities, and business and non-profit organizations.

It is vital that we as a society consider, in a thoughtful manner, the significance of this kind of scientific development. With the Commission's collective expertise in the areas of science, policy, and ethical and religious values, I am confident that it will carry out this responsibility with the care and attention it deserves.

Sincerely,



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The Commission is grateful to the members of the public who discussed their views during the public meetings and contributed written comments. The Commission's gratitude extends as well to the agency officials who provided assistance, often on short notice and under tight deadlines. Special thanks go to Alta Charo, Jacqueline Corrigan-Curay, Jason Dietz, Daniel Drell, Michael Firko, Bob Hargrove, Freeda Isaac, Theresa Lawrence, Sally McCammon, Larisa Rudenko, Greg Schweer, Allan Shipp, Deborah Smegal, Jessica Tucker, and Rob Weyandt.

Lastly, the Commission is enormously indebted to its talented staff for their expert work and unwavering commitment throughout this study. Valerie H. Bonham ably led the staff and guided this report to its timely completion. The Commission thanks its other staff members and consultants—Andy Burness, Judith E. Crawford, Alison Faith Davis, John Donnelly, Debbie Forrest, Kathi E. Hanna, Chris Havasy, Holly Fernandez Lynch, David G. Miller, Anne Pierson, Jason L. Schwartz, Kayte Spector-Bagdady, and Esther Yoo—for their many important contributions. The Commission also thanks Diane M. Gianelli for serving as Acting Executive Director and ably guiding the Commission during its formative period.

EXECUTIVE SUMMARY

The 21st century is widely heralded as the century of biology. Building on the fundamental understanding achieved in the second half of the last century, revolutionary advances are expected to improve many aspects of our lives, from clean energy and targeted, safer medicines to new industries. Prominent among emerging technologies is "synthetic biology," which aims to apply standardized engineering techniques to biology and thereby create organisms or biological systems with novel or specialized functions to address countless needs.

The idea of managing or manipulating biology to identify or develop specific characteristics is not new. Scientists have used DNA to create genetically engineered cells and organisms for many years; the entire biotechnology industry has grown around our expanding abilities in this area. The shelves of grocery stores across the United States are stocked with genetically engineered foods. Medical testing for genetically linked diseases is widely used by people across society.

By contrast, the idea of assembling living organisms wholesale from nonliving parts has intrigued human imagination for centuries with no success outside of fiction. For some, that possibility came one step closer last May with the announcement that scientists at the J. Craig Venter Institute had created the world's first self-replicating synthetic (human-made from chemical parts) genome in a bacterial cell of a different species. Intense media coverage followed, and the announcement ricocheted across the globe within hours as proponents and critics made striking claims about potential risks and benefits of this discovery and whether it amounted to an early-stage example of "creating life."

In response, President Barack Obama asked the Presidential Commission for the Study of Bioethical Issues (the Commission) to review the developing field of synthetic biology and identify appropriate ethical boundaries to maximize public benefits and minimize risks. The Commission approached this task through inclusive and deliberative engagement with a wide variety of sources, including scientists, engineers, faith-based and secular ethicists, and others who voiced, as expected, sometimes conflicting views on the science, ethics, and social issues surrounding synthetic biology. Through public meetings

in Washington, D.C., Philadelphia, and Atlanta, the Commission created a forum for open dialogue to hear and assess competing claims about the science, ethics, and public policy relating to synthetic biology.

What the Commission found is that the Venter Institute's research and synthetic biology are in the early stages of a new direction in a long continuum of research in biology and genetics. The announcement last May, although extraordinary in many ways, does not amount to creating life as either a scientific or a moral matter. The scientific evidence before the Commission showed that the research relied on an existing natural host. The technical feat of synthesizing a genome from its chemical parts so that it becomes self-replicating when inserted into a bacterial cell of another species, while a significant accomplishment, does not represent the creation of life from inorganic chemicals alone. It is an indisputable fact that the human-made genome was inserted into an already living cell. The genome that was synthesized was also a variant of the genome of an already existing species. The feat therefore does not constitute the creation of life, the likelihood of which still remains remote for the foreseeable future. What remains realistic is the expectation that over time research in synthetic biology may lead to new products for clean energy, pollution control, and more affordable agricultural products, vaccines, and other medicines. The Commission therefore focused on the measures needed to assure the public that these efforts proceed with appropriate attention to social, environmental, and ethical risks.

President Obama gave the Commission a rare and exceptional opportunity in the world of presidential bioethics commissions to be forward looking instead of reactive. We are ahead of the emerging science, and this unique opportunity underscores the need for the government to act now to ensure a regular, ongoing process of review as the science develops. The Commission calls on the government to make its efforts transparent, to monitor risks, to support (through a peer-review process) the most publicly beneficial research, and to educate and engage with the public as this field progresses. The government must regularly review risk assessment and other issues as the science of synthetic biology progresses. Only through openness and active engagement with all the relevant communities will the government ensure ongoing public support and appropriate oversight. The Commission emphasizes the need to

engage the public over time through improved science education, a publicly accessible fact-checking mechanism for prominent advances in biotechnology, and other efforts promoting clearer communication on the state of science.

Basic Ethical Principles for Assessing Emerging Technologies

To reach its recommendations, the Commission identified five ethical principles relevant to considering the social implications of emerging technologies: (1) public beneficence, (2) responsible stewardship, (3) intellectual freedom and responsibility, (4) democratic deliberation, and (5) justice and fairness. The principles are intended to illuminate and guide public policy choices to ensure that new technologies, including synthetic biology, can be developed in an ethically responsible manner.

The ideal of *public beneficence* is to act to maximize public benefits and minimize public harm. This principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. Public beneficence requires that when seeking the benefits of synthetic biology, the public and its representatives be vigilant about risks and harms, standing ready to revise policies that pursue potential benefits with insufficient caution.

The principle of *responsible stewardship* reflects a shared obligation among members of the domestic and global communities to act in ways that demonstrate concern for those who are not in a position to represent themselves (e.g., children and future generations) and for the environment in which future generations will flourish or suffer. Responsible stewardship recognizes the importance of citizens and their representatives thinking and acting collectively for the betterment of all. Importantly, it calls for *prudent vigilance*, establishing processes for assessing likely benefits along with assessing safety and security risks both before and after projects are undertaken. A responsible process will continue to assess safety and security as technologies develop and diffuse into public and private sectors. It will also include mechanisms for limiting their use when necessary.

Democracies depend on *intellectual freedom* coupled with the *responsibility* of individuals and institutions to use their creative potential in morally accountable ways. Sustained and dedicated creative intellectual exploration begets much of our scientific and technological progress. While many emerging technologies raise "dual use" concerns—when new technologies intended for good may be used to cause harm—these risks alone are generally insufficient to justify limits on intellectual freedom. As a corollary to the principle of intellectual freedom and responsibility, the Commission endorses a principle of *regulatory parsimony*, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good. This is particularly important in emerging technologies, which by their very definition are still in formation and are not well suited for sharply specified limitations. While clear guidelines to protect biosecurity and biosafety are imperative, undue restriction may not only inhibit the distribution of new benefits, but it also may be counterproductive to security and safety by preventing researchers from developing effective safeguards.

The principle of *democratic deliberation* reflects an approach to collaborative decision making that embraces respectful debate of opposing views and active participation by citizens. It calls for individuals and their representatives to work toward agreement whenever possible and to maintain mutual respect when it is not. Public discussion and debate with open interchange among all stakeholders can promote the perceived legitimacy of outcomes, even if those outcomes are unlikely to satisfy all interested parties. An inclusive process of deliberation, informed by relevant facts and sensitive to ethical concerns, promotes an atmosphere for debate and decision making that looks for common ground wherever possible and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests.

The principle of *justice and fairness* relates to the distribution of benefits and burdens across society. Biotechnology and emerging technologies such as synthetic biology, for good or ill, affect all persons. Emerging technologies like synthetic biology will have global impacts. For this reason, every nation has a responsibility to champion fair and just systems to promote wide availability of information and fairly distribute the burdens and benefits of new technologies.

Recommendations

With these guiding principles in mind, the Commission considered the array of public policy issues surrounding the emerging science of synthetic biology and makes the following recommendations. The reasons behind each recommendation are provided in the body of the report, and all readers are urged to consider carefully this more comprehensive account. In the cases of recommendations 1, 3, 5, 9, 11, 12, and 17, the Commission recommends ongoing review by the government, in consultation with the relevant scientific, academic, international, and public communities, with initial action completed within 18 months and made public. Some of these actions could easily be completed sooner, and the government is encouraged to do so and make its progress public.

Promoting Public Beneficence

Under the principle of public beneficence, the Commission recommends that the government review and make public findings regarding the scope of its research funding, especially for risk assessment and ethical and social issues raised by synthetic biology. This will promote public engagement and ensure needed transparency regarding federal efforts in the field of synthetic biology.

Recommendation 1: Public Funding Review and Disclosure

Through a central body such as the Executive Office of the President, the federal government should undertake a coordinated evaluation of current public funding for synthetic biology activities, including funding for research on techniques for risk assessment and risk reduction, and for the study of ethical and social issues raised by synthetic biology. This review should be completed within 18 months and the results made public.

Most potential products of synthetic biology are in very early stages of development. Therefore, basic research is critical to further expansion of this science and its effective translation into useful products. Necessary funding decisions should be made with the goal of advancing the public good, whether these decisions support synthetic biology research or other fields. The Commission

does not offer an opinion on the relative merits of particular research directions, but recommends that such decisions receive ongoing evaluation as to the state of the science and its potential applications.

Recommendation 2: Support for Promising Research

Advancing the public good should be the primary determinant of relative public investment in synthetic biology versus other scientific activities. The National Institutes of Health, the Department of Energy, and other federal agencies should continue to evaluate research proposals through peer-review mechanisms and other deliberative processes created to ensure that the most promising scientific research is conducted on behalf of the public.

Information sharing is a critical mechanism for promoting scientific progress and innovation. The principle of public beneficence requires researchers, inventors, patent holders, and others to work together to develop creative strategies to maximize opportunities for innovation. The government should consider best practices and other policy guidance, if needed, to ensure that access to basic research results and tasks is not unduly limited.

Recommendation 3: Innovation Through Sharing

Synthetic biology is at a very early stage of development, and innovation should be encouraged. The Executive Office of the President, as part of the coordinated approach urged in Recommendation 4, should lead an effort to determine whether current research licensing and sharing practices are sufficient to ensure that basic research results involving synthetic biology are available to promote innovation, and, if not, whether additional policies or best practices are needed. This review should be undertaken with input from the National Institutes of Health, other agencies funding synthetic biology research, such as the Department of Energy and the National Aeronautics and Space Administration, the U.S. Patent and Trademark Office, industry, academia, and public civil society groups. The review should be completed within 18 months and the results made public.

Promoting Responsible Stewardship

The Commission endorses neither a moratorium on synthetic biology until all risks are identified and mitigated, nor unfettered freedom for scientific exploration. Instead, the Commission believes that the field of synthetic biology can proceed responsibly by embracing a middle ground—an ongoing process of prudent vigilance that carefully monitors, identifies, and mitigates potential and realized harms over time. Responsible stewardship requires clarity, coordination, and accountability across the government. While new agencies, offices, or authorities are not necessary at this time, the Executive Office of the President should lead an interagency process to identify and clarify, if needed, existing oversight authorities and ensure that the government is informed on an ongoing basis about developments, risks, and opportunities as this field grows. This process must be undertaken by an office with sufficient authority to bring together all parts of the government with a stake in synthetic biology and be sufficiently authoritative to effectively engage or oversee engagement with foreign governments.

Recommendation 4: Coordinated Approach to Synthetic Biology

The Commission sees no need at this time to create additional agencies or oversight bodies focused specifically on synthetic biology. Rather, the Commission urges the Executive Office of the President, in consultation with relevant federal agencies, to develop a clear, defined, and coordinated approach to synthetic biology research and development across the government. A mechanism or body should be identified to: (1) leverage existing resources by providing ongoing and coordinated review of developments in synthetic biology, (2) ensure that regulatory requirements are consistent and non-contradictory, and (3) periodically and on a timely basis inform the public of its findings. Additional activities for this coordinating body or process are described in other recommendations.

Because synthetic biology poses some unusual potential risks, as "amateur" or "do-it-yourself" (DIY) scientists and others outside of traditional research environments explore the field, these risks must be identified and anticipated, as they are for other emerging technologies, with systems and policies to assess and respond to them while supporting work toward potential benefits.

Recommendation 5: Risk Assessment Review and Field Release Gap Analysis

Because of the difficulty of risk analysis in the face of uncertainty—particularly for low-probability, potentially high-impact events in an emerging field—ongoing assessments will be needed as the field progresses. Regulatory processes should be evaluated and updated, as needed, to ensure that regulators have adequate information. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should convene an interagency process to discuss risk assessment activities, including reasons for differences and strategies for greater harmonization across the government. It should also identify any gaps in current risk assessment practices related to field release of synthetic organisms. These reviews should be completed within 18 months and the results made public.

Coordination and careful risk analysis are essential steps for responsible stewardship, but they are not sufficient. There are several additional approaches, which are known today and continue to evolve as our abilities in this field grow, to limit uncertain risks in synthetic biology. Technology can be harnessed to build in safeguards. A number of safety features can be incorporated into synthetic organisms to control their spread and life span. Surveillance or containment of synthetic organisms is a concrete way to embrace responsible stewardship.

Recommendation 6: Monitoring, Containment, and Control

At this early stage of development, the potential for harm through the inadvertent environmental release of organisms or other bioactive materials produced by synthetic biology requires safeguards and monitoring. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should direct an ongoing review of the ability of synthetic organisms to multiply in the natural environment and identify, as needed, reliable containment and control mechanisms. For example, "suicide genes" or other types of self-destruction triggers could be considered in order to place a limit on their life spans. Alternatively, engineered organisms could be made to depend on nutritional components absent outside the laboratory, such as novel amino acids, and thereby controlled in the event of release.

The timing of deliberate release of synthesized organisms into the environment and the need to analyze risks prior to release raises special concern. We must proceed carefully, particularly when the probability or magnitude of risks are high or highly uncertain, because biological organisms may evolve or change after release. For any field release, there must be adequate consideration of risk.

Recommendation 7: Risk Assessment Prior to Field Release

Reasonable risk assessment should be carried out, under the National Environmental Policy Act or other applicable law, prior to field release of research organisms or commercial products involving synthetic biology technology. This assessment should include, as appropriate, plans for staging introduction or release from contained laboratory settings. Exceptions in limited cases could be considered, for example, in emergency circumstances or following a finding of substantial equivalence to approved products. The gap analysis described in Recommendation 5 should determine whether field release without any risk assessment is permissible and, if so, when.

Synthetic biology is an international enterprise. Oversight and regulatory mechanisms should adopt an analogous approach, so that the United States is involved in regular discussions with other national and transnational organizations so they may seek coordination and consistency when possible.

Recommendation 8: International Coordination and Dialogue

Recognizing that international coordination is essential for safety and security, the government should act to ensure ongoing dialogue about emerging technologies such as synthetic biology. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, through the Department of State and other relevant agencies such as the Department of Health and Human Services and the Department of Homeland Security, should continue and expand efforts to collaborate with international governments, the World Health Organization, and other appropriate parties, including international bioethics organizations, to promote ongoing dialogue about emerging technologies such as synthetic biology as the field progresses.

Responsible conduct of synthetic biology research, like all areas of biological research, rests heavily on the behavior of individual scientists. Creating a culture of responsibility in the synthetic biology community could do more to promote responsible stewardship in synthetic biology than any other single strategy. There are actors in the world of synthetic biology, namely engineers, chemists, materials scientists, computer modelers, and others, who practice outside of conventional biological or medical research settings. These groups may not be familiar with the standards for ethics and responsible stewardship that are commonplace for those working in biomedical research. This poses a new challenge regarding the need to educate and inform synthetic biologists in all communities about their responsibilities and obligations, particularly with regard to biosafety and biosecurity.

Recommendation 9: Ethics Education

Because synthetic biology and related research cross traditional disciplinary boundaries, ethics education similar or superior to the training required today in the medical and clinical research communities should be developed and required for all researchers and student-investigators outside the medical setting, including in engineering and materials science. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, in consultation with the National Academy of Sciences, the National Academy of Engineering, the scientific community, and the public, should convene a panel to consider appropriate and meaningful training requirements and models. This review should be completed within 18 months and the results made public.

Additionally flowing from the principle of responsible stewardship, the Commission observed that careful and deliberate attention should be paid to discussions of potential moral objections as the field advances. Such moral objections include concerns that synthetic biology may conflict with essential conceptions of human agency and life; that its overall impact may be harmful to biodiversity, ecosystems, or food and energy supplies; and that it may fail to respect the proper relationship between humans and nature. The Commission devoted particular time and attention to discussing these possible moral objections during its deliberations. It heard relatively few objections from reli-

gious or secular ethicists concerning the present status of the field. Although the field currently is capable of significant but limited technical achievements, potential developments might raise further moral objections—for example, applications relying on the synthesis of genomes for higher order or complex species. Current objections to synthetic biology on moral grounds are often based on concerns regarding activities that the field is currently incapable of carrying out. However, continued evaluation and efforts to reach and maintain consensus will be needed as this field develops.

Recommendation 10: Ongoing Evaluation of Objections

Discussions of moral objections to synthetic biology should be revisited periodically as research in the field advances in novel directions. Reassessment of concerns regarding the implications of synthetic biology for humans, other species, nature, and the environment should track the ongoing development of the field. An iterative, deliberative process, as described in Recommendation 14, allows for the careful consideration of moral objections to synthetic biology, particularly if fundamental changes occur in the capabilities of this science and its applications.

Promoting Intellectual Freedom and Responsibility

The principle of intellectual freedom and responsibility asserts that restrictions on research, whether by self-regulation by scientists or by government intervention, should limit the free pursuit of knowledge only when the perceived risk is too great to proceed without limit. A moratorium at this time on synthetic biology research would inappropriately limit intellectual freedom. Instead, the scientific community—in academia, government and the private sector—should continue to work together to evaluate and respond to known and potential risks of synthetic biology as this science evolves. This effort may require the government to expand current oversight or engagement activities with non-institutional researchers. National Institutes of Health or the Department of Energy, for example, could be charged to sponsor education programs and workshops that bring together these groups. They could fund training grants or related programs to promote a culture of responsibility among this community. To exercise the appropriate level of oversight, the government will need to monitor the growth and capacity of researchers outside of institutional settings.

Recommendation 11: Fostering Responsibility and Accountability

The government should support a continued culture of individual and corporate responsibility and self-regulation by the research community, including institutional monitoring, enhanced watchfulness, and application of the *National Institutes of Health Guidelines for Recombinant DNA Research*. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate, and re-evaluate periodically, the effectiveness of current research oversight mechanisms and determine what, if any, additional steps should be taken to foster accountability at the institutional level without unduly limiting intellectual freedom. Academic and private institutions, the public, the National Institutes of Health, and other federal funders of synthetic biology research should be engaged in this process. An initial assessment should be completed within 18 months and the results made public.

The norms of safe and responsible conduct that have evolved over time for many researchers in institutional settings may not be understood or followed by those new to the field or outside of these settings. It is important to note that presently there appears to be no serious risk of completely novel organisms being constructed in non-institutional settings including in the DIY community. Scrutiny is required to ensure that DIY scientists have an adequate understanding of necessary constraints to protect public safety and security, but at present the Commission sees no need to impose unique limits on this group.

Recommendation 12: Periodic Assessment of Security and Safety Risks

Risks to security and safety can vary depending on the setting in which research occurs. Activities in institutional settings, may, though certainly do not always, pose lower risks than those in non-institutional settings. At this time, the risks posed by synthetic biology activities in both settings appear to be appropriately managed. As the field progresses, however, the government should continue to assess specific security and safety risks of synthetic biology research activities in both institutional and non-institutional settings including, but not limited to, the "do-it-yourself" community. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, working with the Department of Homeland Security, the

Federal Bureau of Investigation and others, should undertake and periodically update this assessment. An initial review should be completed within 18 months and the results made public to the extent permitted by law.

Certain risks—generally involving national security—often warrant additional protections. Completely free exchange of data and materials might endanger public safety, but unilateral action to limit exchange could damage American research efforts in synthetic biology if U.S. scientists and students are excluded from full collaboration with the international community. Several recent advisory groups have recommended ongoing discussions among research universities, industry, and government on this topic. The Commission agrees that scientists should be actively engaged in these debates.

Recommendation 13: Oversight Controls

If the reviews called for in Recommendation 12 identify significant unmanaged security or safety concerns, the government should consider making compliance with certain oversight or reporting measures mandatory for all researchers, including those in both institutional and non-institutional settings, regardless of funding sources. It may also consider revising the Department of Commerce's export controls. Any such change should be undertaken only after consultation with the scientific, academic, and research communities and relevant science and regulatory agencies such as the National Institutes of Health, the Department of Homeland Security, and the Environmental Protection Agency. Export controls should not unduly restrain the free exchange of information and materials among members of the international scientific community.

Promoting Democratic Deliberation

Through democratic deliberation, questions about synthetic biology can be explored and evaluated on an ongoing basis in a manner that welcomes the respectful exchange of opposing views. This principle yields several opportunities for government and non-government actors alike to work together to ensure that synthetic biology advances in ways that respect divergent views and that avoid some of the misunderstanding and confusion, which at times,

have hampered other scientific endeavors. To enhance democratic deliberation and thereby ensure that the progress in synthetic biology is widely understood and policy choices are thoughtfully considered, the Commission makes the following recommendations.

Recommendation 14: Scientific, Religious, and Civic Engagement

Scientists, policy makers, and religious, secular, and civil society groups are encouraged to maintain an ongoing exchange regarding their views on synthetic biology and related emerging technologies, sharing their perspectives with the public and with policy makers. Scientists and policy makers in turn should respectfully take into account all perspectives relevant to synthetic biology.

Recommendation 15: Information Accuracy

When discussing synthetic biology, individuals and deliberative forums should strive to employ clear and accurate language. The use of sensationalist buzzwords and phrases such as "creating life" or "playing God" may initially increase attention to the underlying science and its implications for society, but ultimately such words impede ongoing understanding of both the scientific and ethical issues at the core of public debates on these topics. To further promote public education and discourse, a mechanism should be created, ideally overseen by a private organization, to fact-check the variety of claims relevant to advances in synthetic biology.

This publicly accessible fact-check mechanism is among the most concrete ways by which public perception and acceptance of emerging technologies could be improved. Education also plays a key role in building public support for otherwise unfamiliar technologies. In light of our Nation's dependence on socially responsible scientific innovation for economic progress and individual well-being, the urgency of expanding effective science and ethics education cannot be exaggerated. Dialogue among individuals and public, private, and community groups demonstrates that science and its oversight do not belong exclusively to experts, highly trained professionals, or government officials. Science is a shared resource, affecting and belonging to all citizens.

Recommendation 16: Public Education

Educational activities related to synthetic biology should be expanded and directed to diverse populations of students at all levels, civil society organizations, communities, and other groups. These activities are most effective when encouraged and supported by various sources, not only government, but also private foundations and grassroots scientific and civic organizations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, with input from the scientific community, the public, and relevant private organizations, should identify and widely disseminate strategies to promote overall scientific and ethical literacy, particularly as related to synthetic biology, among all age groups.

Promoting Justice and Fairness

The principle of justice and fairness, at this very early stage of synthetic biology, yields two general recommendations that can be applied to both this technology and other emerging technologies. It directs those in government to consider rules for distribution of risks and benefits in research, and it directs those both in and outside of government to consider processes for just distribution of benefits and risks.

Recommendation 17: Risks in Research

Risks in research should not be unfairly or unnecessarily borne by certain individuals, subgroups, or populations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should lead an interagency evaluation of current requirements and alternative models to identify mechanisms that ensure that the risks of research in synthetic biology, including for human subjects and other affected parties, are not unfairly or unnecessarily distributed. Relevant scientific, academic, and research communities, including those in the private sector, should be consulted. This review should be completed within 18 months and the results made public.

Recommendation 18: Risks and Benefits in Commercial Production and Distribution

Risks to communities and the environment should not be unfairly distributed. Manufacturers and others seeking to use synthetic biology for commercial activities should ensure that risks and potential benefits to communities and the environment are assessed and managed so that the most serious risks, including long-term impacts, are not unfairly or unnecessarily borne by certain individuals, subgroups, or populations. These efforts should also aim to ensure that the important advances that may result from this research reach those individuals and populations who could most benefit from them. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate current statutory mandates or regulatory requirements for distribution of risks and benefits and consider developing guidance materials and voluntary recommendations to assist manufacturers as appropriate.

In summary, the ability to easily manufacture and manipulate DNA in the laboratory has enhanced scientists' productivity and opened new directions for scientific exploration. In the future, scientists may be able to create entirely new organisms and systems previously unknown in the world today. But breakthroughs such as this raise a host of complex and sometimes controversial issues. They can help humanity in many ways, but they invariably carry some risks and often raise public concerns and fears. With these unprecedented achievements comes an obligation to consider carefully both the promise and potential perils that they could realize.

The recommendations detailed in this report provide a publicly accountable basis for ensuring that the field of synthetic biology advances to improve human health and public welfare with processes in place to identify, assess, monitor, and mitigate risks on an ongoing basis as the field matures. Risk assessment should precede field release of the products of synthetic biology. Ongoing assessment and review is required in several areas to avoid unnecessary limits on science and social progress, and to ensure appropriate restrictions to protect individual safety and our shared environment. Ongoing dialogue about concerns regarding the implications of synthetic biology for

humans, other species, nature, and the environment should continue as synthetic biology develops from its infancy to a fully mature field of scientific inquiry and innovation.

CHAPTER 1
Introduction

On May 20, 2010, the J. Craig Venter Institute announced it had created the world's first self-replicating synthetic genome in a bacterial cell of a different species.[1] Although scientists have used recombinant DNA techniques to engineer pieces of the genetic code for many years, this achievement marked the first time that all of the natural genetic material in a bacterial cell was replaced with a synthetic (i.e., human made or chemically synthesized) copy of the genes necessary for that organism to function. This announcement made headlines around the globe. Reaction was immediate, and it spanned the spectrum from expressions of enthusiasm to cries of alarm. Thoughtful deliberation about the meaning of this achievement was impossible in the hours that elapsed between the breaking news and the initial round of commentaries that ensued.

There is general agreement that this first self-replicating synthetic genome is an exceptional achievement, but there is also vigorous debate about just how momentous the Venter Institute's success is. Some scientists consider it a quantum leap; others see it as an incremental stride.[2] Whether one considers the accomplishment a major advance, a more modest technical step, or some combination of the two, one cannot deny the importance of understanding the potential implications of this and related accomplishments for humankind. The ability to synthesize vaccines, drugs, biofuels, and crops could do much to advance human welfare. At the same time, these innovations raise concerns about what we do not know—that is, whether there are attendant human or environmental risks—and what we perhaps should not know, that is, how to engineer forms of "life" to serve our own purposes.

Rather than offer an immediate opinion on the possible ethical and public policy implications—both positive and negative—of this scientific and technical accomplishment, President Barack Obama asked the Presidential Commission for the Study of Bioethical Issues (the Commission) as its first order of business to recommend how the developing field of synthetic biology and related biotechnologies can best maximize public benefits, minimize risks, and observe appropriate ethical boundaries.[3] He turned to the Commission to conduct "a study of the implications of this scientific milestone, as well as other advances that may lie ahead in this field of research." It was directed to consider the "potential medical, environmental, security, and other

benefits of this field of research, as well as any potential health, security, or other risks." The President charged the Commission to provide recommendations within six months on "any actions the federal government should take to ensure that America reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks." Much stands to be gained by the government taking a deliberative and open approach to decision making in this and many other complex scientific and technical areas of public importance.

Recent advances in biotechnology have transformed the life sciences, yielding a level of innovation rarely witnessed in human history. These achievements raise a host of complex and often controversial issues. Breakthroughs can help humankind in many ways, but they invariably carry some risks. Discoveries of new ways of improving or enhancing life raise public hopes and expectations, but they also raise public concerns and, often, fears. Proponents of synthetic biology cite its potential to reduce our reliance on fossil fuels and transform medical care and human health, among other possible benefits. Critics express concerns about "playing God," threatening biodiversity and the organization and natural history of species, demeaning and disrespecting the meaning of life, and threatening longstanding concepts of nature. With these unprecedented opportunities and achievements comes an obligation to consider carefully both the promise and potential perils that they could realize.

Airing these expectations and concerns in a public forum maximizes the potential for public benefit and illuminates risks and possible harms—physical, environmental, and social—that deserve our attention and careful consideration. In addressing the President's charge the Commission therefore attempted to be an inclusive and deliberative body, encouraging the exchange of well-reasoned perspectives with the goal of making recommendations that will serve the public well and will advance the public good. It gathered specific information about the state of synthetic biology, reviewed the findings and recommendations of numerous U.S. and international groups, and listened to sometimes conflicting scientific, ethical, and social perspectives. It sought common ground where possible and generally found it. When common ground was impossible to find, the Commission cultivated mutual respect through active engagement with differing views.

The Commission's Process

In conducting its work, the Commission invited experts and representatives of the public to explore contested territory from multiple perspectives. Some guests presented information about recent and upcoming achievements in the science of synthetic biology, including current and future applications and benefits. Others shared their perspectives on anticipated risks, related regulatory and oversight issues, and ethical considerations. The Commission solicited questions from the public as well as from its own members. This format contributed to highly interactive and valuable sessions. In addition, the Commission encouraged the public to provide written comments throughout its deliberations, and nearly 40 individuals and groups submitted comments. It also consulted with relevant federal agencies and private entities considering similar questions.

Formal deliberations began with an overview of potential benefits. Without any realistic promise of benefits, no risks would be worth taking. Expert panelists cited a host of potential benefits including more efficient and effective drug development; accelerated synthesis of vaccines in response to pandemics; and the ability to engineer algae and other microbes to spur advances in clean-burning fuel, agriculture, bioremediation, and medicine. The Commission also heard about the promise of a robust bio-economy beginning to materialize in the form of novel technological platforms. These and other areas of research in synthetic biology offer significant opportunities for economic growth and job creation.

After discussing the possible benefits of synthetic biology, the Commission considered the current and foreseeable risks posed by this rapidly evolving field. Although the risks at this early stage in the field's development are well managed and relatively small in comparison to the anticipated benefits of the field, they do exist, and several themes emerged in Commission discussions.

First, sheer prudence suggests that we as a society must respect the intricacies of the natural world. Biological systems have developed over billions of years, and their interactions with the environment are astoundingly complex. We are far from being proficient speakers of the language of life, and our capacity

to control synthetic organisms that we design and release into the world is promising but unproven.

Second, understanding our own limitations is an essential prelude to minimizing the risks that will accompany ongoing breakthroughs in synthetic biology and related fields. Like other new technologies, synthetic biology poses uncertain risks. Rapidity of change, both in the field of biology and in the public's understanding of it, as well as accelerating information exchange and technological competence heighten these concerns. Today, predicting cell function from gene sequence alone is very difficult and often impossible.[4] While the successful synthesis of a functional bacterial chromosome is an essential technological step for the development of synthetic biology, it represents a preliminary advance. We remain far from having the scientific and technical expertise required to create truly novel functioning organisms. We must be cognizant, however, of our limited current understanding of what synthetic biology and related technologies may produce in the future and be willing to reassess benefits and harms as the field develops.

Third, ancillary effects and challenges should be recognized and considered. The rise of an economy based on biotechnology may expand jobs and lead to significant financial benefits, but it could also result in economic displacement, excessive demands on already scarce resources, and increased social and economic stratification. Anticipating all of the ramifications of our actions is impossible, but determining how to respond to this uncertainty is the better part of wisdom. The Commission also considered related questions regarding how the U.S. government can best respect intellectual freedom in scientific inquiry and nurture the development of synthetic biology in a way that maximizes its potential benefits while reducing the risks and likelihood of direct and indirect harms.

Critical to all of these themes is the importance of earning public trust in the integrity of both the scientific and engineering communities and the applicable regulatory systems. The Commission therefore focused on the need for greater public education and engagement on these issues as a prerequisite for public acceptance of this new technology and assurance of constructive criticism moving forward.

Basic Ethical Principles for Assessing Emerging Technologies

In approaching its task, the Commission was mindful of the need for an ethical framework for considering the implications of new and emerging technologies like synthetic biology, which itself represents one step in a long continuum of scientific innovation.[5] This is a unique opportunity to consider the ethics of an emerging technology at a very early stage of its development.[6] The Commission found many efforts to shape policy, governance, and regulation related to synthetic biology, but few examples of an ethical framework upon which to gird such proposals. Accordingly, in weighing alternative policy preferences and perspectives, it identified five ethical principles relevant to considering the social implications of synthetic biology as well as all emerging technologies. These principles provide a useful vehicle through which to evaluate the current state of the field and formulate the Commission's recommendations.

The guiding principles are: (1) public beneficence, (2) responsible stewardship, (3) intellectual freedom and responsibility, (4) democratic deliberation, and (5) justice and fairness. These principles should be understood as provisional guideposts. The Commission encourages others to subject these principles, and the recommendations based on them, to further refinements and revisions, as it has done and will continue to do in the future.

Public Beneficence

The ideal of public beneficence is to act to maximize public benefits and minimize public harm. The principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. In the case of emerging technologies like synthetic biology, this improvement may be by means of providing improved or more widely available forms of medical and health care, food, shelter, transportation, clothing, and eco-friendly fuel, along with other means of improving people's lives. Scientific and technological discovery often have the added potential of increasing economic opportunities, which also redound to the public good.

The *Belmont Report*, a landmark statement of ethical principles for research involving human subjects, defined beneficence to require that "[p]ersons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being."[7] Two general rules stem from this principle: first, do no harm; and second, maximize possible benefits and minimize possible harms.

For synthetic biology and other emerging technologies, we need to apply the principle of beneficence beyond the individual level, the primary emphasis of the *Belmont Report*, to the institutional, community, and public levels, while not overlooking possible harms and benefits to individuals. Policy makers should adopt a societal perspective when deciding whether to pursue particular benefits of synthetic biology research in the face of risks and uncertainty. When deciding whether to restrict these pursuits, a similar consideration of community interests and potential positive and negative impacts is essential.

Public beneficence requires that when seeking the benefits of synthetic biology, the public and its representatives be vigilant about risks and harms, standing ready to revise policies that pursue potential benefits with insufficient caution. The Commission explores the concomitant challenges of meaningful and valuable risk-benefit analysis and potential strategies to address them in the "Responsible Stewardship" section, below.

Responsible Stewardship

Among living beings, humans are in a unique position to be responsible stewards of nature, the earth's bounty, and the world's safety. Human society and governments have a duty to proceed prudently in promoting science and technologies, many of which can improve human welfare but also can harm the environment, create security risks, or otherwise lead to adverse consequences for vulnerable populations or future generations. The principle of responsible stewardship reflects a shared obligation among members of the domestic and global communities to act in ways that demonstrate concern for those who are not in a position to represent themselves (e.g., children and future generations) and for the environment in which future generations will flourish or suffer.

Scientists, policy makers, and the public are tasked with appreciating that the tools of science and technology possess both remarkable potential to enhance future lives and a spectrum of risks capable of causing harm. Both demand attention and action.

Responsible stewardship recognizes the importance of citizens and their representatives thinking and acting collectively for the betterment of all, especially those who cannot represent themselves. These activities must respect the significant impact—both positive and negative—that our decisions have on our world, both today and in the future.

Benefits and risks extend to humans, nonhuman species, and the environment, each with unique needs and vulnerabilities. Emerging technologies present particularly profound challenges for responsible stewardship because our understanding of these potential benefits and risks is largely incomplete, preliminary, and uncertain. The prospect of intentional misuse by malicious actors further complicates efforts to respond adequately to the spectrum of benefits and risks.

Responsible stewardship addresses these varied challenges by calling for actions that embrace potential benefits while mitigating risks over time and across all populations. It calls for broader risk-benefit discussions than what would typically be required based on a concern for public beneficence alone. The principle of responsible stewardship rejects two extreme approaches: an extreme action-oriented approach that pursues technological progress without limits or due regard for public or environmental safety, and an extreme precautionary approach that blocks technological progress until all possible risks are known and neutralized. While the action-oriented approach is irresponsibly brazen, the precautionary approach is overly wary. Both fail to carefully assess the most likely and significant benefits against the most likely and significant harms. Through the development of agile, measured oversight mechanisms, responsible stewardship rejects positions that forsake potential benefits in deference to absolute caution and those that ignore reasonably foreseeable risks to allow unfettered scientific exploration.

This principle is applied to synthetic biology and other emerging technologies through open decision-making processes informed by the best available science. Responsible stewardship calls for *prudent vigilance*, establishing processes for assessing likely benefits along with safety and security risks both before and after projects are undertaken. A responsible process will continue to evaluate safety and security as technologies develop and diffuse into public and private sectors. It will also include mechanisms for limiting their use when indicated.

Prudent vigilance does not demand extreme aversion to all risks. Not all safety and security questions can be definitively answered before projects begin, but prudent vigilance does call for ongoing evaluation of risks along with benefits. The iterative nature of this review is a key feature of responsible stewardship. It recognizes that future developments demand that decisions be revisited and amended as warranted by additional information about risks and potential benefits. The duty to be responsible stewards of nature, the earth's bounty, and the world's safety rests on concern not only for human health and well-being today but also, and importantly, for future generations and the environment looking forward.

Intellectual Freedom and Responsibility

Democracies depend on intellectual freedom coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways. Sustained and dedicated creative intellectual exploration begets much of our scientific and technological progress. Without the free marketplace of ideas we would not have many of the scientific discoveries and advancements that have aided us in harnessing energy, sustaining life, and raising our collective standard of living. Intellectual freedom, therefore, is critical for developing innovative technologies that can compete in the global marketplace, and it is a necessary condition for industrial and academic collaborations that yield useful products and tools. While many emerging technologies raise concerns about their potential malevolent use, these risks alone are generally insufficient to justify limits on intellectual freedom. If we as a society stifle intellectual freedom for fear of enabling harm, we will be unprepared and vulnerable if that harm is unleashed upon us. A robust public

policy regarding the responsible conduct of science must promote the creative spirit of scientists and unambiguously protect their intellectual freedom.

At the same time, responsible science should reject the technological imperative: the mere fact that something new can be done does not mean that it ought to be done. The history of science here and abroad is sadly full of examples of intellectual freedom exercised without responsibility that resulted in appalling affronts to vulnerable populations, the environment, and the ideals of the profession of science itself. Scientists who act irresponsibly are capable not only of harming themselves and other individuals, but also of harming their communities, their nations, and international relations. Society as a whole has a stake in what scientists and engineers do, and they must not operate as if their research is totally independent of the groups who will experience both the benefits and burdens of their work. Risks may be especially great when those who provide the means and those who experience benefits are not the same. It is society that collectively provides the means for scientists to do their work and it is to society collectively that scientists bear profound responsibility.

As a corollary to the principle of intellectual freedom and responsibility, the Commission endorses a principle of regulatory parsimony, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good. Regulatory parsimony is particularly important in emerging technologies, which by their very definition are still in formation and are not always well-suited for sharply specified limitations. The blunt instruments of statutory and regulatory restraint may not only inhibit the distribution of new benefits, but they can be counterproductive to security and safety by preventing researchers from developing effective safeguards.[8] With sufficient freedom to operate, tomorrow's achievements may render moot the risks of today. Self-regulation also promotes a moral sense of ownership within a professional culture of responsibility.

Democratic Deliberation

The principle of democratic deliberation reflects an approach to collaborative decision making that embraces respectful debate of opposing views and active

participation by citizens. It calls for individuals and their representatives to work toward agreement whenever possible and to maintain mutual respect when it is not.[9]

At the core of democratic deliberation is an ongoing, public exchange of ideas, particularly regarding the many topics—in science and elsewhere—in which competing views are advocated, often passionately. Through formal and informal deliberative processes, decision makers and the people they represent should strive for mutually acceptable reasons to justify the policies that they adopt. These justifications should be expressed in ways that are accessible to those to whom such policies apply.

Citizens, individually and collectively, are active participants in democratic deliberation, engaging in dialogues both among themselves and with their representatives charged with developing policy. Public discussion and debate promote the legitimacy of whatever outcomes are reached, even if those outcomes are unlikely to please all interested parties. A process of active deliberation and justification promotes an atmosphere for debate and decision making that looks for common ground wherever possible and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests.

Importantly, democratic deliberation recognizes that while decisions must eventually be reached, those decisions need not (and often should not) be permanent, particularly when subsequent developments warrant additional examination. Democratic deliberation can correct the inevitable mistakes that arise when decisions are made collectively, provided that it is an ongoing, dynamic process. It recognizes the importance of challenging previously reached conclusions in light of new information or perspectives. It therefore requires citizens to take seriously the possibility that the views of one's opponents may be shown to be correct in the future and to be open to changing their own views.

With careful attention to the processes through which decisions are reached and justified, democratic deliberation promotes outcomes that are inclusive, thoughtfully considered, and respectful of competing views.

The principle of democratic deliberation, although a less familiar principle in bioethics than the principles of beneficence and justice, is particularly well-suited to the assessment of emerging technologies, including synthetic biology.[10] These fields offer the promise of remarkable potential benefits to science and society, yet they also raise risks regarding unintended consequences or possible malicious use. Each of these areas is clouded by uncertainty, complicating efforts to promote innovation while minimizing the likelihood of harm. Finding this balance demands careful ongoing review of the science and its applications. It presents an ideal opportunity for broad engagement and dialogue among the scientific community, policy makers, and the public. This active public engagement can enhance the decisions that are reached and the overall public understanding of them, as well as the related issues in science and technology that are central to the future of this new technology, as well as to our Nation and the world.

Justice and Fairness

The principle of justice and fairness relates to the distribution of benefits and burdens across society. Emerging technologies like synthetic biology, for good or ill, affect all persons. Society as a whole has a claim toward reasonable efforts on the part of both individuals and institutions to avoid unjust distributions of the benefits, burdens, and risks that such technologies bring. This same claim extends internationally to all those who may be affected—positively or negatively—by synthetic biology and its applications. As much as possible, and consistent with establishing essential incentives for creating new knowledge and translating it into vibrant markets, a fundamental principle of fairness suggests that society should seek to ensure that the benefits and burdens of new technologies are shared.

A commitment to justice and fairness is a commitment to seek to ensure that individuals and groups receive that to which they are entitled, that is, what they can reasonably and legitimately expect. Identifying, anticipating, and assessing what is reasonable to expect and determining how to measure and compare potential risks and benefits are complex activities, even in the best of circumstances and with the most complete data. They are made more difficult by the uncertainties surrounding scientific advances and the emergence of new technologies. How, for

example, are we to measure and compare the benefits of a technological innovation that leads to an effective medical treatment available on an unprecedented scale at low cost against the costs imposed by the disruption and displacement of previously existing technologies and the people whose livelihoods depends upon them? Advances produced through biotechnology can be highly beneficial but costly. How can and should we ensure that such advances reach those who could benefit most rather than being available only to those who can afford to pay? While such questions are difficult to answer, society must work to provide answers that are both just and fair.

The principle of justice and fairness also suggests that society should seek to ensure that the unavoidable burdens of technological advances do not fall disproportionately on any particular individual or group. Technological innovation benefits from public investment and from societal contribution toward safe and supportive research environments, and so it is reasonable that society expect a return on that investment.

Justice and fairness extend not only from individual societies to their constituents but also from individual societies to the international community overall. Emerging technologies like synthetic biology can and likely will have global impacts. For that reason, every nation has a responsibility to champion fair and just systems to promote the widest availability of information, the broadest distribution of beneficial technologies, and the most expansive culture of responsibility for biosafety and biosecurity.

About This Report

With these guiding principles in mind, the Commission considered the array of ethical public policy issues surrounding the field of synthetic biology. It reviews the science and potential benefits of this field in Chapters 2 and 3. Chapter 4 summarizes the existing oversight framework for new and emerging technologies like synthetic biology. Chapter 5 examines the implications of synthetic biology as viewed through the five principles described above and offers recommendations to ensure that society reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks.

[1] Gibson, D.G., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 329(5987):52-56.

[2] *See, e.g.*, Endy, D., Terman Fellow and Assistant Professor of Bioengineering, Stanford University. (2010). Overview and Context of the Science and Technology of Synthetic Biology. Presentation to the Presidential Commission for the Study of Bioethical Issues, July 8, 2010. Available at: http://bioethics.gov/transcripts/synthetic-biology/070810/overview-and-context-of-the-science-and-technology.html; Prather, K., Assistant Professor, Department of Chemical Engineering, Massachusetts Institute of Technology. (2010). Applications of Synthetic Biology. Presentation to the Presidential Commission for the Study of Bioethical Issues, July 8, 2010. Available at: http://bioethics.gov/transcripts/synthetic-biology/070810/applications-of-synthetic-biology.html; Petsko, G.A. (2010). Hand-made biology. *Genome Biology* 11:124.

[3] Letter from President Barack Obama to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, May 20, 2010. Available at: http://bioethics.gov/documents/Letter-from-President-Obama-05.20.10.pdf.

[4] National Academies, Board on Life Sciences. (2010). *Sequence-Based Classification of Select Agents: A Brighter Line*. Washington, D.C.: National Academies Press; National Science Advisory Board for Biosecurity. (2010). *Addressing Biosecurity Concerns Related to Synthetic Biology*. Available at: http://oba.od.nih.gov/biosecurity/biosecurity_documents.html.

[5] *The Belmont Report*, issued in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, was pathbreaking in the field of bioethics. It articulated and applied a three-pronged ethical framework: respect for persons, beneficence, and justice. These principles have become a widely used tool through which to assess questions in human subjects research and related topics. However, the *Belmont Report's* principles demand refinement in light of new knowledge, different circumstances, and changing experiences. By proactively reflecting on and applying the ethical principles most relevant to our actions, we pursue a practical wisdom—knowledge that aims to produce the best results for society and the world.

[6] The Commission contrasts its work in this respect with that of the National Bioethics Advisory Commission, which was asked by President William Clinton to review ethical issues related to reproductive cloning *after* the successful cloning of an adult sheep. *See* National Bioethics Advisory Commission (1997). *Cloning Human Beings*. Available at: http://bioethics.georgetown.edu/pcbe/reports/past_commissions/nbac_cloning.pdf.

[7] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.

[8] For example, the "Variola Amendment" to the Intelligence Reform and Terrorism Prevention Act of 2004 made it criminal to produce, engineer, or synthesize the variola virus. The "variola virus" was in turn defined to include "any derivative of the variola major virus that contains more than 85 percent of the gene sequence of the variola major virus or the variola minor virus." 18 U.S.C. § 175c. The broad definition of "variola virus" made it unclear what was actually covered by the statute, and a strict interpretation of the definition would have potentially, and inadvertently, criminalized beneficial research such as production of the smallpox vaccine.

[9] Gutmann, A., and D. Thompson. (1996). *Democracy and Disagreement*. Cambridge, Mass.: Belknap Press; Gutmann, A., and D. Thompson. (1997). Deliberating about bioethics. *The Hastings Center Report* (May/June):38-41; Gutmann, A., and D. Thompson. (2000). Why deliberative democracy is different. *Social Philosophy and Policy* 17:161-180; Gutmann, A., and D. Thompson. (2002). Just deliberation about health care. In *Ethical Dimensions of Health Policy*. M. Danis, C. Clancy, and L. Churchill (eds.). Oxford: Oxford University Press.

[10] Daniels, N. (2008). *Just Health: Meeting Health Needs Fairly*. Cambridge: Cambridge University Press, 103-139; Fleck, L. (2009). *Just Caring: Health Care Rationing and Democratic Deliberation*. Oxford: Oxford University Press.

CHAPTER 2
Science of Synthetic Biology

Synthetic biology is the name given to an emerging field of research that combines elements of biology, engineering, genetics, chemistry, and computer science. The diverse but related endeavors that fall under its umbrella rely on chemically synthesized DNA, along with standardized and automatable processes, to create new biochemical systems or organisms with novel or enhanced characteristics. Whereas standard biology treats the structure and chemistry of living things as natural phenomena to be understood and explained, *synthetic* biology treats biochemical processes, molecules, and structures as raw materials and tools to be used in novel and potentially useful ways, often quite independent of their natural roles. It joins the knowledge and techniques of biology with the practical principles and techniques of engineering. "Bottom-up" synthetic biologists, those in the very earliest stages of research, seek to create novel biochemical systems and organisms from scratch, using nothing but chemical reagents. "Top-down" synthetic biologists, who have been working for several decades, treat existing organisms, genes, enzymes, and other biological materials as parts or tools to be reconfigured for purposes chosen by the investigator.

For the purposes of this report, the Commission focused on the molecular and cellular engineering techniques of synthetic biology and the most foreseeable benefits of this very early field. In time, synthetic biology products for clean energy, pollution control, agriculture, and medicine, may change our lives and our shared environment through the development of novel applications. Because the potential applications of synthetic biology are speculative at this time, and the field is advancing in exciting directions, it is inviting both optimism and unease among scientists and the public.

From Molecular Biology to Synthetic Biology

Synthetic biology is deeply rooted in molecular biology, a field that emerged decades ago with the discovery of the structure and composition of DNA. DNA molecules provide the instructions that direct cell growth, development, and differentiation in every living organism. They contain a sequence of four types of chemical building blocks—adenosine, thymine, cytosine, and guanine (A, T, C, and G)—that combine, ladder-like and in various order, into "base pairs" that are combined into sets called "genes" (see Figure 1).

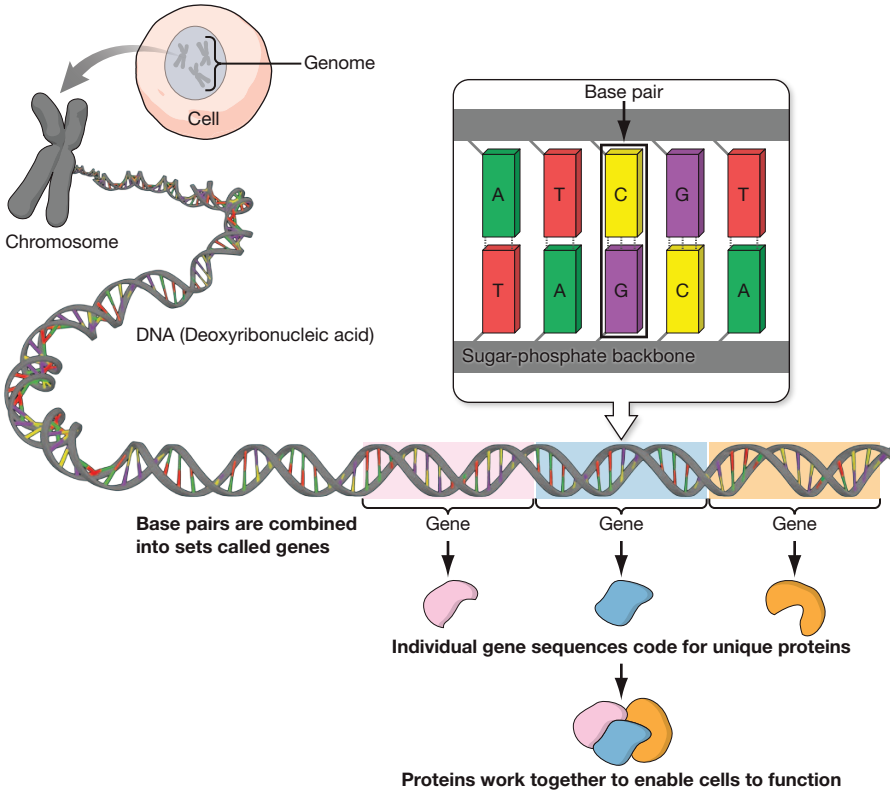

Figure 1: DNA, genes, and proteins.

Individual gene sequences code for particular proteins, which are what enable cells to function. Collectively, the complete DNA sequence of an organism is called its "genome." Genome variation is what makes individual organisms unique.

Though not described as such at the time, the earliest achievements in what is today called synthetic biology can be traced to the birth of genetic engineering in the 1970s. Genetic engineering, sometimes called gene-splicing or recombinant DNA research, is the intentional manipulation of an organism's genetic material using tools that cut, move, and reattach (recombine) DNA segments within and across different organisms.

In 1972, Stanford University biochemist Dr. Paul Berg created the first recombinant DNA molecules by splicing DNA from a bacterial virus into that of a monkey virus, SV40.[1] Two years later, scientists created the first transgenic mammal by introducing foreign DNA into mouse embryos.[2] Today, transgenic mice are a staple of biomedical research. They are used to regulate the expression of individual genes in order to understand how those genes interact with the environment and, in turn, affect human health. Using transgenic mice also enables researchers to increase or decrease specific proteins and better understand their individual roles and functions.[3]

As recombinant DNA technology began to develop in the 1970s, individual scientists, policy makers, and nations undertook profound debate about the safety and permissibility of this research—whether it was too dangerous to proceed at all—in the face of deep uncertainty.[4] Like synthetic biology today, great promise and potential risks were identified.[5] Expert and lay groups intensely debated concerns about possible adverse human health and environmental effects.

In 1974, a group of American scientists called for a moratorium on DNA research and the scientific community voluntarily obliged. To resolve this stalemate, in 1975 scientists from around the world, policy makers, lawyers, and press met together at the Asilomar Conference Center in Pacific Grove, California, to debate safety issues. The deliberations at the Asilomar Conference on Recombinant DNA led to formation of guidelines to ensure safety and a scientific peer review group, today known as the Recombinant DNA Advisory Committee of the National Institutes of Health (NIH). Both the guidelines and the Recombinant DNA Advisory Committee remain as critical components of the genetic engineering research oversight system (see Chapter 4 for further discussion). Many of the processes first proposed at the Asilomar

Conference remain in place, though some have changed in the intervening years as understanding of risks has improved. Scientists and policy makers have pointed to Asilomar as valuable precedent when considering debates regarding research in synthetic biology.

By the end of the 1970s, scientists had created the first commercial product of genetic engineering. An extraordinary benefit for human health, human insulin produced using recombinant DNA technology transformed treatment for diabetes.[6] Following its entrance to the market, public acceptance of this new technology grew and fears decreased significantly.[7]

In the early 1980s, researchers developed another revolutionary technique, called polymerase chain reaction (PCR). The PCR method enabled researchers to amplify and make simple changes to DNA pieces. PCR acts like a molecular copy machine, allowing scientists to enlarge individual DNA sections and manipulate them more easily.

By the early 1990s, automated DNA sequencing became available. This technology considerably accelerated the process of determining the order of individual gene segments, called "nucleotides," or, when very small (typically less than 20 base pairs), "oligonucleotides." Through large-scale genome sequencing efforts, primarily the public and private Human Genome Project, scientists were able identify the complete genetic codes of numerous naturally occurring organisms, including bacteria, viruses, and higher organisms such as mice and humans. The genome of a bacterial cell typically includes 5 to 10 million base pairs, although the synthesized genome of the bacteria in the J. Craig Venter Institute research, described below, contained just over 1 million base pairs.[8] By comparison, a fruit fly genome includes 165 million base pairs, and the human genome includes more than 3 billion base pairs. These significant differences in scale help place the achievement of the Venter Institute team in context. While it represents the first successful synthesis of a complete genome of a single-celled bacterium, it is a relatively small genome compared to those of other species.

After scientists could sequence naturally occurring DNA, they developed techniques to synthesize, or chemically construct, DNA and pieces of DNA.[9]

Figure 2 shows an early DNA synthesis machine and the individual chemicals, including nucleic acids, used to construct sequences. Within the last few years, researchers have developed methods to accurately synthesize increasingly longer segments of DNA and to bring them together into even larger segments of DNA. Stemming from this research, a small industry of commercial DNA synthesis providers has emerged. Five of the main companies, roughly 80 percent of the market, are based in the United States.[10]

Figure 2: Early DNA synthesis machine. (Courtesy of Life Technologies)

The development of DNA synthesis technology has enabled scientists to make entire genes, and, eventually, the complete genome of a microorganism using synthetic methods alone. By synthesizing a complete genome for a bacterial cell and transferring it to a cell with its own genome that was later lost, researchers at the Venter Institute created a self-replicating bacterial cell with entirely chemically constructed DNA (see Figure 3).[11]

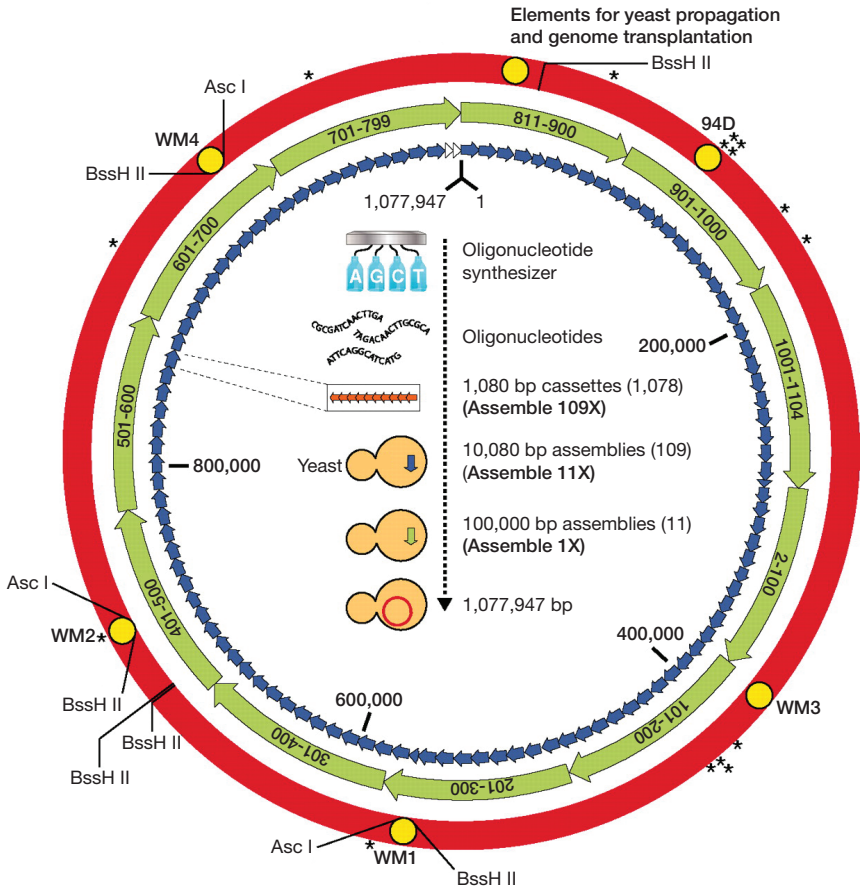

Figure 3: The assembly of a synthetic *M. mycoides* genome in yeast. Source: Gibson, D.G., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 329(5987):52-56.

Of note, many scientists observe that this achievement is not tantamount to "creating life" in a scientific sense because the research required a functioning, naturally occurring host cell to accept the synthesized genome. At the same time, this development should not be undersold. For many, this work represents the "proof of principle" that synthetic biology techniques can be used to construct cells and other organisms with novel characteristics.[12] While this small step does not give us the ability to grow larger-scale organisms, human tissue, or other tools of regenerative medicine, it is an incremental step on which future technical and scientific achievements will build.

THE FIRST SELF-REPLICATING SYNTHETIC BACTERIAL CELL

A May 21, 2010 publication in the journal *Science* by researchers from the Venter Institute announced the design, synthesis, and assembly of the 1.08 million base pair chromosome of a modified *Mycoplasma mycoides* bacterial genome. Beginning with an accurate, digitized genome of the bacteria, the researchers added four watermark sequences to identify the genome more clearly. They then designed more than 1,000 cassettes of DNA including approximately 1,080 base pairs each, with 80 base pair overlaps on each cassette representing adjacent sequences. The fragments were assembled sequentially in yeast. First, 10 cassettes each combined to make 10,000 base pair intermediates. Ten of those intermediates next were assembled to produce eleven 100,000 base pair intermediates, which were then combined into the complete genome. The newly synthesized genome was initially grown in yeast before being isolated and transplanted into cells of another bacterium, *Mycoplasma capricolum*. The genome of the recipient cells were lost as the cells were incubated, resulting in viable, self-replicating *Mycoplasma mycoides* cells containing only DNA from the synthetic genome.

Early molecular biology laid the groundwork for today's synthetic biology, but more recent technological advances have accelerated its development. First, scientists have developed the ability to mechanically synthesize increasingly longer DNA segments accurately and more rapidly than had been possible previously. Second, the costs for DNA synthesis have fallen dramatically over the past decade, dropping from about $30 to well under $1 per base pair.[13]

Computer modeling, not readily available until recently, is also facilitating the design of novel genetically engineered biological systems. As with electrical or civil engineering, modeling is intended to help scientists predict the behavior of a system before it is actually built. Although biological systems are not nearly as easily modeled as an electronic circuit or a bridge, at least at this time, sophisticated simulations, mostly in single-cell systems, are contributing to improved computer modeling of synthetic biological systems.

Synthetic Biology Techniques and Strategies

As discussed previously, to date synthetic biology has been characterized by top-down and bottom-up approaches.[14] The techniques overlap to some extent, and both approaches share a common goal: to engineer specific biological functions with predictability and reliability. In the future, these approaches may come together. For now, it is useful to consider both as illustrative of different experimental methods to reach the same goal.

Top-Down Approach

Through the top-down approach, in use since the 1970s, scientists use synthetic biology to re-design existing organisms or gene sequences with the goal of stripping out unnecessary parts, or replacing or adding specific parts to achieve new or amplified characteristics and functions (see Figure 4). Using this approach, scientists aim to remove parts of an organism or genetic code to create what some have dubbed a "chassis organism" that can then be modified through the addition or subtraction of engineered genetic circuits or metabolic pathways.[15]

One recent example of the top-down approach in synthetic biology is the identification of a "minimal genome."[16] This research provided proof of principle that the total genetic material of a small bacterium, its genome, could be pared down into a functioning unit consisting of only a subset of the organism's original genes.

Top-down synthetic biology is also defined by borrowing properties from one or more living systems to create something new. One example is combining

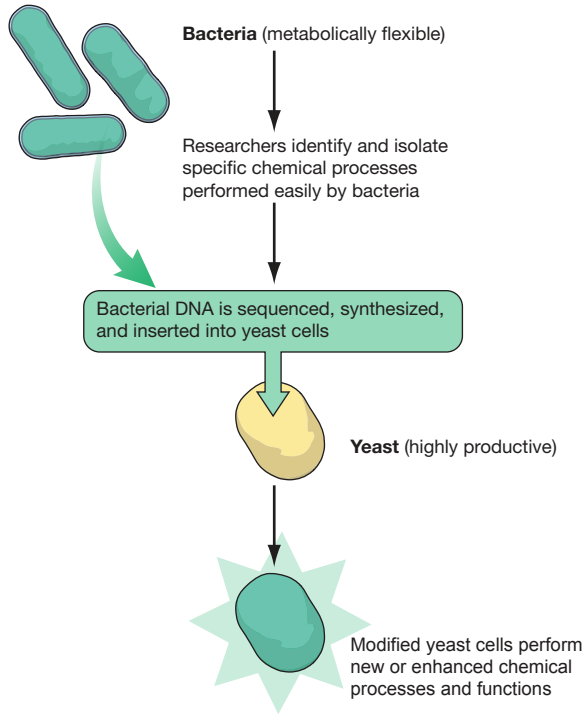

Figure 4: Example of a top-down approach to synthetic biology.

the productivity of yeast cells with the metabolic flexibility of bacteria. In this approach, researchers identify a range of chemical processes performed easily by various types of bacteria and insert these processing abilities into industry-standard yeast cells. In one case, the result was an efficient way to manufacture simple, yet high-value chemicals called methyl halides, used as agricultural fumigants and as fuel ingredients, starting with readily available plant matter such as corn stalks, sugar cane, and switchgrass.[17] Top-down synthetic biology is made easier through the use of increasingly accessible and inexpensive DNA sequencing and DNA synthesis technologies. Scientists can use them to "trawl" for bacterial genes that perform useful tasks and then copy and paste that DNA into yeast, without ever touching (or laboriously culturing) the bacteria, as was once required.[18]

Bottom-Up Approach

In bottom-up synthetic biology, which is relatively new and significantly more challenging, scientists aim to build living systems from raw materials starting with non-living components. For example, a team of scientists is aiming to create completely artificial systems using only non-living materials that mimic the behavior of actual cells. The products of this research are called chemical cells, or "Chells."[19] Bottom-up approaches also include efforts to create genetically engineered circuits and switches to turn specific functions on and off in response to identified stimuli. In some cases, the bottom-up approach could theoretically result in an entirely new organism or material with functions that may be different from currently existing organisms or cells. In other cases, parts with known functions may function differently when assembled into a new material or organism.

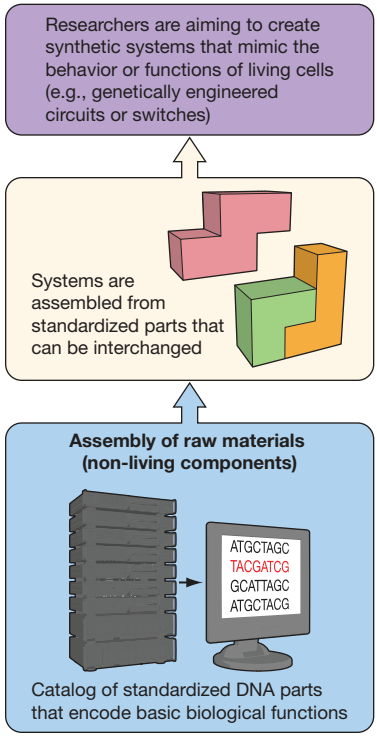

Figure 5: Example of a bottom-up approach to synthetic biology.

Bottom-up approaches are sometimes characterized by their reliance on assembling systems from chemically synthesized standardized parts that perform desired functions in a predictable manner and can be interchanged.[20] Like Legos® or computer components, a goal of this work is to develop a set of basic chemically synthesized pieces with identified and predictable functionality across different platforms. Exemplifying this strategy, the Registry of Standard Biological Parts, or "BioBricks,"™ physically houses an open catalog of standardized DNA parts that encode basic biological functions and can be easily combined and exchanged among

different devices and laboratories.[21] These standardized parts are made available to the public free of charge to further research in this field, and they are central to the annual International Genetically Engineered Machine (iGEM) student competition.

Defining Synthetic Biology

Despite these historical antecedents and complementary methodologies, providing a single definition for synthetic biology is a challenge even to those active in the field. Synthetic biology has attracted interest and investment from a range of different specialties. Biologists, chemists, engineers, and others bring their collective knowledge and expertise to this inherently interdisciplinary science. For this reason, synthetic biology may be viewed from various perspectives, which together help to explain its utility and versatility. A common thread is that synthetic biology is a scientific discipline that relies on chemically synthesized DNA, along with standardized and automatable

iGEM

The iGEM competition resembles a giant science fair for budding synthetic biologists. iGEM is a global synthetic biology competition involving mostly undergraduate students, although non-synthetic biology faculty, and high school students also participate. At the heart of the competition is BioBricks, a repository of standard DNA parts. Several months before the actual competition, competing teams receive a kit of DNA parts. Working at their own schools over a summer, teams design and build synthetic systems that operate in living cells. Examples of recent projects include an arsenic biosensor, wintergreen-scented bacteria, and color-coded microbes. Teams earn medals in a range of categories. Among the more popular of these is "human factors." Here, competitors win points for innovations that directly affect how people work together. Beyond building biological systems, the broader goals of iGEM include growing and supporting a community of science guided by social norms.

processes, to address human needs by the creation of organisms with novel or enhanced characteristics or traits.

To a biologist, synthetic biology is a window through which to understand how living things operate. It provides a direct and compelling means to test, through sequencing, modeling, and reproduction, our current understanding of the life sciences. The ability to model and manipulate living systems using synthetic biology is yielding new knowledge that will better define the functions of genes and physiological systems. In addition to advancing basic science, synthetic biology has important potential applications for medicine, including the design of safe and effective vaccines and targeted approaches to detect and cure diseases like cancer (see pp. 64-68).

From the perspective of a chemist, synthetic biology is a tool for manufacturing novel molecules and molecular systems for various uses. Scientists have used synthetic biology to directly manipulate chemical reactions in living systems, for example, in hopes of making medicines quickly and inexpensively.[22] They have also produced, on a small scale, novel biofuels that can harness energy from plants and the sun.[23] Collectively, these methods could reduce the use and deleterious effects of hazardous chemicals and petroleum-based products.

Synthetic biology viewed through an engineering lens is an opportunity to apply the techniques and tools of engineering to complex living organisms. Many aspects of engineering are based on the principle of standardization, which enables the reliable production of useful commodities. Engineers working in the field of synthetic biology hope to bring a similar level of standardization, predictability, and reproducibility to biology. Examples of engineered biological systems currently under study include synthetic systems that perform sophisticated medical functions—measuring components in body fluids and adjusting them through targeted administration of therapies—as well as biologically engineered "microcleansers" that can clean up oil spills or other forms of industrial waste.[24]

Is Synthetic Biology New?

The answer to this question is complex. Some scientists see synthetic biology as a revolutionary and qualitatively new field of science.[25] Others see current developments in the field as incremental advances in the decades-long growth of molecular biology, genetic engineering, and microbiology.[26] The term synthetic biology itself was first used as early as 1974 by Waclaw Szybalski who saw molecular biology's promise evolving from description to manipulation of genetic systems, heralding a new era of synthetic biology.[27]

One characteristic that distinguishes the synthetic biology of today from the molecular biology of years past is the significant role played by standardized parts, computers, and automation, accelerating a trend prevalent throughout biotechnology. Companion fields like nanotechnology and biomedical imaging share a reliance on automation and reusable, standardized parts.

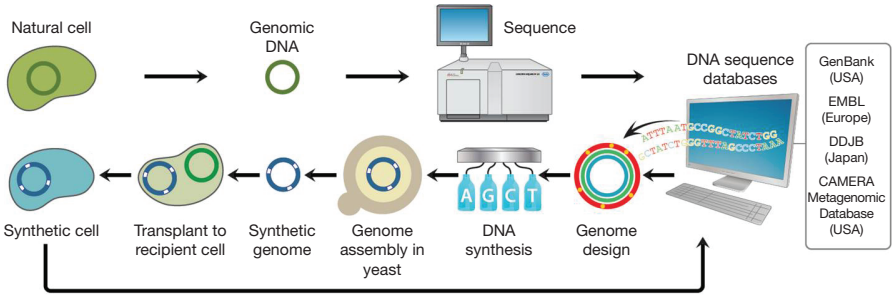

Figure 6: Overview of one process using synthetic biology techniques to produce synthetic cells. (Courtesy of J. Craig Venter Institute)

Recent technological advances and economic efficiencies in DNA synthesis and sequencing permit synthetic biologists to make, move, and manipulate DNA on a much larger scale than was possible only a few years ago. In contrast to conventional research in biology, the quest for predictable functions and standardization lies at the heart of synthetic biology. In this way, the field reflects the influence of engineering on its development.

The Future of Synthetic Biology

Synthetic biology holds great promise as a route to develop novel applications for medicine, agriculture, energy, and other industries. For example, the future may hold microorganisms that are "tailor-made for production of a specific chemical from a specific starting material . . . ." [28] Few of these potential products are anticipated immediately, however, and considerable technical and intellectual challenges remain.

Building a single cell from parts in the laboratory is a vastly different challenge than building an organism that interacts effectively and predictably in nature.[29] The design of synthetic or artificial organisms that can survive in natural environments is likely to be more challenging and unpredictable than doing so in a controlled setting.[30] It is extremely difficult to anticipate with confidence how a synthetic organism will react to and interact with a novel natural environment, adding to concerns about the risks of some applications of this field (see Chapter 3 for further discussion of applications).

Complexity and variation are linked. They both reflect the fact that DNA alone is not sufficient to create the biological functions necessary for the creation of biofuels, vaccines, soil sensors, or any desired product of synthetic biology. DNA can only function if it exists within an environment that provides the cellular components such as ribosomes, proteins, and other structures necessary to read, translate, and implement its genetic code. How any specific DNA sequence functions in a cell is also dependent on secondary modifications in its structure (though methylation) or folding pattern (through changes in histone proteins) that can promote or inhibit the transcription of genes, an area known as *epigenetics*. Much is still unknown

regarding the interactions between and within cells, actual or "artificial," as well as between cells and their environments.

Currently, the behavior of synthetic biological systems remains unpredictable.[31] Function cannot typically be accurately predicted based on DNA sequence alone or by the shape and other characteristics of the proteins and the biological systems for which it codes.[32] Also unknown is how synthetic biological systems will evolve. In most cases, biological systems that have been engineered by scientists quickly revert to "wild type" (i.e., evolve to lose their engineered function rather than gain a new one).[33] Although this notion may be reassuring, it does not rule out the possibility that systems might evolve in unpredictable and harmful ways, particularly if released outside the laboratory.

The potential promise of synthetic biology is immense. Research in synthetic biology has led to the development of genetic circuits and modules with predictable behavior, creation of novel combinations of cells in the laboratory that behave synergistically, and ever-expanding DNA construction capabilities.[34] The field, however, is young. Our understanding of complexity and variation in natural and synthetic parts and systems is far from complete, and the technical tools and skills required for large-scale synthesis and production continue to be refined. If carefully nurtured and guided, however, synthetic biology may provide an opportunity to integrate engineering and the biological sciences into the living world, with potential benefits to national and international security, food and energy supply, public health, and economic well-being.

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CHAPTER 3
Applications, Benefits, and Risks

Synthetic biology offers opportunities to apply biological and engineering principles to benefit humankind in unprecedented ways. Clean energy sources, targeted medicines and more efficient vaccine production, new chemicals, environmental cleansers, and hardy crops are some of the potential applications of this burgeoning field of science. While most of the fruits of synthetic biology remain in early stages of development, some applications are expected to come to market within a few years.[1] Success in these research efforts will yield new jobs as novel products and product streams develop. The pace of acceleration of synthetic biology is likely to increase dramatically in the years ahead.

Despite its promise, synthetic biology raises concerns about risks to human health, the environment, and biosecurity. Some of these potential harms include unanticipated adverse human health effects, negative environmental effects (anticipated or unanticipated) from field release and dual-use concerns when research undertaken for "legitimate scientific purpose…may be misused to pose a biologic threat to public health and/or national security."[2]

This chapter provides an overview of the potential applications, benefits, and risks of synthetic biology. Because renewable energy is expected to yield the first large-scale commercial products of synthetic biology, the Commission discusses this area first. Next, the Commission reviews potential health applications and benefits. Many products remain in research and development, but a few are nearing commercialization. Finally, the Commission provides a summary of potential agricultural, environmental, and biosecurity applications of synthetic biology, all of which are in more preliminary stages of development. Within these discussions the potential health, security, and other risks are examined, as well as anticipated technical challenges.

Renewable Energy Applications of Synthetic Biology

In general, biofuels are renewable energy sources derived from biomass, which includes material derived from plants, animals, and organic waste. Several methods can be used to harvest energy from biomass, including burning, chemical treatment, or biodegradation using the metabolic power of microorganisms. Processing biomass into biofuels or electricity through more complex

chemical and biochemical reactions, as opposed to simple combustion, limits environmental impact by minimizing the production of waste and decreasing net greenhouse emissions. Current practices for farming biomass for energy use employ a range of biological sources including grains, grasses, oil seed crops, trees, sugar, and corn.

Ethanol is the most common biofuel worldwide. It is produced mainly from corn or sugar cane. Biodiesel, another currently used biofuel, is made from vegetable oils, animal fats, or recycled restaurant grease. There are challenges to widespread commercial development of either of these fuels. For ethanol production, challenges include inefficiencies and energy costs for production, as well as concerns about the volume of plant sources needed and possible collateral impact on food prices. Biodiesel also involves significant energy costs for production.

Promise and Potential Benefits

Biofuels and related products produced through synthetic biology offer the potential to reduce global dependence on fossil fuel, cut harmful emissions, and minimize economic and political volatility surrounding fossil fuel reserves. Some biofuels produced with synthetic biology processes are expected to be available commercially within the next few years. Other research may not yield commercial products for a decade or more.

The various synthetic biology alternatives to current biofuel production methods include producing cellulosic ethanol (derived from cell walls rather than corn) and manufacturing other bioalcohols with synthetically manipulated biomass. Biofuel can also be produced from modified algae that use the natural process of photosynthesis to manufacture bio-oils, such as biodiesel, more easily than current chemical processes.[3]

The biochemical conversion of biomass into energy involves chemical reactions performed by biological systems. Enzymes in microorganisms such as bacteria break down biological materials into their component parts, from which energy can be extracted more easily. Perhaps the simplest example of biochemical conversion is a backyard composting bin, in which microorganisms gradually

degrade vegetation in the presence of oxygen. As is apparent from the surge of warm air that emerges upon opening the lid of the bin, this form of bioconversion is an energy-yielding process.

Synthetic biologists aim to improve the speed and efficiency of converting biomass into advanced, second- or third-generation biofuels with cleaner and more favorable energy-usage profiles.[4] This challenge may be met by creating "super-fermenting" yeast and bacteria through synthetic biology. These organisms have the potential to boost the power and potential of current industrially used microorganisms by means of new or altered genes. Synthetic biology also offers new biomass sources, or feedstocks, that are more efficient, reliable, low-cost, and scalable than current sources. These include forest and agriculture residues, some grasses, algae, oilseeds, and potentially sewage.[5]

Aside from biofuels, synthetic biology may also play an important environmental role by harnessing energy in novel, cleaner ways than traditional non-renewable energy production processes. Large global reserves of hydrocarbons, such as oil, gas, shale, and oil sands, might be leveraged with synthetic biology tools. Coal bed methane, for example, is a globally available source of natural gas. Its reserves are vast and largely untapped. Synthetic biology research is underway to harvest this methane through microbial digestion and other processes.[6]

Bioalcohols

Unlike ethanol derived from corn or sugar cane, cellulosic ethanol is made from cellulose fibers, a major component in the cell walls of all plants. Processing plant biomass not used for food, for example, waste corn stalks, straws, grass clippings, prairie grasses, and wood chips, could reduce economic and other pressures imposed by relying on corn for ethanol. However, cellulosic ethanol is a relatively low-yield bioalcohol and, like ethanol fuel derived from more conventional chemistries, still tends to corrode storage and transport equipment.

NEW PRODUCT PIPELINE: BIOALCOHOLS

Amyris (Emeryville, California) is using a synthetic biology platform to convert sugar into a range of products, including yeast-derived cellulosic alcohol fuel. The oil-based fuel is harvested in a similar fashion to the technique used by the Joint Bioenergy Institute (akin to separating cream from milk).[7]

British Petroleum and **DuPont** created a partnership to develop, produce, and market biobutanol.[8]

Gevo (Englewood, Colorado) genetically engineered bacteria to make biobutanol, a promising new biofuel. It also successfully converted cellulosic biomass into isobiobutanol and converted the fuel into jet fuel.[9]

Global Bioenergies (Evry, France) created yeast and bacteria with the capacity to transform sugar into hydrocarbons chemically identical to those distilled from oil. Bio-isobutane is the targeted end product; this hydrocarbon gas can be converted into high-octane gasoline.[10]

The U.S. Department of Energy's **Joint Bioenergy Institute** (Emeryville, California) is using synthetic biology to biodegrade plant biomass into biodiesel, which is skimmed off the top of a fermentation broth.[11]

LS9, Inc. (South San Francisco, California) developed the UltraClean™ product line that employs synthetic biology to produce its DesignerMicrobes™. These microorganisms use sugar cane or cellulosic biomass to create high-energy transportation fuels.[12]

The various commercial products and products presented and described in this report are intended to provide examples of current projects, not to endorse any particular entities.

A potentially more promising bioalcohol made by synthetic biology and used for energy production is butanol. Like ethanol, butanol is produced by the fermentation of sugars and starches or through the breakdown of cellulose. The crude product is then refined to make usable fuel. A particular advantage of butanol (and a similar biofuel called isobutanol) is that it can be used

directly in a traditional gasoline-powered engine. It also has a relatively high-energy density, resulting in better gas mileage than ethanol.[13] Some bacteria have the built-in enzymes to manufacture butanol, but the natural process is not very fast or high-yield. Synthetic biologists have engineered the easy-to-manipulate bacterium *E. coli* to improve this bacterial biochemical reaction to make butanol more industrially useful.[14]

Photosynthetic Algae

Another tool for creating biofuels via synthetic biology is through the use of photosynthetic algae. Algae are low-input, high-yield feedstocks that, under experimental conditions, produce substantially more energy per acre than land crops such as corn or soybeans.[15] To create biofuel from algae, the cells are grown, harvested, and treated chemically or thermally to recover the oil content inside algal cells, the so-called "bio-oil." While experimental yields have not yet been duplicated on a commercial scale, an alternative strategy currently under development with synthetic biology is engineering algal cells to secrete oil continuously through their cell walls and thereby increase yield. This time-saving step may support large-scale industrial operations in the near future.[16]

Proponents of farming algae note that it is biodegradable and therefore relatively harmless to the environment if spilled. Algae can also be grown on land and in water that is otherwise unsuitable for crops and food production. Making bio-oils using algae is expected to be less polluting and more efficient than converting vegetable oils or animal fats into biofuel.[17]

Through its capacity to consume carbon dioxide, algae offer the added benefit of mitigating greenhouse gas emissions. Unlike ethanol, algae-derived bio-oils, such as gasoline, diesel, and jet fuels, have been found to have very similar physical and chemical properties in comparison to currently used petroleum-based products, suggesting that these fuels are likely to be compatible with current transportation technologies and infrastructure.

NEW PRODUCT PIPELINE: PHOTOSYNTHETIC ALGAE

Aurora Algae (Alameda, California and Florida) is growing algae in open-pond systems consisting of readily available seawater. The pilot facility in Florida produces approximately three tons of algal biomass per year, with the ultimate goal of producing 40,000 tons of algal biomass per year.[18]

Joule (Cambridge, Massachusetts) engineers algae to make and secrete liquid hydrocarbons, bioethanol, and other fuel materials from sunlight and waste carbon dioxide (the sole feedstock) in a single-step, continuous process. Pilot operations are currently underway, with commercial development slated for 2012.[19]

Solazyme (South San Francisco, California) uses photosynthetic algae to produce an oil-based fuel, Soladiesel®, at industrial manufacturing scale with production capabilities currently in the tens of thousands of gallons. In July 2010, Solazyme delivered 1,500 gallons of algal-derived jet fuel to the Navy.[20]

Synthetic Genomics Inc. (La Jolla, California) engineered algal strains to create a biocrude oil that can be used as a feedstock in refineries, using a continuous biomanufacturing process that sidesteps the intermittent cycle of growing and harvesting. In July 2009, Synthetic Genomics entered into a $600 million multi-year agreement with ExxonMobil.[21]

The various commercial products and products presented and described in this report are intended to provide examples of current projects, not to endorse any particular entities.

Hydrogen Fuel

Hydrogen fuel is an additional area of focus for commercial applications of synthetic biology. Hydrogen is a highly desirable fuel source because it is clean-burning, producing water as a by-product. Hydrogen also has the second highest energy density per unit of weight of any known fuel.[22]

Several possible routes to generate biohydrogen are under investigation. One method uses engineered *E. coli* as a host organism to produce hydrogen in

addition to other biofuels.[23] Engineered algae are also being examined as sources of biohydrogen.[24] Finally, and perhaps most promisingly, researchers are investigating ways to produce high yields of hydrogen using starch and water via a synthetic enzymatic pathway.[25] The latter system is particularly attractive, as it may enable sugar to be converted into hydrogen fuel inside a vehicle itself. This would mitigate the problem of storage that exists today, as hydrogen takes up inordinate amounts of space at regular atmospheric pressure and compression of the gas requires energy and makes storage both difficult and dangerous.[26]

The synthetic processes being explored, if successful, will differ markedly from the current method of producing hydrogen fuel, which involves converting natural gas using steam. Natural gas techniques are costly, inefficient, and heavily reliant on fossil fuels. The synthetic biology-driven process is expected to cost significantly less while providing substantially higher yields, though research remains early in the developmental pipeline.

Risks and Potential Harms

Synthetic biology offers many potential methods to improve energy production and reduce costs, which deservedly generate attention and enthusiasm. A full assessment of these promising activities requires comparable attention to the current limitations, challenges, and anticipated risks or harms. This assessment is particularly important at this time because renewable energy applications may be the first synthetic biology products to come to market.

Contamination by accidental or intentional release of organisms developed with synthetic biology is among the principal anticipated risks. Unlike synthetically produced chemicals, which generally have well-defined and predictable qualities, biological organisms may be more difficult to control. Unmanaged release could, in theory, lead to undesired cross-breeding with other organisms, uncontrolled proliferation, crowding out of existing species, and threats to biodiversity.[27]

Consider biofuel production systems that employ synthetic biology and pond-grown algae. One hypothetical, worst-case scenario is a newly engineered type of high-yielding blue-green algae cultivated for biofuel production unintentionally leaking from outdoor ponds and out-competing native algal growth.[28] A durable synthetic biology-derived organism might then spread to natural waterways, where it may thrive, displace other species, and rob the ecosystem of vital nutrients, with negative consequences for the environment.

This scenario is theoretical. Considering it and developing appropriate precautions is nevertheless appropriate because of the rapid development of synthetic biology-generated photosynthetic algae for fuel production and the uncertain nature of the harm that may arise from accidental release. One of the advantages of synthetic biology is that many of the tools being developed include strategies to remediate such risks. Some of the approaches proposed include the engineering of so-called "terminator" genes or "suicide" switches that can be inserted into organisms, precluding them from reproducing or surviving outside of a laboratory or other controlled setting in the absence of unique chemical conditions.[29] Some are clearly sufficient to neutralize the risk of release, and others require further study as synthetic biology progresses.

Another risk in the energy sector is harm to ecosystems from the required dedication of land and other natural resources to production of biomass as feedstock for biofuels. If large areas of land were to be dedicated to biofuel development, this could put new and intense pressures on land, potentially affecting food production, communities, and current ecosystems. Because these applications of synthetic biology are still young, the impact of biofuel production on land use remains unknown. Some argue that efforts to develop and grow additional cellulosic biofuel will dramatically change and adversely impact the way land is used in the United States and abroad.[30] Others suggest that biofuel production can proceed safely with only minor adjustments in current land use practices.[31] Existing biodiverse prairie and meadow grasses may actually enhance the growth of feedstock for second-generation biofuels.[32] On balance, many anticipate the potential efficiencies and attendant reduction in reliance on fossil fuels offered by energy production using synthetic biology would offset anticipated risks to the environmental ecosystem as it exists today. But considerable uncertainty remains.

Health Applications of Synthetic Biology

Synthetic biology has the opportunity to advance human health in a variety of ways. Improved production of drugs and vaccines, advanced mechanisms for personalized medicine, and novel, programmable drugs and devices for prevention and healing are among a few of the expected achievements.

Promise and Potential Benefits

There is a long tradition of employing plants and other biological organisms to detect and cure human disease. Genetic engineering technology has been used for more than three decades in medicine to engineer bacteria with the ability to produce commercially relevant molecules like insulin and vaccines for hepatitis B virus and human papillomavirus.[33] Synthetic biology applications related to health build on this history, but most remain early in the research and development pipeline. The quick pace of biomedical research in general, and synthetic biology research in particular, suggests that this could change soon. This research is being conducted at universities and biotechnology or synthetic biology companies in the United States and overseas.[34]

Medicines

Synthetic biologists have refined a chemical technique called metabolic engineering to enhance the production of medicines. Through this process, scientists alter an organism's metabolic pathways—the series of chemical reactions that enable the organism to function at the cellular or organism level—in order to better understand and manage how those pathways work. They can redesign these pathways to produce novel products or augment the production of current products, like drugs. Synthetic biology can also be used to engineer molecules and cells that express proteins or pathways responsible for human disease. At some point these products may be used in efficient, large-scale screening methods to identify novel drugs for disease treatment or prevention.

One well-known example of synthetic biology in medicine is the re-engineering of a microorganism to make the antimalarial drug artemisinin more cheaply and efficiently. Malaria affects approximately two to three hundred million people each year and results in between 700,000-1,000,000 deaths, largely among young children in sub-Saharan Africa.[35] Artemisinin is a naturally occurring chemical derived from the plant artemesia, or sweet wormwood. It is an effective malaria treatment, but is difficult to obtain due to limitations on plant yield and high production costs. To address this problem, synthetic biologists at the University of California genetically engineered *E. coli* bacteria to produce a high volume precursor that can be chemically converted to artemisinin.[36] This semi-synthetic artemisinin is being developed today by the pharmaceutical company Sanofi-Aventis in collaboration with the California researchers and the Institute for OneWorld Health. If successful, these efforts should substantially reduce the drug's production cost and increase and stabilize world supply. Full-scale production is expected to begin shortly, with marketing expected in 2012.[37]

> "Making a few micrograms of artemisinin would have been a neat scientific trick," said Dr. Jay Keasling, whose laboratory originally developed the synthetic biological concept for making artemisinin. "But it doesn't do anybody in Africa any good if all we can do is a cool experiment in a Berkeley lab. We needed to make it on an industrial scale."[38]

Vaccines

Synthetic biology techniques are also being studied and used to accelerate the development of vaccines. Influenza vaccine production is among the key areas of focus. To develop a vaccine, one first needs to identify the virus strain, with its unique genetic code, against which the vaccine will be used. Synthetic biology tools, including rapid, inexpensive DNA sequencing combined with computer modeling, may streamline production time by accelerating this first step.

One industry group is developing a "bank" of synthetically created seed viruses for influenza vaccines that it hopes will enable more rapid vaccine production by reducing virus identification time.[39] DNA-based vaccines created "on-the-spot" to match actual, circulating viral genetic material may be a more efficient process for producing vaccine seed stock in the future.[40] However, these strategies are preliminary and may prove no more efficient or effective than conventional reverse engineering techniques. More research and experience is needed.

Advancing Basic Biology and Personalized Medicine

Twenty years ago, cloning, or replicating, a single gene was enormously time consuming. Today, such a task can be done in minutes by a machine, a development that has fueled rapid advances in synthetic biology. The ability to easily manufacture and manipulate DNA in the laboratory has enhanced scientists' productivity and opened new directions for scientific exploration. Researchers see great potential for synthetic biology to advance knowledge of fundamental biological principles. Expanding the DNA "alphabet" beyond its traditional four nucleotides—A, C, G, and T—to include non-naturally occurring nucleotides also gives synthetic biologists more flexibility in studying, detecting, and treating disease. For example, scientists recently used polymerase chain reaction (PCR) with novel nucleotides, a process that increases DNA's information potential and thus enables the manufacture of proteins with new properties.[41] To this end, researchers have already developed diagnostic tests using these DNA nucleotides to screen for human immunodeficiency virus, cystic fibrosis, and other diseases.[42]

In general, personalized medicine aims to apply the science of genomics to develop individually tailored, and thereby more effective, approaches to disease prevention and health care.[43] Synthetic biology offers useful strategies for advancing this goal. Many current cancer treatments focus on non-selective cell killing or on delivery to specific tissues. A growing body of knowledge supporting a molecular classification of tumors may facilitate the development of specifically designed detection devices matched to individual tumors. A synthetic biology approach currently under study is a cancer treatment that focuses on up to six cellular identifiers rather than one, effectively enabling

the treatment to be targeted more carefully and precisely toward the cells intended to be killed, while sparing healthy ones.[44]

Custom protein and biological circuit design may eventually enable the delivery of "smart proteins" or programmed cells that self-assemble at disease sites. Similarly, synthetic organisms could be developed to create a trigger to deliver or withhold treatment depending upon a local disease environment (such as low levels of oxygen) and provide targeted killing of cancer cells.[45] These and other novel approaches to tailored disease treatment may substantially improve outcomes and reduce the costs and burden of disease across the population.

While the benefits of synthetic biology to health care may prove monumental, significant hurdles remain. With the exception of semi-synthetic artemisinin and potential, near-term improvements in vaccine design, most of the anticipated health benefits of synthetic biology remain in the preliminary research stage. We are unlikely to see commercial applications from much of the biomedically oriented synthetic biology research for many years, although the pace of discovery is unpredictable.

Risks and Potential Harms

In addition to practical challenges, biomedical applications of synthetic biology raise potential risks for humans and the environment that are, in part, similar to those identified in the biofuels discussion and those commonly understood within the biomedical or greater engineering research communities today. Human health risks may arise from adverse effects of intentional or inadvertent release of the organisms engineered using synthetic biology. Infectious diseases may be transmitted to laboratory workers after needle sticks or to family members following airborne transmission of disease agents manipulated using synthetic biology techniques. Risks may also accrue to the wider human community or the environment if organisms proliferate without adequate means to limit reproduction.

Similarly, novel organisms developed with synthetic biology to treat illness may trigger unanticipated adverse effects in patients. The use of cell therapies of bacterial, or potentially, mixed microbial origin may cause infections or

unexpected immune responses. New organisms developed with the emerging technology of synthetic biology may pose unusual, if not unprecedented, risks resulting from their potential as biological organisms to reproduce or evolve.

Many of these risks are qualitatively similar to the risks that arise in horticultural biomedical and biotechnology research. There are well-established mechanisms in place to identify and manage future risks (see Chapter 4). Additionally, as with energy applications, internal mechanisms to reliably contain function and reduce or eliminate these risks are being developed. "Biological isolation," which is also termed "biosafety engineering," aims to build in molecular "brakes" or "seatbelts" that restrain growth or replication of partially or fully synthetic organisms.[46] Synthetic organisms can be engineered to be contained physically or temporally. Additional data are needed to assess how well biologically engineered safeguards, such as "kill switches" that activate after a defined number of generations, will work.

Agricultural, Food, and Environmental Applications of Synthetic Biology

Synthetic biology may also help to shift, if not substantially mitigate, some of the existing threats to our global food supply and environmental health. These potential benefits are in some ways more preliminary than the expectations for energy and health, but research and development in these fields are well underway.

Promise and Potential Benefits

In agriculture, efforts to manipulate crops and breed animals for specific purposes are not new. Many traditional farming practices, from plant breeding to animal husbandry, aim to direct evolution to achieve desired outcomes. Use of recombinant DNA technology, cloning, and other biotechnology tools have enhanced these practices. Taking these activities one step further, synthetic biologists are experimenting with high-yield and disease-resistant plant feedstocks that can be supplemented with efficient and environmentally friendly microorganisms to minimize water use and replace chemical fertilizers.[47] Researchers are altering the properties of plants through methods that combine metabolic components from various organisms in order to gain nutritional benefits, such as higher levels of food-grade protein.[48]

Efforts to remove waste using biological means date to at least 1972, when a researcher at General Electric applied for a patent on a form of *Pseudomonas* bacteria genetically engineered to digest oil slicks.[49] Environmental applications of synthetic biology are generally targeted to pollution control and ecological protection. The impact of naturally occurring oil-devouring microorganisms at the site of the 2010 oil spill off the U.S. Gulf Coast, for example, demonstrated how these organisms could reduce some types of pollution.[50] Synthetic biologists are eager to understand and direct these biological capabilities, or even enhance them, to respond to existing and future waste generated by human activities.

NEW PRODUCT PIPELINE: CROP ENHANCEMENT AND POLLUTION CONTROL

A synthetic biology-produced Pyrethium-grown compound may find use as natural insecticide.[51]

Synthetic biology-produced DNA sensors may be able to perform a range of roles, including detecting food spoilage and monitoring soil nutrition.[52]

Synthetic biology technology has been proposed to control biodegradation of a range of sources including toxic chemical pollutants such as industrial coolants, solvents, explosives, and residues from burning oil, coal, and tar.[53]

Other environmentally relevant examples of synthetic biology applications include laboratory-constructed microbial consortia, known as synthetic biofilms, which are being developed for use as environmental biosensors. These sensors could be used, for example, to monitor soil for nutrient quality or signs of environmental degradation. The design of biological "wetting agents," or biosurfactants, could increase the efficiency of bioremediation efforts and minimize the extent of damage from pollutants.[54] Biosurfactants are naturally produced by bacteria, yeasts, or fungi and are environmentally friendly in freshwater, marine, and terrestrial ecosystems. Synthetic biology may offer the ability to enhance the features of microbially produced biosurfactants to tailor them to specific spills or otherwise polluted areas.

Risks and Potential Harms

Synthetic biology applications in the context of agriculture, food, and the environment raise concerns broadly similar to those raised about genetic engineering in the past and those discussed above with respect to safety, resource management, and biodiversity. In brief, these risks include harms to humans, plants, or animals from, for example:[55]

- uncontrolled environmental escape or release and attendant disruption to ecosystems,
- new or sturdier pests—animal or plant—that may be difficult to control, and
- increased pesticide resistance and growth of invasive species.

As in the discussion of energy and health applications, the risks may be assessed and managed through existing protections long in use for biomedical and greater engineering research. Synthetic biology applications in the context of agriculture, food, and the environment may require more targeted efforts, however, including use of inbred checks, such as "suicide genes" or "kill switches" to ensure that they cannot propagate unintentionally.

Many potential applications of synthetic biology go well beyond the genetic engineering practiced throughout the biotechnology industry today. In the future, the field may be capable of creating entirely new organisms and systems previously unseen in the world today. Synthetic biology's critics and proponents alike worry that creating new organisms that have uncertain or unpredictable functions, interactions, and properties could affect ecosystems and other species in unknown and adverse ways. The associated risks of escape and contamination may be extremely difficult to assess in advance, as such novel entities may have neither an evolutionary nor an ecological history.[56]

Countering these concerns, at least somewhat, is experience showing that synthetic cells and systems in research settings have tended to be short-lived by comparison to those that have evolved in nature. Scientists have observed that synthetic organisms allowed to develop in the laboratory have consistently evolved toward nonfunctionality.[57] These are encouraging preliminary findings, but they do not eliminate the need for precautions in the event that

a future synthetic organism behaves differently than expected outside of the contained laboratory setting.

Another concern related to synthetic biology's impact on natural systems—crops grown for either biofuel or food consumption—is the broader effect on how society views and protects biodiversity. Does a chemically synthesized organism increase or decrease biodiversity, as measured by traditional taxonomy-based classification schemes? This concept becomes important in policy discussions pertaining to the use and potential abuse of land and other natural resources.

Biosecurity

Generally, the term "biosecurity" refers to the efforts needed to prevent misuse or mishandling of biological agents and organisms with the intent to do harm. The National Science Advisory Board for Biosecurity (NSABB), an independent federal advisory committee charged with advising the U.S. government on biosecurity issues and "dual use" research—that which may be used for either good or ill—defines the term as follows: "[b]iosecurity refers to the protection, control of, and accountability for high-consequence biological agents and toxins, and critical relevant biological materials and information, to prevent unauthorized possession, loss, theft, misuse, diversion, or intentional release."[58]

Unlike applications and potential applications of synthetic biology in the energy, health, agricultural, and environmental sectors, possible benefits in the biosecurity arena have not garnered significant public attention. Nor have they received comparable investment from academia, industry, or the government. It is nonetheless easy to anticipate some potential benefits.

Synthetic biology may enhance biosecurity by enabling researchers to identify biological agents of concern that may be developed synthetically or semi-synthetically. In the same way that the J. Craig Venter Institute "branded" the bacterium it synthesized this year with traceable information in the organism's genetic code, researchers may uniquely tag the genetic code of new organisms that they develop. When combined with other measures

to ensure biosecurity, this tagging process may provide an additional and effective deterrent to malicious use.

Similarly, biosecurity may be improved using the techniques discussed above for applications in energy, human health, agriculture, and the environment. As noted, "suicide" genes or terminator technologies built into the genome of a new organism to inhibit growth or survival outside of a contained environment may offer particularly effective means to counter biosecurity threats. Related tools could be crafted to ensure organism death in the face of particular chemicals or contexts. Uncertainties remain, however, with regard to the effectiveness of such strategies.

Concerns about dual use or intentional misuse of synthetic biology to do harm are among the most prominent critiques of this emerging technology. One of the most widely voiced risks attributed to synthetic biology is that it may be used, in the wrong hands, to intentionally create harmful organisms for bioterrorism. Recent examples of virus reconstruction using traditional recombinant DNA techniques fuel these concerns. These examples include the laboratory creation of infectious polio virus, the mycoplasma genome, and the 1918 strain of influenza virus.[59]

Frequently lost in these discussions about synthetic biology risks is recognition that DNA alone is not sufficient to create an independently functioning biological entity, such as a disease-causing virus that could spread. Despite the relative ease of access to known DNA sequences through public databases like GenBank[60] (an annotated collection of all publicly available genetic sequences), and equivalent databases across the globe, most experts in the scientific community agree that mere knowledge of a viral genome is far from sufficient to be able to re-constitute it or create a disease-forming pathogen. Rather, one must have an appropriate host and conditions for a virus to grow. Few individuals or groups today have the financial means or the technical skills to accomplish such ends, even when scientifically feasible. As the many technical challenges in synthetic biology affirm, it is not yet possible to craft functioning biological organisms from synthesized genomic material alone.

Risks and Potential Harms

With regard to biosecurity risks arising from synthetic biology, NSABB has twice issued reports and made recommendations to the federal government—first in 2006 and again in 2010.[61] In 2006, the group focused on synthesis of select agents and toxins, which are defined in law as certain infectious components of identified "select agent viruses," meaning those that the U.S. government has found to pose a severe threat to human health.[62] Following a review of the science at that time, the group made specific recommendations to reduce biosecurity risks, many of which the United States has since implemented, such as the establishment of a screening infrastructure for genetic sequence providers and others.[63]

NSABB's report "Addressing Biosafety Concerns Related to Synthetic Biology," issued in April 2010, offered four specific recommendations to ensure biosecurity in the current field of synthetic biology:

- Synthetic biology should be subject to institutional review and oversight since some aspects of this field pose biosecurity risks.
- Oversight of dual use research should extend beyond the boundaries of life sciences and academia.
- Outreach and education strategies should be developed that address dual use research issues and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology.
- The U.S. government should include advances in synthetic biology and understanding of virulence/pathogenicity in efforts to monitor new scientific findings and technologies.

These recommendations reflect an attempt to balance the considerable potential benefits of synthetic biology with the risks resulting from intentional or unintentional misuse of this technology and its products. Noticeably absent were recommendations to restrict access to genetic sequences separate from those components of Select Agents and toxins already limited by the U.S. Select Agent regulations (see Chapter 4). In large part, this determination appears to reflect the fact, as noted, that sequences alone will not yield, nor often be sufficient to predict, functions.

NSABB's work is not unique. Many experts and interested groups in the United States and abroad have recently devoted considerable time and energy to evaluating the biosecurity risks of advancing synthetic biology practices.[64] This still-young field benefits from a clear consensus among scientists and policymakers that biosecurity risks, while perhaps overstated by some, nevertheless are serious and warrant ongoing and proactive re-examination as technical capacity evolves. The tools used to mitigate these risks may also be the tools to mitigate environmental, health, and other potential risks. The tools to address risk depend on an expanding scientific knowledge base as much as potential benefits do.

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CHAPTER 4
Oversight

A wide array of existing federal laws and regulations apply to the emerging field of synthetic biology. The scope of federal authority depends on whether the activity involves research or production; whether federal funds are involved; the nature of the application (e.g., to generate drugs, food, cosmetics, or fuels); and whether the product is subject to national security or export controls. Applicable also are local institutional, municipal, and state requirements, many of which focus on safety and security.

This chapter presents a brief overview of the components of the U.S. oversight system as it relates to synthetic biology. It is intended to be a descriptive summary of the major regulatory laws and agencies without Commission recommendations or opinion (presented in Chapter 5). It focuses on the exclusive, as well as shared and overlapping, federal authorities governing research, development, and commercialization. Generally, synthetic biology is treated like other comparable areas of science and technology, and the federal government relies, in part, on local institutional-level oversight to identify and reduce risks.

The government's initial efforts at oversight of genetic engineering activities arose in the mid-1970s and focused, consistent with the state of the science at the time, on laboratory-contained research.[1] When the first genetically engineered organisms were being considered for field testing in the mid-1980s, the U.S. government issued a trans-agency guidance document, called "The Coordinated Framework," for regulating the research and development of biotechnology products. Fundamentally, the policy calls for the government to regulate genetically engineered products through existing legal frameworks established for products developed without genetic engineering. For example, drugs developed by means of genetic engineering are regulated under the pre-market review and approval standards of the Food and Drug Administration (FDA) for new drugs.[2] The key to this policy, reflected in regulations across the government, is its focus on risk rather than methodology. Regulation is predicated on a risk-benefit assessment of the characteristics of the final product (i.e., its intrinsic characteristics and features), not the method by which it is made.[3] Products presenting higher risks or greater uncertainty are subject to higher degrees of oversight. This approach enables existing agencies and regulations to serve, with revisions in current rules as technology evolves,

as the oversight framework for emerging biotechnology. Periodic reassessment, ideally through an ongoing process of open public dialogue, is required as new knowledge and new understanding of risks emerge. The Coordinated Framework's standards continue to drive the federal government's approach to oversight of biotechnology, including synthetic biology.

Through this system, some oversight protections apply broadly to anyone working with specific organisms or creating certain environmental effects. Other oversight is more narrowly focused, applying exclusively, for example, to researchers or the research setting. Regulatory programs of the U.S. Department of Agriculture (USDA) or FDA apply case-by-case to particular goods like food or drugs. USDA regulations govern also the interstate movement of certain infectious agents, agricultural pathogens, and pests. The Environmental Protection Agency (EPA) regulates the safety of new chemicals not addressed by other statutes, including industrial chemicals and pesticides, and oversees emergency management programs for the clean up of environmental hazards. The Occupational Safety and Health Administration (OSHA), Department of Transportation (DOT), and Department of Commerce (DOC) play roles as well, setting safety standards respectively for the workplace, interstate transfer of infectious agents, and export of disease-causing organisms or knowledge and technologies that may pose security risks.

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) help to ensure the safe and ethical conduct of synthetic biology research through promulgation of risk assessment and containment standards for laboratories and investigators. NIH specifically oversees research involving recombinant DNA molecules and receives advice from the NIH Recombinant DNA Advisory Committee (RAC), a group of non-federal experts governed by the openness and public meeting provisions in the Federal Advisory Committee Act.[4] Biosafety standards and requirements of review are set forth in the *NIH Guidelines for Recombinant DNA Research (NIH Guidelines).* The *NIH Guidelines* require risk-based classification and containment for NIH-funded research involving the construction or use of recombinant DNA molecules, as well as organisms and viruses containing these molecules. Synthetic nucleic acids are addressed to the extent that recombinant methods are used in their assembly.[5] NIH is currently considering a proposal to amend

the *NIH Guidelines* to specifically include research with synthetic nucleic acids, regardless of whether recombinant techniques are used. NIH published this proposal in March 2009,[6] and, in June 2010, after consideration of public comment, RAC recommended that the NIH Director adopt these changes. CDC and NIH also promulgate a widely accepted industry standard, *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, which establishes specific procedures for laboratory safety.[7]

CDC, USDA, the Department of Health and Human Services (DHHS), and the Federal Bureau of Investigation (FBI) also play specific roles in addressing concerns about biosecurity. The Federal Select Agent Program (FSAP), administered by CDC and USDA with the Animal and Plant Health Inspection Service (APHIS), regulates individuals and entities possessing, using, or transferring "select agents and toxins" within the United States.[8] Select Agents and toxins are pathogens or biological toxins that have been declared by DHHS and USDA to "have the potential to pose a severe threat to public health and safety."[9] The FBI conducts the security risk assessment of individuals requesting access to Select Agents.[10]

Taken together, these provisions form a protective patchwork quilt of regulations and guidance for research, the workplace, environmental risks, and in some cases pre-market review of safety and efficacy for new products. Anticipated advances in synthetic biology, however, raise questions about the capacity of this system to provide effective oversight of the entire field. Concerns about biosafety and biosecurity, for example, are frequently voiced. Biosafety focuses on protecting people, plants, animals, and the environment from accidental exposure to a pathogen or toxin with potential adverse effects. Biosecurity focuses on keeping biological agents and technologies out of the hands of those who might misuse them. For both biosafety and biosecurity, risk assessment—which typically extrapolates from data on known risks to characterize new and uncertain risks—may be particularly complicated for synthetic biology as novel or previously uncharacterized organisms are developed.

Oversight Challenges

The effective oversight of biotechnology relies on the assessment of the risks posed by the products generated and the process used to generate them. These assessments are predicated on understanding the biologic characteristics of the agent, its host, and the environment in which it will function.[11] In synthetic biology, a major concern is whether the scale of manipulation, using *de novo* chemical synthesis instead of conventional recombinant DNA techniques, raises sufficiently new levels of uncertainty about products, such as their characteristics or safety profile, to warrant new levels or forms of oversight.

The first generation of synthetic biology products is, or may likely be, relatively simple and similar to other genetically engineered products.[12] In the short term, agents generated through synthetic biology are unlikely to raise novel risk assessment or risk management issues. One of the biggest challenges in the oversight of synthetic biology, however, is its capacity to create novel entities that are increasingly dissimilar to known agents or organisms, making potential risks harder to assess. As the field begins to develop more complex, novel, and artificial agents and products, assessing the risks posed will be challenging, particularly for those products with the potential to be released into the environment[13] (see also Chapter 2 for a discussion of risks and benefits).

The increasing ease of access to the materials and supplies used to generate synthetic agents poses another unique oversight challenge. Gene and oligonucleotide sequences or parts can be commercially obtained with ease, and reagents and automated equipment for synthesizing nucleic acid sequences are available as well.[14] Deviant uses of synthetic biology could therefore, at least theoretically, occur outside of the scope of existing oversight mechanisms. At this stage, however, technical challenges to creating novel organisms are such that it is difficult to imagine the creation of a substantial threat.

Finally, current federal oversight of biotechnology is, in some cases, limited to entities that are owned or funded by the federal government. This means that research currently being conducted using private funds is not subject to some federal oversight.

Federal Authorities

Many federal agencies have jurisdiction over research and production activities involving synthetic biology. The Coordinated Framework organized lead responsibilities for oversight of intentional, beneficial uses of biotechnology, but did not compartmentalize oversight. The oversight is integrated, and overlap is minimized but necessarily exists as the framework is built to respond flexibly to changing science.

This shared oversight is described below, generally, in terms of the particular sectors discussed earlier in this report, but the discussion should not be understood to suggest silos or pigeonholes in the oversight system.

Biosecurity

Several regulatory schemes and initiatives are focused on reducing biosecurity risks arising from biotechnology. These include FSAP, export and interstate transfer limitations, and the 2010 guidance for synthetic double-stranded DNA providers.[15]

Federal Select Agent Program

FSAP is administered by DHHS/CDC and USDA's APHIS.[16] Congress established FSAP to limit the possession, use, and transfer of biological agents and toxins, designated as "Select Agents," that have the potential to pose a severe threat to public health and safety, animal and plant health, or to the safety of animal or plant products.[17] Facilities that possess, use, or transfer Select Agents, including for use in synthetic biology, must be registered with FSAP, and individuals or entities seeking to use, transfer, or possess Select Agents must apply for registration and approval for these activities. Select Agents that are regulated by both CDC and APHIS are referred to as "overlap" agents and involve threats to both sectors.[18]

The Select Agent regulations extend both to specific agents as well as certain genetic elements, recombinant nucleic acids, and recombinant organisms. Among the regulated genetic components are: (1) nucleic acids that can

produce infectious forms of any of the Select Agent viruses; (2) recombinant nucleic acids that encode for the functional form(s) of Select Agent toxins if the nucleic acids (a) can be expressed in vivo or in vitro, or (b) are in a vector or recombinant host genome and can be expressed in vivo or in vitro; and (3) Select Agents and toxins that have been genetically modified.[19] These regulations are specifically targeted to address scientific advancements such as synthetic biology. The nucleic acid sequence information of Select Agents is not regulated.[20]

Each individual or entity applying for registration must designate a "Responsible Official" who will ensure compliance with the regulations, including conducting annual inspections and overseeing proper disposition of Select Agents.[21] Registration is granted to entities only after a risk assessment is performed for the individuals who have access to, or the ability to gain possession of, a Select Agent or toxin. Additionally, registration is contingent upon a facility inspection by FSAP, and approval of additional documents such as security, biosafety, and incident response plans. Any certificate of registration issued is only valid for three years and for a single physical location, and no individual may access a Select Agent at any time without approval by the DHHS Secretary or the APHIS Administrator.[22] All records relating to Select Agents and toxins must be kept for three years and produced upon request.[23] Any theft, loss, or release of a Select Agent must be reported to the relevant agency immediately and an APHIS/CDC Form 3 must be submitted within seven calendar days.[24] Inspectors may inspect records and premises where Select Agent activities are carried out without prior notification.[25]

APHIS/CDC issued guidance recently for those who create or use synthetic biology and may therefore be subject to the Select Agent regulations.[26] This guidance was partially in response to the National Science Advisory Board for Biosecurity's (NSABB's) report, *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents*, which discusses the regulatory and oversight framework as it relates to synthetic genomics and Select Agents.[27] Elsewhere, the FBI has implemented a "tripwire" initiative in partnership with the U.S. synthetic biology industry to report suspicious requests for genetic sequences. The FBI also has conducted outreach to academia and industry and do-it-yourself (DIY) communities to improve biosecurity for synthetic biology research and uses.[28]

Export Administration Regulations

The Bureau of Industry and Security within DOC administers the Export Administration Regulations.[29] These regulations govern the export and re-export of dual-use commodities, software, and technology from the United States and apply to any individual or entity seeking to export.[30] Included in this group may be researchers collaborating with overseas colleagues, manufacturers with foreign plants, and gene synthesis providers shipping orders outside of the United States. Particularly relevant to the oversight of synthetic biology are provisions designed to restrict access to materials that have dual use applications (i.e., materials with both commercial applications and military or other defense applications).[31]

Items subject to the Bureau of Industry and Security's licensing authority are listed on the Commerce Control List (CCL).[32] Category 1 of the CCL contains "materials, chemicals, 'microorganisms,' and toxins."[33] Products are then classified according to "reasons for control:" (1) national security and dual use; (2) missile technology; (3) nuclear nonproliferation; (4) chemical and biological weapons; and (5) anti-terrorism, crime control, regional stability, short supply, United Nation sanctions, etc.

For each controlled item, detailed licensing requirements and policies for screening potential recipients are imposed. Licenses are provided depending on the nature of the threat. The end user receiving the product must also be screened against lists of proscribed individuals and organizations. Relevant screening lists include: (1) the Entity List (parties who may trigger a license requirement under Export Administration Regulations), (2) the Denied Persons List (parties denied export privileges), (3) the Unverified List (parties where the Bureau of Industry and Security has been unable to identify the end user in prior transactions), (4) the Specially Designated Nationals List (parties barred by the Treasury, Office of Foreign Assets Control), (5) the Debarred List (parties barred by the State Department under International Traffic in Arms Regulations), and (6) Nonproliferation Sanctions (parties that have been sanctioned under various statutes).[34]

Interstate Transfer Regulations

DOT sets rules for the safe and secure transportation of hazardous materials,[35] which may encompass materials necessary for, or created by, synthetic biology. Designated hazardous materials include substances (e.g., wastes and pollutants) that DOT believes are capable of posing an unreasonable risk to health, safety, or property during transport.[36] All persons transporting hazardous waste by air, rail, highway, or water must follow the regulations put out by the Pipeline and Hazardous Materials Safety Administration (PHMSA), an agency within DOT. Specified packaging, labeling, and transport requirements are imposed. For example, packages containing hazardous waste must be able to withstand conditions normally involved in transportation such as changes in pressure, temperature, and humidity, as well as vibrations and shocks.[37] Hazardous materials must also be labeled appropriately to warn transporters (and possible emergency responders) of the type of material contained in the packaging.[38] Hazardous material employees must receive training on PHMSA regulations so they can perform their functions safely.[39]

PHMSA is authorized to conduct inspections and enforce these regulations with civil penalties. Inspectors may send warning letters alerting transporters to probable violations or issue citations if they believe the alleged violation does not have a "direct or substantial impact on safety."[40] Any person who knowingly violates a requirement of these regulations may be liable for a civil penalty up to $55,000 per transportation or shipping violation, and up to $110,000 if the violation results in death, serious illness, serious injury, or substantial destruction of property.[41] In addition, anyone who knowingly, willfully, or recklessly violates the regulations and releases a hazardous material may be imprisoned for up to 10 years for any resulting death or bodily injury.[42] DOT reserves additional authority through the Federal Motor Carrier Safety Administration, the Federal Railroad Administration, the Federal Aviation Administration, and the U.S. Coast Guard.[43]

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

In October 2010, DHHS issued guidance for screening orders of synthetic double-stranded DNA. The guidance addresses the potential biosecurity concerns associated with the use of double-stranded DNA synthesis to reconstruct regulated pathogens and toxins. The guidance recommends "baseline standards…regarding the screening of orders so that they are filled in compliance with current U.S. regulations and to encourage best practices in addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls."[44] Compliance with the guidance is voluntary, but many of its specific recommendations reflect underlying statutory or regulatory mandates. Meeting its standards will help ensure that synthetic double-stranded DNA provided for use in synthetic biology will be in compliance with applicable federal regulations, namely the Select Agent regulations and the export administration regulations.[45]

The guidance emerged from a multi-year, public engagement process. Designed as "best practices," the intention of the guidance is efficient update as new information and technical skills emerge. The drafters explained: "[t]he target audience for this guidance is the gene and genome synthesis industry, because the technical hurdles for *de novo* synthesis of Select Agents and Toxins from double-stranded DNA are much lower than for *de novo* synthesis of these agents from single-stranded oligonucleotides."[46] This guidance proposes a screening framework for "commercial providers of synthetic double-stranded DNA that is 200 base pairs…or greater in length to address concerns associated with the potential for misuse of their products."[47] The framework includes "customer screening and sequence screening, follow-up screening as necessary, and consultation with U.S. Government contacts, as needed."[48]

Biosafety

Biosecurity and biosafety concerns frequently overlap, as do the oversight strategies employed to address them. In the earliest days of the genetic engineering era, oversight efforts focused on safety concerns shared by the public as well as scientists conducting this novel research. As the field has grown

and matured in the 40 years since then, the tools developed to address these concerns have evolved as well.

NIH Guidelines for Research Involving Recombinant DNA Molecules

NIH established the *NIH Guidelines* in 1976. They were created in light of public concern about emerging techniques for manipulating genetic material, and the 1975 Asilomar Conference on Recombinant DNA in which scientists from academia, industry, and government came together to establish shared principles for containment and safety in such research. The *NIH Guidelines* specify practices for constructing and handling recombinant DNA molecules and organisms and viruses containing recombinant DNA molecules. Compliance with the *NIH Guidelines* is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA[49] and would encompass synthetic biology falling within these confines as well. With input from NIH RAC, NIH has modified the *NIH Guidelines* nearly 30 times since their inception in order to keep pace with advances in science and biosafety. Satisfying their terms is a condition of NIH funding, and they are also widely accepted and followed voluntarily by scientists and organizations, both public and private, across the research enterprise. In addition, other government agencies, including DOE, the Department of Veterans Affairs, and USDA, currently have policies in place that state that all recombinant DNA research conducted or funded by those agencies must comply with the *NIH Guidelines*.[50] Through an active process of public engagement and deliberation, they have become a "gold standard" that is cross-referenced by numerous resources, including *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*) (see discussion below).[51]

The oversight process prescribed in the *NIH Guidelines* begins at the local level. Through the work of Institutional Biosafety Committees (IBCs)—local groups that include experts in safety and scientific practice—individual research plans are reviewed on a regular basis to assure that biosafety protections, including laboratory containment, are appropriate for the risk posed. Minimum containment measures (Biosafety Levels [BSL] 1-4) based on the known and unknown risks of particular experimental agents and designs are set forth in the *NIH Guidelines*, and institutions may impose additional

measures as deemed necessary to comply with their responsibilities under the guidelines.[52] Many IBCs also review other forms of research that entail biosafety risks as part of their institutionally assigned responsibilities.[53] Generally, NIH places primary responsibility on institutions to conduct oversight locally and non-compliance is expected to be self-reported.[54]

Following the advice of NIH RAC and other experts, in 2009 NIH proposed to clarify the scope of the *NIH Guidelines* to specifically cover nucleic acid molecules made solely by synthetic means. The proposed revisions, which are undergoing final review, aim to clarify the applicability of the *NIH Guidelines* to research with synthetic nucleic acids and to provide principles and procedures for risk assessment and management of such research.[55] NIH expects to finalize these amendments this year.

Private work may also interconnect with the federal oversight structure if the institution receives federal research funds. For example, although the work done by the J. Craig Venter Institute on the self-replicating synthetic genome was not federally funded, the Venter Institute is a major federal grant recipient, and thus, is required to adhere to the *NIH Guidelines*, regardless of the source of funding for a particular project.[56] In application, this means that along with IBC review, the Venter Institute followed the corresponding risk group and biosafety measures for the organisms it was working with as prescribed by the *NIH Guidelines*. In addition, the Venter Institute also must follow regulations directed toward private workplaces, such as the OSHA laboratory standards described below.

Biosafety in Microbiological and Biomedical Laboratories (BMBL)

CDC and NIH developed *BMBL* to address the "safe handling and containment of infectious microorganisms and hazardous biological materials,"[57] including those which may be used for synthetic biology. *BMBL* centers on the principles of containment and risk assessment. Containment under *BMBL* includes the "microbiological practices, safety equipment, and facility safeguards" required to protect people who work with biological material, the public, and the environment from exposure. Risk assessment allows the "appropriate selection of microbiological practices, safety equipment, and

facility safeguards" required to prevent what *BMBL* deems "laboratory-associated infections."[58] *BMBL* complements the *NIH Guidelines* and is broader in its focus. Laboratories that receive federal funding for research may be required to comply, if, for example, the agency requires compliance as a policy matter for its intramural labs, or as a term and condition of specific extramural funding. There is no federal law that requires compliance for all researchers regardless of funding. Thus, generally, they set a voluntary standard.[59] Biosafety standards evolve as scientific knowledge progresses, and *BMBL*, like the *NIH Guidelines*, is intended to evolve and adapt.

Workplace Oversight

OSHA regulates working conditions for employees in most private sector and federal government workplaces.[60] In addition, many states (State Plan States) have occupational safety and health programs that have been approved by federal OSHA and cover public sector (state and local government) as well as private industry employers.[61] Therefore, the regulations of OSHA or an equivalent State Plan State program will be relevant to most synthetic biology laboratories or workplaces. Under OSHA, employers must create an environment that is "free from recognized hazards that are causing or are likely to cause death or serious physical harm."[62] The regulations of OSHA or an equivalent State Plan State program lay out safety principles and precautions for working with and disposing of hazardous chemicals as well as toxic and hazardous substances. Particular attention is paid to ventilation, sanitation, protective equipment, machinery, and emergency procedures.[63] Hazardous waste cleanup and first aid procedures are also imposed.[64] Employers must evaluate the hazards of chemicals at their work place and inform employees about potential harms through "comprehensive hazard communication programs" including container labeling, warnings, and safety data sheets.[65]

The regulations of OSHA or an equivalent State Plan State program also protect employees who may be exposed to blood or other potentially infectious materials such as human bodily fluids, human unfixed tissues or organs, and Human Immunodeficiency Virus (HIV)-containing cells or culture medium.[66] Regulations require employers exposing employees to such substances to have exposure control plans, delineated methods of compliance, and special protocols pertaining to the HIV and the Hepatitis B virus.[67]

EPA also plays a role in workplace oversight through the Toxic Substances Control Act (TSCA). Under TSCA, EPA assesses risks to workers from exposure to new intergeneric microorganisms. EPA can impose personal protective equipment requirements and engineering control restrictions to control worker exposure to potentially harmful substances.[68]

Energy

Oversight provisions for synthetic biology in the energy sector include the general security and safety standards described above. They also include specific provisions aimed at various products, for example, biofuels, biosensors (for various applications), and chemical oil dispersants. These provisions may also apply in other sectors, such as health or agriculture as well.

New Chemicals Including Microorganisms

EPA, under TSCA, regulates new chemicals and microorganisms, including those that could be derived from recombinant DNA technologies and synthetic biology.[69] These new chemicals and new microorganisms can have uses in the energy sector but TSCA also addresses other industrial and commercial applications. Under the law, individuals or entities seeking to market or import new chemicals or microorganisms into the United States for commercial purposes must give EPA notice. New microorganisms subject to this requirement include "'intergeneric' microorganisms (including bacteria, fungi, algae, viruses, protozoa, etc.) formed by combining genetic material from organisms in different genera" and "microorganisms formed with synthetic DNA not from the same genus."[70] At least 90 days notice and submission of any known or "reasonably ascertainable" data on the intergeneric microorganism are required.[71] EPA scientists then conduct a risk assessment to ensure that the microorganism will not present an unreasonable risk of injury to health or the environment. EPA reviews the proposed use(s) of the new intergeneric microorganism. It evaluates potential human health and environmental hazards as well as potential environmental, worker, and general population exposures from manufacturing, processing, use, and disposal. EPA may require that additional data be developed by the submitter to enable it to make a reasoned evaluation and may limit or impose restrictions depending on the findings of the risk assessment weighed

against the benefits of the microorganism.[72] The same process applies to proposed commercial research and development testing of new microorganisms that are released into the environment. Individuals or entities seeking to conduct such field trials must also file 60 days notice and data with EPA.[73]

Certain intergeneric microorganisms are exempt from the requirement for full notification if the manufacturer meets specified criteria defining eligible microorganisms and specified use conditions (including conditions relating to containment, inactivation, and a number of criteria on the introduced DNA). The limited set of microorganisms eligible for exemption are those that have undergone categorical risk assessment as a species, or as a group of strains within a species, whereby specific features of the category and the history of safe use of members of the exempt category were reviewed. The criteria used, and list of eligible microorganisms, were subject to public comment at the time of proposal and had significant input from major scientific societies. This exemption is most applicable to the use of microorganisms to manufacture specialty and commodity chemicals. Also exempt are intergeneric microorganisms used for documented research in contained structures or research required to comply with the *NIH Guidelines*. The exemption for research and development conducted in contained structures must also address inactivation controls that take into account considerations such as the organism's ability to survive in the environment, potential routes of release, and procedures for transfer of materials between facilities.[74]

EPA's oversight of synthetic biology under TSCA may be limited in ways that pose particular challenges as synthetic biology evolves. First, the amount of information EPA requires to be submitted with a notification that is useful for assessing the risks of microorganisms is limited.[75] Manufacturers need not test new chemicals for toxicity, pathogenicity, or other harmful effects before they submit a notification to EPA.[76] Therefore, EPA may have limited information on which to base its risk assessment. However, if EPA determines that the available information is insufficient to permit a reasoned evaluation of the health and environmental effects of a new intergeneric microorganism and that the microorganism may pose an unreasonable risk, EPA typically will allow submitters to suspend the notification review period to enable such data to be developed. EPA can also impose restrictions on the manufacture,

processing, distribution in commerce, use, or disposal of a new intergeneric microorganism to limit exposures and releases until sufficient data are developed. However, with the potential for increasing complexity with synthetic biology products, predictability of the properties of microorganisms will be more complicated. Under TSCA, EPA does require immediate reporting by industry of new information on existing substances which reasonably supports the conclusion that the substance presents a substantial risk to human health or the environment.[77]

A second challenge is that the reach of the law is limited to commercial or commercial research and development activities.[78] It is unclear that all potential users or developers of synthetic biology products, for example, noncommercial research efforts by DIY users, are covered.

Human Health

FDA is the primary regulatory agency that exercises specific authority over drugs and devices for human health. Research activities related to such products are also subject to concurrent biosecurity and biosafety protections described above, including the *NIH Guidelines*, *BMBL*, and TSCA rules of EPA, as applicable.

Food and Drug Administration

New drugs and devices must satisfy FDA's safety and effectiveness standards before they can be introduced into the U.S. market.[79] For drugs, these standards require pre-market review and approval. For devices, FDA requires manufacturers to show substantial equivalence to a marketed device. FDA regulated foods, discussed below, and cosmetics generally reach the market without pre-market approval, although food additives and colorings are reviewed.

Synthetic biology potentially may be used in some fashion in all of the products that FDA regulates. For decades in the health care area, FDA has reviewed and approved numerous biotechnology-derived pharmaceuticals and devices, including drugs and devices created from bioengineered organisms.[80] It approved its first recombinant product, human insulin, in 1982.[81] FDA has

issued guidance to explain its thinking about the application of its laws and regulations in the biotechnology sector.[82] It draws no distinction between traditional recombinant techniques and synthetic techniques for genetic engineering. Gene segments "may be obtained from other organisms, or synthesized from scratch in a laboratory."[83]

Before, during, and after approval for clinical testing or marketing, the manufacturer or researcher (e.g., the "sponsor") of a product must work closely with FDA and provide ongoing data about safety and effectiveness.[84] FDA also oversees pre-clinical testing, manufacturing processes, and advertising and promotional labeling.[85] The agency imposes minimum ethical standards on clinical research that it oversees, including requiring the informed consent of research participants, safety and ethics review at the local level, and adverse event reporting.[86]

FDA retains considerable and ongoing authority to monitor safety and protect consumers. It may require manufacturers to submit a "risk evaluation and mitigation strategy," including use of patient registries or screening tests, to manage known or potential risks at the time of approval or after the product has gone to market.[87] It may withdraw approval, urge a voluntary recall, petition a court for injunction or seizure, require label changes, or issue warnings if so warranted.[88] Severe penalties may also be imposed on violators of FDA's requirements. Perpetrators can face civil penalties up to $1,000,000 per violation and criminal sanctions including up to 10 years imprisonment.[89]

As new technologies and applications arise, such as those that may be created by synthetic biology, FDA has responded and clarified its oversight. In 1985, it held that research using recombinant DNA technology should follow safety and containment provisions of the *NIH Guidelines*.[90] Genetically engineered animals, which may be used, for example, to produce pharmaceuticals or food for human and animal consumption, are regulated under FDA's animal drug provisions because the genetically engineered construct (the modified DNA produced by traditional recombinant or synthetic means) itself is an article that meets the definition of a "drug," something "intended to affect the structure or any function of the body of…animals."[91] FDA's new animal drug approval process, similar to the process for human medicines, generally

requires pre-market review and approval. For genetically engineered animals of a species not traditionally consumed as food, and for which animal health and environmental risks are shown to be low, FDA may exercise "enforcement discretion" and decline to require pre-market approval, as it did with aquarium fish engineered to glow in the dark.[92]

Agriculture, Food, and Environment

Many of the laws and regulations discussed above apply to research and commercial activities involving synthetic biology in the agriculture, food, and environment sectors. Under TSCA, for example, EPA undertakes prior review of new chemical substances, like biofertilizers, and other environmental applications of biotechnology, like bioremediation and mineral extraction. In addition, algae developed for chemical production other than energy, when grown in the open, would be construed as a potential environmental release and receive TSCA oversight. Major oversight programs involving plant and animal pests and pesticides are administered concurrently by USDA and EPA respectively. FDA oversees certain food safety and production activities.

Environmental Impact

Under the National Environmental Policy Act (NEPA), all federal agencies undertaking major action must take into account the impact their action may have on the environment.[93] Before reaching a final decision on any proposed action that may have a significant effect, the government must evaluate, through a public process, the anticipated environmental impact of the action along with any reasonable alternatives.[94] Public comment is requested at several points in this process.[95] Pursuant to NEPA and the Clean Air Act, EPA reviews all "environmental impact statements," and makes its comments available to the public. EPA also reviews selected environmental assessments.[96] NEPA does not require agencies to select the alternative with the least environmental impact.[97] The NEPA process, however, helps ensure that agencies are making informed decisions, responding to public concern, and taking into account mitigation of environmental impact. Typically used in situations such as new construction or major changes in federal land use, NEPA requirements may also be applied to laboratory research and scientific advancements. While

the drafting of an environmental impact statement is time consuming, the NEPA process adds an important layer of protection to uncertain or controversial decisions surrounding synthetic biology.

Plant and Animal Pests

USDA's APHIS is responsible for regulating the introduction (importation, interstate movement, and environmental release) of genetically engineered organisms that are known to, or could, pose a plant pest risk.[98] Genetically engineered organisms are considered to be "regulated articles" if the donor organism, recipient organism, vector, or vector agent used in their creation is known to be a plant pest, the plant pest status of that organism is not known, or there is a reason to believe that one of these organisms may be a plant pest, and therefore may encapsulate synthetically created organisms.[99] APHIS derives the authority to regulate the introduction of genetically engineered organisms from the Plant Protection Act of 2000.[100] This act defines a plant pest as a living stage of an organism (such as an insect, bacterium, fungus, or virus) that "may directly or indirectly injure, cause damage to, or cause disease in any plant or plant product."[101] The regulations apply to genetically engineered microorganisms, insects, and other traditional types of plant pests and to any genetically engineered plants if plant pest organisms (bacterial and viral plant pathogens) are the donor organisms and vector agents are used in the creation of these genetically engineered plants.[102]

APHIS currently uses a permit and notification system to authorize the introduction of regulated articles; all regulated articles are eligible for the permitting procedure, and certain regulated genetically engineered plants are eligible for the notification procedure.[103] The notification procedure is an administratively streamlined process. Currently, most regulated genetically engineered plants are introduced under notification, and approximately 10 percent of APHIS authorizations are done under the permitting procedure. A permit may be withdrawn where any permit condition established by APHIS is violated.[104]

In making a regulatory determination for a permit or notification for a regulated article, APHIS bases its determination on whether the actions under notification or permit are unlikely to result in the introduction or dissemination of a plant pest. This determination takes into account various risk factors, including, among other things, a low risk that the genetically engineered organism or its progeny can persist, reproduce, or establish without human assistance.

A person may petition the agency to evaluate submitted data and assess whether a particular regulated article is unlikely to pose a plant pest risk, and, therefore, should no longer be subject to APHIS regulations for genetically engineered organisms.[105] If, based on submitted information, the agency concludes that the article is unlikely to pose a plant pest risk, the agency may make a determination to approve the petition and confer non-regulated status on the regulated article. Thereafter, APHIS would no longer require permits or notification for the introduction of this genetically engineered organism.[106]

For animals and genetically engineered animal products, APHIS controls import, export, and interstate movement through a similar licensing process. To apply for a product license, test reports and research data must be submitted that establish the purity, safety, potency, and efficacy of the product. Product labels, including all claims made on them and in advertisements, must also be submitted.[107] Facility licenses are approved once a USDA administrator has approved the conditions of the production facility and production methods and verified that the applicant is sufficiently qualified.[108] Researchers and sponsors must show that their experimental product will not contaminate any current products and will be carefully disposed of and controlled.[109] Authorization to ship experimental products is allowed only in very strict circumstances and to limited destinations.[110]

No products may be imported into the United States without a permit.[111] Biological product permits can be issued for research and evaluation, distribution and sale, and transit shipment.[112] Strict requirements for containment, disease profile of the shipping country, qualifications of the recipient, and safety of the product, among others, are applied during the application process.[113] Ongoing inspection of production facilities and products may

be undertaken.[114] Manufacturers and importers must keep detailed records of the production process, testing results, and inventory and disposition of the product.[115] These detailed APHIS regulations would therefore add many helpful pieces to the patchwork quilt of protections for different types and uses of synthetic biology.

Pesticides

Before pesticides can be commercialized or used in the United States, they must meet specific health and safety standards under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[116] FIFRA requires EPA to determine that a pesticide will not pose an unreasonable risk of harm to human health or the environment.[117] Both naturally occurring and genetically engineered microorganisms and plants, including those created by synthetic biology, are regulated in this way.

EPA's pre-market approval and post-market adverse event reporting requirements rely on careful scientific evaluation. The agency must determine "with a reasonable certainty" that "no harm to human health" and no "unreasonable risks to the environment" will occur when the product is used as intended and according to label directions.[118] EPA requires applicants to perform various tests and submit comprehensive data before approval.[119] EPA also sets "tolerances," meaning maximum pesticide residue levels, for the amount of the pesticide that can remain in or on foods or feed crops.[120]

For research on pesticides, EPA's oversight is more limited. It does not require pre-approval for laboratory or contained-setting research.[121] Field testing, which is a prerequisite for commercial marketing approval, usually requires EPA pre-clearance through an experimental use permit or notification.[122] Experimental use permits are granted if, in EPA's view, the experimental use will not yield unreasonable adverse effects on the environment. As with marketing approval, applicants must submit detailed information including safety and pre-field testing data, to support their permit request.

States also regulate pesticides under FIFRA and applicable state laws. Some states impose more restrictive requirements and others defer to EPA's oversight.[123]

Genetically Engineered Foods

All genetically engineered animals, regardless of whether they are intended for food use, are within FDA's jurisdiction, as explained above, because the recombinant DNA constructs that alter the animal's structure or function meet the definition of new animal drugs. FDA oversees the safety and effectiveness of these animals through its pre-market review and approval processes. Applicable law does not require pre-market clearance for "food," whether derived from plant or animal. However, FDA requires evidence that food additives are safe at their intended level of use before they may be added, which is relevant for the products of genetic engineering.[124]

FDA has two main authorities over foods. First, it has post-market authority to seize foods that pose a risk to public health.[125] Second, it may regulate as food additives the substances (e.g., enzymes) added to plants. For example, in 1994 the agency reviewed a genetically engineered tomato with improved ripening qualities and regulated a gene product added to the tomato as a food additive.[126] Where a substance is not "generally recognized as safe" or otherwise exempt, FDA must review and approve the use of the additive before marketing, regardless of the technique used to add it to food.[127]

FDA is authorized to assure that the foods under its purview bear labels that are truthful and not misleading.[128] For foods from genetically engineered plants, FDA policy expressly indicates that name changes are appropriate only if "the resulting GE [genetically engineered] food product" is "materially different from its traditional counterpart," meaning that "the GE food product differs in nutritional quality, taste, etc."[129] In the tomato example cited above, FDA found use of the traditional name "tomato" appropriate because the genetically engineered product did not meaningfully differ in chemical composition from a traditional tomato. In contrast, FDA did require a special label for oil derived from a genetically engineered soybean plant because it contained significantly higher amounts of oleic acid than traditional soybean oil.[130] Production methodology (i.e., whether a product is produced through biotechnology or through conventional breeding) is not considered "material" information, and therefore such information is not required to be disclosed on the food label.[131] FDA follows this same standard for foods from genetically

engineered animals, although no genetically engineered animals have been approved for food at this time.

Environmental Impact and Clean Up

At the far end of the oversight scheme, particularly at this early stage of synthetic biology research and development, are remediation programs. EPA oversees programs for prevention and emergency management of chemical accidents;[132] oil pollution prevention and discharge;[133] and emergency planning and notification.[134] Under EPA, the Office of Solid Waste and Emergency Response also has both emergency and long-term clean up programs under the Comprehensive Environmental Response, Compensation, and Liability Act, as well as the Resource Conservation and Recovery Act. The scientific risk assessment and response strategies employed in these operations are likely to evolve as the field of synthetic biology itself evolves.

Summary

Multiple federal departments and agencies have significant oversight responsibilities for synthetic biology. The scope of these authorities extends from the laboratory to the field, the environment, the workplace, and the market. Some agencies impose specific safety conditions on research funded with federal dollars or at institutions that receive federal funds. Others reach all research, development, and commercial activities that raise specific threats or risks of harm. Generally, there is at least one federal agency—NIH, CDC, FDA, USDA, OSHA, DOT, DOC, or EPA—with specific oversight responsibility for a proposed application and frequently there is overlapping jurisdiction. Where prior experience or the character of the activity warrants heightened scrutiny, like drug and device development or pesticide use, pre-market review or approval is usually required. Genetically engineered animals require approval by FDA prior to entering into commerce.

This patchwork quilt of measures is built on long-standing practices that have adapted to new technologies over time. Risk assessment in this field may be particularly challenging and require both new techniques and new standards. Further adaptation and restructuring may be required as the applications

of synthetic biology grow and their consequences are better understood. As elaborated on in Chapter 5, the Commission's overview has indicated that the government should undertake a more comprehensive review, through a central body such as the Executive Office of the President, to assure that the existing patchwork quilt is indeed affording the U.S. public and the environment with adequate protections as the field of synthetic biology advances.

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[8] APHIS/CDC. (2010). *Select Agents and Toxins*. Available at: www.selectagents.gov/Select%20Agents%20and%20Toxins.html.

[9] 42 C.F.R. § 73.3; 9 C.F.R. § 121.3; 7 C.F.R. § 331.3.

[10] APHIS/CDC. (2010). *Security Risk Assessments: Overview*. Available at: www.selectagents.gov/sra.html.

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[12] Rodemeyer, M., Lecturer, Department of Science, Technology and Society, School of Engineering and Applied Science, University of Virginia. (2010). Risks and Regulation of Products of Synthetic Biology Products. Presentation to the President's Commission for the Study of Bioethical Issues, July 9, 2010. Available at: www.bioethics.gov/transcripts/synthetic-biology/070910/federal-oversight-of-synthetic-biology.html; Rodemeyer, M. (2009). *New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology*. Report for the Woodrow Wilson International Center for Scholars Synthetic Biology Project/Syn Bio 2. Page 40. Available at: www.synbioproject.org/library/publications/archive/synbio2/.

[13] Ibid.

[14] Patterson, A., op cit. For example, in 2002 virologist Eckard Wimmer announced that his team had created live poliovirus "from scratch" using DNA they ordered by mail, and a viral genome map on the internet. Ball, P. (2004) Starting from scratch. *Nature* 431:624-626.

[15] *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*, 75 Fed. Reg. 62820 (Oct. 13, 2010).

[16] APHIS/CDC. *Applicability of the Select Agent Regulations to Issues of Synthetic Genomics*. Available at: www.selectagents.gov/SyntheticGenomics.html.

[17] 7 C.F.R. Part 331; 9 C.F.R. Part 121; 42 C.F.R. Part 73.

[18] 7 U.S.C. § 8411.

[19] 7 C.F.R. § 331.3(c); 9 C.F.R. §§ 121.3(c), 121.4(c); 42 C.F.R. §§ 73.3(c), 73.4(c).

[20] APHIS/CDC. *Applicability of the Select Agent Regulations to Issues of Synthetic Genomics*, op cit.

[21] 7 C.F.R. § 331.9; 9 C.F.R. § 121.9; 42 C.F.R. § 73.9.

[22] 7 C.F.R. § 331.7; 9 C.F.R. § 121.7; 42 C.F.R. § 73.7.

[23] 7 C.F.R. § 331.17; 9 C.F.R. § 121.17; 42 C.F.R. § 73.17.

[24] 7 C.F.R. § 331.19; 9 C.F.R. § 121.19; 42 C.F.R. § 73.19.

[25] 7 C.F.R. § 331.18; 9 C.F.R. § 121.18; 42 C.F.R. § 73.18.

[26] APHIS/CDC. *Applicability of the Select Agent Regulations to Issues of Synthetic Genomics*, op cit.

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[31] 15 C.F.R. § 730.3.

[32] 15 C.F.R. § 738.1.

[33] 15 C.F.R. § 738.2(a).

[34] Bureau of Industry and Security. *Lists to Check*. Available at: www.bis.doc.gov/complianceandenforcement/liststocheck.htm.

[35] 49 U.S.C. § 5103.

[36] 49 C.F.R. § 171.8.

[37] 49 C.F.R. § 173.24.

[38] 49 C.F.R. Part 172, Subpart E.

[39] 49 C.F.R. Part 172, Subpart H.

[40] 49 C.F.R. §§ 107.309-107.310.

[41] 49 C.F.R. § 107.329.

[42] 49 C.F.R. § 107.333.

[43] 49 C.F.R. §§ 174-177.

[44] Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (2010), op cit., at 62820.

[45] Ibid.

[46] *Screening Framework Guidance for Synthetic Double-Stranded DNA Providers*, 74 Fed. Reg. 62319, 62319 (Nov. 27, 2009).

[47] Ibid.

[48] *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (2010)*, op cit.

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[64] 29 C.F.R. § 1910.120.

[65] 29 C.F.R § 1910.1200.

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[112] 9 C.F.R. § 104.2(a).

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CHAPTER 5
Analysis and Recommendations

The President asked the Commission to recommend how the developing field of synthetic biology and related technologies can maximize public benefits, minimize risks, and observe appropriate ethical boundaries. A framework of basic ethical principles can provide guidance in the assessment of an emerging technology such as synthetic biology. In this case, as described in Chapter 1, five principles are identified that are most relevant to assessing ethical considerations related to synthetic biology and other emerging technologies:

1. Public Beneficence
2. Responsible Stewardship
3. Intellectual Freedom and Responsibility
4. Democratic Deliberation
5. Justice and Fairness

The Commission relied on these principles to conduct its analyses and build its recommendations, as presented in this chapter. It is the Commission's hope that these principles will be applicable not only to synthetic biology, but also to assessing other emerging technologies.

Public Beneficence

The ideal of public beneficence is to act to maximize public benefits and minimize public harm. This principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. In the case of emerging technologies like synthetic biology, this improvement may be by means of providing improved or more widely available forms of medical and health care, food, shelter, transportation, clothing, and eco-friendly fuel, along with other means of improving people's lives. Scientific and technological discovery often have the added potential of increasing economic opportunities, which also redound to the public good.

This section focuses on how society and its members—individually and collectively—can provide an environment for synthetic biology to flourish for the benefit of as many people and communities as possible. The Commission observed during its deliberations considerable enthusiasm for the field among scientists, industry representatives, and the public. The anticipated benefits portend dramatic potential improvements in energy production, the economy, health care, and other areas that would enhance public welfare. The development of strategies that will allow the field to continue to grow in ways that offer the greatest potential net benefit to individuals and communities, both in the United States and worldwide, should be a high priority for public policy.

Promoting Public Well-Being and Prioritizing the Public Good

Citizens and their representatives have good reason to be engaged observers in the development of synthetic biology, particularly in light of the potentially transformative benefits to society of potential uses. Chapter 3 presented current examples of synthetic biology applied in research and development programs designed to benefit humankind. Environmentally friendly biofuels and affordable antimalarial drugs are among the near-term products of synthetic biology already receiving significant attention. These are important current examples of how advances in synthetic biology may deliver widespread benefits that promote social welfare. Continued investment in this field

should be directed to these types of applications and others that offer similarly expansive opportunities to address serious problems that affect our collective well-being.

The Commission's deliberations called attention to the diversity of interests and practitioners participating in the synthetic biology community. Despite their range of disciplinary backgrounds, nationalities, and institutions, synthetic biologists appear united in contributing their expertise to the development of novel products that address global needs. Distinguishing between academic, public, and commercial research in synthetic biology is extremely difficult, as many researchers are active contributors in each domain. In many ways, drawing this distinction is unnecessary. The organizational home of an individual practitioner may not limit his or her ability to work with others to accomplish shared research goals.

This intermingling of academic and commercial research—both basic and applied—provides fertile ground for innovation.[1] The development of semi-synthetic artemisinin, an antimalarial drug, is one example that demonstrates how academic, public, non-profit, and industry interests have come together to promote global well-being. In this case, researchers at a public university interested in exploring synthetic biology identified the production of artemisinin, a treatment for malaria, as potentially improvable using synthetic biology techniques. An estimated one million people, primarily children under the age of 5 years, die annually from malaria.[2] Researchers began with public dollars and expanded their work in partnership with a private foundation. The results are being commercialized by a for-profit pharmaceutical manufacturer, and a non-profit foundation is planning for eventual distribution. While the story is not over and initial drug production remains in process, the model shows how collaboration between academia, the private sector, and industry can use synthetic biology to address significant societal problems.

The artemisinin story illustrates one way that a diverse group of interests and funding sources—both public and private—can collaborate on research and development activities involving synthetic biology. As with many emerging technologies at an early stage, however, public information about the amount of public and private investment in this field is minimal.[3]

Public funding of research can bring an enhanced measure of focus, oversight, and accountability to any emerging technology. Absent national security protections, government-funded research in the United States is publicly disclosed. Public funding also promotes transparency and accountability that might not exist in purely private efforts.

Private funds may not be widely available for research into risk assessment practices or the ethical and social safeguards that aim to maximize public benefit while minimizing the risks of new technologies like synthetic biology. In synthetic biology, there are some notable exceptions of private funding for efforts to examine ethical, legal, and social issues, including commendable activities supported directly by the J. Craig Venter Institute and the Alfred P. Sloan Foundation.[4] The scope and impact of these efforts are, however, generally quite limited. In order to understand the possibilities and moral limits of synthetic biology public funding may be necessary to augment such efforts. The products of this work are critical to ongoing efforts to evaluate safety and to promote public acceptance of this emerging field. Research exploring the normative and conceptual issues related to these topics can be a valuable complement to the empirical, quantitative, or qualitative work that typically receives greater support from public funding sources.

To promote public engagement and assure needed transparency regarding federal efforts in the field of synthetic biology, the government should review and make public findings regarding the scope of its research funding at this time.

Recommendation 1: Public Funding Review and Disclosure

Through a central body such as the Executive Office of the President, the federal government should undertake a coordinated evaluation of current public funding for synthetic biology activities, including funding for research on techniques for risk assessment and risk reduction, and for the study of ethical and social issues raised by synthetic biology. This review should be completed within 18 months and the results made public.

The evaluation recommended here would ensure effective use of public funds, promote transparency, develop priorities, and avoid redundancy. This recommendation and the examples below align with the Commission's interest in

justice and fairness. It aims for the potential benefits of synthetic biology to extend to as many individuals and communities as is reasonably possible, addressing this country and the world's most urgent and compelling needs (see pp. 161-166). Public funding can be an important tool in realizing these goals and doing so in ways that are sensitive to ethical and safety concerns.

Most potential products of synthetic biology are in very early stages of development. Basic research is critical to further expansion of this science and its effective translation into useful products. Basic research—work that focuses on enhancing our understanding of fundamental principles of science and the natural world—is also important to the growth of the field. Direct commercial applications are not typically the intended outcomes of basic research, yet this work can also be extremely valuable to society. A commitment to basic research reflects a belief that knowledge is itself a public good.

More practically, scientific fields invariably develop in unanticipated ways. The aggressive pursuit of fundamental research generally results in a broader understanding of a maturing scientific field like synthetic biology than approaches solely focused on developing specific applications to address contemporary needs. This understanding of basic principles may be a particularly valuable way to prepare for the emergence of unanticipated risks that would require rapid identification and creative responses.

At the same time, synthetic biology research is in competition for scarce resources with other areas of science and other societal needs. Decisions will be required regarding which research directions deserve funding over others. These decisions should be driven in part by which strategies offer the most promise based on scientific, technical, and social considerations.

Potential profitability is also a significant motivator of research and development investments. When research is fairly new, as in the emerging field of synthetic biology, the promise is often high but the incentives for investment can be low because of uncertain success or marketability. Some drugs that address asymptomatic risk factors or "lifestyle" issues (e.g., drugs that do not treat life threatening conditions or pain), rather than specific disease processes, have received significant attention from the pharmaceutical industry because

there is a large market and potential for profit in the United States and other developed nations. Some of these drugs can be quite beneficial to patients, such as statins to reduce elevated cholesterol levels. Drug manufacturers frequently devote research resources to the development of very similar versions of competitors' already successful, profitable products instead of pursuing novel research directions with a less certain path to success or profits.

Other more prevalent and deadly diseases lacking therapeutic or preventive options today receive lower investment priority, especially diseases more common in developing nations. Absent a reliable market in the United States or other wealthy countries, manufacturers often choose not to devote significant investment dollars to these diseases, choices reflecting rational responses to the market. Government and others interested in promoting public well-being, such as private foundations, can effect change by re-drawing the financial landscape for research and development in these areas.

Recent congressional and Administration emphasis on "high risk/high reward" research offers one example of how the public good can be promoted when market forces alone may not succeed. The National Institutes of Health (NIH) has created several programs that specifically support creative, highly innovative research approaches that might otherwise be too novel or too risky to receive funding through traditional channels.[5] In 2007, Congress also expressly directed the agency to award research grants for these types of potentially high-impact research projects.[6] In the private sector, the Bill and Melinda Gates Foundation, through its "Grand Challenges in Global Health" program, is changing the financial picture by awarding substantial grants—nearly $500 million dollars in recent years—to stimulate scientific innovation among traditional and nontraditional researchers to treat and prevent diseases most prevalent in developing nations.[7]

The development of novel antibiotics is one example in which incentives could help stimulate research interest toward an important public need that might otherwise not receive sufficient attention.[8] Similarly, funding or incentives to spur research into age-related degenerative diseases of the nervous system (including dementia and gait disorders) may help in the quest for cures for Alzheimer's disease, Parkinson's disease, and related disorders prevalent in aging populations.

The Commission's deliberations focused specifically on synthetic biology, following its charge from President Obama, but alternative research strategies are also appropriately being pursued to address many of the national and global concerns for which synthetic biology may provide solutions. The Commission supports public and private investment in synthetic biology-related research as one important avenue of research among others.

Recommendation 2: Support for Promising Research

Advancing the public good should be the primary determinant of relative public investment in synthetic biology versus other scientific activities. The National Institutes of Health, the Department of Energy, and other federal agencies should continue to evaluate research proposals through peer-review mechanisms and other deliberative processes created to ensure that the most promising scientific research is conducted on behalf of the public.

Synthetic biology is advancing rapidly. Future funding decisions should be made through ongoing evaluation of the state of the science and its potential applications. Policy makers, the scientific community, and the public should continue to assess the adequacy of existing peer review and funding mechanisms to address future advances in synthetic biology-related science and technology. Private interests, including for-profit and nonprofit entities, should likewise consider global public needs that can be uniquely advanced through their efforts.

Realizing Economic Opportunities

Most current attention to the potential benefits of synthetic biology focuses on applications related to health, energy, and the environment. Investment in synthetic biology also can bring economic benefits, both from the direct activities related to research and development and from the eventual commercialization of successful technologies. These benefits have the potential to strengthen communities through the creation of jobs and other opportunities, thereby enhancing citizens' quality of life. Forecasting the potential impact of synthetic biology on job creation and economic growth is difficult, but the Commission received public comments estimating that the use of synthetic

biology in the chemical industry alone could generate global revenue of $1 trillion and create 1.2 million direct jobs.[9] Additional revenue and jobs would be expected from synthetic biology activities related to pharmaceutical and agricultural applications.

Potential economic benefits may be particularly valuable to communities in developing nations, where health, access to resources, and economic stability are closely linked to one another and to disparities in health and welfare. This underscores the importance of adopting a global perspective when considering the potential benefits of synthetic biology.

Although the potential economic benefits cannot be known with precision, this potential should nonetheless be continually assessed as part of activities to promote synthetic biology. Technological solutions alone cannot eliminate the fundamental causes of global inequality, but they can contribute to comprehensive programs to address them. This theme is addressed when considering the principle of justice and fairness.

Intellectual Property and the Sharing of Scientific Knowledge

Information sharing and reasonable access to discoveries and inventions have long fueled the scientific enterprise. These activities enable scientists to leverage each other's work in order to more quickly advance new projects and translate basic research into products. Impediments to innovation and information sharing, some say, arise from the patent and copyright system. These mechanisms afford inventors and authors a time-limited right to prohibit others from using their work or similar work of the same design. One concern consistently raised with regard to biotechnology is the potential limiting effects of intellectual property claims over research results, particularly in basic research.[10] Patents on discoveries and restrictive or exclusive licensing agreements may encourage, but also may deter or increase the development costs of subsequent inventions that build on the basic discovery. Some who provided testimony to the Commission argued that the current system unduly limits scientific advances; others took the opposite view and asserted that the current system works well.

The patent system is designed to encourage innovation and investment by providing incentives to inventors to disclose their discoveries to the public so that others can build on them. In return, the inventor is granted exclusive rights to the invention and control of its development for a limited period of time. Balancing the interests of the inventor and those who wish to use the invention is a challenging task in science generally, and in biotechnology particularly. These concerns have been the focus of numerous studies, for example, in genomics.[11] Ongoing discussions have focused on the roles and responsibilities of government, the academic community, and the private sector in adopting intellectual property practices that foster an environment in which invention and innovation can thrive. Such discussions are likely to continue as patent law and court decisions in this area evolve.[12]

Synthetic biology raises challenging issues in this area as a result of research interest in creating standard biological "parts" that can be combined to build new biological systems or organisms for potential use in health care, agriculture, and energy (see Chapter 3). The field also is particularly dependent on information technology and the need for common standards.[13]

Concerns about the effects of patenting on synthetic biology mirror those expressed about patents involving DNA and genetic tests—that is, whether patents will be granted that are either too narrow or too broad.[14] Overly broad patents could "restrict collaboration and stifle development in the field, and narrow patents may overcomplicate the process, meaning that hundreds of patents have to be negotiated to produce a system from standardized parts."[15] For example, the Venter Institute is seeking a patent on the synthetic cell it described in May 2010 and on processes for making synthetic genomes. For some, these efforts raise questions about the extent to which a patent on synthetic organisms should be issued and whether doing so is in the public interest.[16] Others in the synthetic biology community have taken steps to keep some portion of the "parts" developed with synthetic biology available in an open-source system (e.g., BioBricks and the Registry of Standard Biological Parts) without traditional patent restraints.[17]

In the last 20 years, we have seen increased emphasis on transparency, data sharing, and creative licensing practices for patentable subject matter.

This trend applies especially, though not exclusively, to publicly funded research. Examples of current data sharing requirements include several NIH policies introduced since the late 1990s, most recently the 2007 NIH Public Access Policy, a congressionally mandated provision for public distribution of research results.[18] Similar policies apply to awardees of the Howard Hughes Medical Institute and the Wellcome Trust, private research funding sources in the United States and the United Kingdom, respectively.[19] Public clinical trial disclosure requirements have arisen from the private sector, through research journal publishers, and the public sector, through congressional actions in 1998 and 2007.[20] Demands for licensing inventions to meet social needs, including providing access to medications or enabling more research and technology development, have fueled innovative licensing practices and creative solutions to so-called "patent thickets" and other limitations on scientific exploration.[21]

The principle of public beneficence requires researchers, inventors, patent holders, and others to work together to develop creative strategies to maximize opportunities for innovation. Licensing alternatives could include methods of compulsory or bundled licensing, patent pooling, and broad, non-exclusive licenses for foundational technology. Because synthetic biology is in large part based on the application of engineering principles through the use of standardized, modular parts, access to those standard components could be especially critical to the development of the field.

Intellectual property issues in synthetic biology are evolving. The Commission offers no specific opinion on the effectiveness of current intellectual property practices and policies in synthetic biology. It recognizes that there are important concerns that deserve ongoing attention, especially as this rapidly developing field evolves. Current litigation, such as *Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al.*, is likely to influence practices and policies in the future. This case presents the question of whether isolated human genes—those with mutations associated with an increased risk of breast cancer—and the comparison of their sequences is patentable.[22] Thus, the government should keep careful watch on this field and consider best practices and other policy guidance, if needed, to ensure that access to basic research results and tasks is not unduly limited.

Recommendation 3: Innovation Through Sharing

Synthetic biology is at a very early stage of development, and innovation should be encouraged. The Executive Office of the President, as part of the coordinated approach urged in Recommendation 4, should lead an effort to determine whether current research licensing and sharing practices are sufficient to ensure that basic research results involving synthetic biology are available to promote innovation, and, if not, whether additional policies or best practices are needed. This review should be undertaken with input from the National Institutes of Health, other agencies funding synthetic biology research, such as the Department of Energy and the National Aeronautics and Space Administration, the U.S. Patent and Trademark Office, industry, academia, and public civil society groups. The review should be completed within 18 months and the results made public.

The Commission urges the government to consider subsequent reviews and coordinated assessment if needed. Information sharing is a critical mechanism for promoting scientific progress and innovation.

Responsible Stewardship

The principle of responsible stewardship calls for prudent vigilance, establishing processes for assessing likely benefits along with assessing safety and security risks both before and after projects are undertaken. A responsible process will continue to assess safety and security as technologies develop and diffuse into public and private sectors. Prudent vigilance does not demand extreme aversion to all risks. Not all safety and security questions can be definitively answered before research begins, but prudent vigilance does call for ongoing evaluation of risks of harm along with benefits. The duty to be responsible stewards of nature, the earth's bounty, and the world's safety rests on concern not only for human health and well-being today but also and importantly for future generations and the environment looking forward.

The principle of responsible stewardship can be interpreted in an operational way to pose the question, "What can and should we, as a society, do in response to the emerging field of synthetic biology to be responsible stewards of nature, the earth's bounty, human health and well-being, and the world's safety, now and into the future?"

Options for action in this area range from doing nothing—that is, allowing the field of synthetic biology to proceed without limits or regard for public or environmental safety—to halting or substantially slowing its progress until risks can be identified and mitigated. One common interpretation of the "precautionary principle" would prescribe the latter approach. There are several definitions of the precautionary principle, but it generally states that if an action or policy has the potential to cause harm but uncertainty exists regarding the likelihood or severity of harm, the responsibility for demonstrating the safety of the approach belongs to those advocating for the policy or action.

The precautionary principle evolved primarily in the context of European debates and resolutions concerning the environment and genetically modified foods, and it is often raised in discussions involving risk and uncertainty in public policy in the United States and internationally.[23] One premise behind the precautionary principle may be that because there is a social responsibility to protect the public or the environment from plausible and avoidable harms,

protections should be relaxed only when science produces evidence that harm is unlikely to result. In some legal systems, such as that of the European Union, the application of the precautionary principle is a statutory requirement.[24]

A contrasting perspective is the "proactionary" principle, which assumes that an emerging biotechnology should be considered "safe, economically desirable and intrinsically good unless and until shown to be otherwise, which means that the burden of proof is on those who want to slow down a given line of research."[25] Advocates of the proactionary principle appeal to a commitment to intellectual freedom, the autonomy of individual decision making, economic growth, national competitiveness, and improved health and well-being. At its most extreme, this principle might allow science and technology to go forward unfettered, but, in general, proponents of this principle have supported some measure of oversight and monitoring.[26]

In order to provide benefits to human conditions and the environment, the Commission thinks it imprudent either to declare a moratorium on synthetic biology until all risks can be determined and mitigated, or to simply "let science rip," regardless of the likely risks. The field of synthetic biology can proceed responsibly by embracing neither the precautionary principle nor the proactionary principle. The Commission instead proposes a middle ground—an ongoing system of *prudent vigilance* that carefully monitors, identifies, and mitigates potential and realized harms over time. It came to this position for several reasons.

First, synthetic biology does not necessarily raise radically new concerns or risks compared to those that have been expressed about other emerging technologies, for example, molecular biology and nanotechnology. In many ways, synthetic biology is an extension of genetic engineering and part of an increasingly interconnected network of scientific disciplines including, among others, nanotechnology and information technology.[27]

Second, many existing oversight mechanisms and bodies (statutory, regulatory, and voluntary) are well situated and in the process of reviewing and monitoring the field of synthetic biology as it develops. The Commission endorses activities aimed at ensuring that those mechanisms and bodies are

sufficiently well coordinated and supported to effectively monitor risks in an ongoing and proactive fashion.

However, synthetic biology does introduce some possible risks that warrant special attention. According to the National Science Advisory Board for Biosecurity (NSABB), synthetic biology poses "varying degrees of uncertainty regarding the predictability of biological properties of partially or completely synthetic agents or materials."[28] It also poses some unusual potential risks, as "amateur" or "do-it-yourself" (DIY) scientists and others outside of traditional research environments explore the field. These risks must be identified and anticipated—as they are for other emerging technologies—with systems and policies to assess and respond to them while supporting work toward potential benefits. In this section, the Commission considers several approaches to promoting responsible stewardship, including oversight mechanisms, establishing safeguards, supporting relevant research, and encouraging and developing a culture of responsibility.

Stewardship through Oversight

Scientists have been conducting biological research that poses risks throughout the history of modern science. Consider Edward Jenner's experiments 200 years ago to develop a smallpox vaccine using cowpox virus, or more recently, gene therapy for rare diseases and studies of pathogens that could kill or sicken thousands through a natural or malevolent environmental release. History tells us that such research has resulted in enormous benefits for society, but it sometimes has had terrible consequences. Over time, safety and security practices and procedures have expanded and evolved to increase the likelihood that risks will be anticipated, mitigated, and monitored and that responses can be activated quickly should harms arise.

In the United States, oversight frameworks already exist for many activities of modern biological science including research involving humans, animals, microorganisms and toxins, and recombinant DNA. Oversight also occurs with regard to laboratory worker safety, use of federal funds in research, and transport and containment of dangerous agents. Oversight is frequently, but not exclusively, tied to public funding or the need to gain regulatory approval in order to market or distribute a product (see Chapter 4).

Long-standing regulatory systems, for example for food, drugs, and chemicals, undergird such approaches, while others developed specifically around the fields of genetic engineering and biotechnology. Some grew out of what were initially, and in some cases remain, voluntary self-policing efforts. These policies tend to be predicated on a risk-benefit assessment that is scaled according to identified risk and that evolves through an ongoing process of open public dialogue.[29] Over time, reflecting principled flexibility, many have been modified as risks, or the lack thereof, became clearer.

Demonstrating the government's increasing attention to this new field, the evolving federal oversight framework for synthetic biology, in the past year alone, includes:

- a proposed revision of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* to address synthetic biology,[30]
- development of a U.S. government *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*,[31]
- development of an Animal and Plant Health Inspection Service (APHIS)/Centers for Disease Control and Prevention (CDC) guidance on how current Select Agent regulations apply to those who create and use synthetic genomic products,[32] and
- consideration by the NSABB of strategies for conducting outreach to all practitioners of synthetic biology, enhancing the culture of responsibility, and promoting international engagement.[33]

These efforts build on the existing oversight responsibilities exercised by various federal agencies, including the Environmental Protection Agency (EPA) (chemical safety), the Food and Drug Administration (FDA) (food, drugs, and medical devices), the Department of Agriculture (crops and animal feed), and the Department of Homeland Security (biosecurity).

Internationally, the community of scientists working in synthetic biology, as well as policymakers and ethicists, are also focusing on ways to assure responsible stewardship. For example, the European Commission supports SYNBIOSAFE, a collaborative project among public and private parties that is researching the safety and ethics of synthetic biology. Governance and oversight strategies for

synthetic biology research and products are similarly being addressed through multiple efforts at the international level.[34]

To assure responsible stewardship in the field of synthetic biology, clarity, coordination, and accountability must exist across the government. The Commission does not believe that new agencies, offices, or authorities must be developed at this time, if ever. Instead, the Executive Office of the President (EOP) should lead an interagency process to identify and clarify, if needed, existing oversight authorities and to ensure that the government is fully informed on an ongoing basis of developments, risks, and opportunities as this field grows.

Recommendation 4: Coordinated Approach to Synthetic Biology

The Commission sees no need at this time to create additional agencies or oversight bodies focused specifically on synthetic biology. Rather, the Commission urges the Executive Office of the President, in consultation with relevant federal agencies, to develop a clear, defined, and coordinated approach to synthetic biology research and development across the government. A mechanism or body should be identified to: (1) leverage existing resources by providing ongoing and coordinated review of developments in synthetic biology, (2) ensure that regulatory requirements are consistent and non-contradictory, and (3) periodically and on a timely basis inform the public of its findings. Additional activities for this coordinating body or process are described in other recommendations.

These activities might be carried out, for example, under the auspices of the Office of Science and Technology Policy in the EOP, or the Emerging Technologies Interagency Policy Coordination Committee. It is essential that they be coordinated by an office with sufficient authority to bring together all parts of the government with a stake in synthetic biology. It is similarly important that this effort be sufficiently authoritative to effectively engage with, or supervise engagement with, foreign governments. A critical component of this coordinated strategy is to assure both the scientific community and the public that biosafety, biosecurity, and environmental risks of synthetic biology are fully addressed.

In any scientific inquiry, risks must be justified by anticipated benefits. Such balancing of risks and potential benefits is often complicated by uncertainty. Because much of science explores the unknown, policy makers should develop policies that acknowledge uncertainty about both risks and potential benefits. Information, flexibility, and judgment are critical to find the appropriate balance and determine the most responsible way to proceed. The rapid development of the field of synthetic biology makes the challenges of decision making under conditions of uncertainty particularly acute.

Recommendation 5: Risk Assessment Review and Field Release Gap Analysis

Because of the difficulty of risk analysis in the face of uncertainty—particularly for low-probability, potentially high-impact events in an emerging field—ongoing assessments will be needed as the field progresses. Regulatory processes should be evaluated and updated, as needed, to ensure that regulators have adequate information. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should convene an interagency process to discuss risk assessment activities, including reasons for differences and strategies for greater harmonization across the government. It should also identify any gaps in current risk assessment practices related to field release of synthetic organisms. These reviews should be completed within 18 months and the results made public.

Individual scientists were among the first to raise concerns about the possible risks posed by synthetic biology research. In fact, synthetic biologists have been discussing among themselves the appropriate safety policies for their field since at least 2004. Members of the synthetic biology community have met in a series of meetings over the past 6 years to discuss concerns about both biosafety and biosecurity. They also considered environmental concerns and appropriate tools for risk assessment.[35] Like SYNBIOSAFE in Europe, the Synthetic Biology Engineering Research Center, a collaborative project funded by the National Science Foundation in the United States, is examining safety, security, and preparedness issues.[36] The willingness and initiative of the scientific community to engage in this level of introspection is both reassuring and essential.[37]

Similar to researchers in the early years of recombinant DNA research in the mid-1970s, those closest to this emerging field have exercised caution. While self-governance is not a sufficient means to mitigate all risks, it is likely an effective way to control many of the risks associated with emerging technologies, including synthetic biology, particularly at this early stage.[38] Individual scientists and students typically are the first to notice the laboratory door ajar, the suspicious behavior, or the lack of safety precautions among colleagues.

The activities of nontraditional scientists involving synthetic biology are also noteworthy. Communities of "amateur" scientists are actively working to increase understanding of potential physical and environmental risks posed by synthetic biology activities. As these communities grow, organized efforts to engage this community in discussions of safety and security and to foster a commitment to responsible stewardship will be increasingly important (see pp. 146-148).

Industry, too, has worked collaboratively to enact policies to promote responsible stewardship. For example, both the International Gene Synthesis Consortium and the International Association of Synthetic Biology—whose members include the vast majority of the gene synthesis providers in the United States and worldwide—have developed best practice guidelines for screening orders and customers. These groups are participating actively in public discussions of regulatory options, collaborating on implementing screening practices, and interacting with the Federal Bureau of Investigation (FBI) on training and notification efforts.[39] Moreover, these organizations and their member companies have committed publicly to improve screening protocols and tools and to incorporate recent U.S. government guidance into practice.[40]

Stewardship through Use of Safety Features and Reviews

Coordination and careful risk analysis are essential steps for responsible stewardship, but they are not sufficient. There are several additional approaches, known today and evolving as our abilities in this field grow, to limit uncertain risks in synthetic biology. Technology can be harnessed to build in safeguards, just as cars have brakes and seatbelts, houses have smoke detectors, and computers have anti-virus software. A number of safety features can be incorporated into synthetic organisms to control their spread and life span.

The intentional and unintentional consequences of novel research designs and new products cannot always be predicted. In the case of a newly engineered synthetic organism, for example, lack of history regarding the behavior of the entity, either environmentally or ecologically, requires that there be a means to track or contain it if it can survive outside of the laboratory.

Surveillance or containment of synthetic organisms is a concrete way to embrace responsible stewardship. These safety features may require some combination of public investment and incentives for additional private funding, and they should be implemented only after they undergo rigorous testing and validation.[41] Promoting and supporting efforts to design and employ safeguards will ensure that they are widely adopted and become a standard tool for practitioners of synthetic biology.

As part of the coordinated approach described in Recommendation 4, and on an ongoing basis as the field progresses, the government should specifically monitor the potential risks of organisms with novel synthetic traits or properties surviving or multiplying in the natural environment. As needed, reliable containment and control mechanisms should be identified and required. Among current options, "suicide genes" or other types of self-destruction triggers could be considered in order to limit the life spans of synthetic organisms.[42] Organisms could also be designed to require nutritional components absent outside the laboratory, such as novel amino acids, thereby controlling them in the event of release. These are options only and should be updated as science progresses. The primary consideration is to ensure that concrete protections are inserted into synthetic organisms to assure safety.

Recommendation 6: Monitoring, Containment, and Control

At this early stage of development, the potential for harm through the inadvertent environmental release of organisms or other bioactive materials produced by synthetic biology requires safeguards and monitoring. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should direct an ongoing review of the ability of synthetic organisms to multiply in the natural environment and identify, as needed, reliable containment and control mechanisms. For example, "suicide genes"

or other types of self-destruction triggers could be considered in order to place a limit on their life spans. Alternatively, engineered organisms could be made to depend on nutritional components absent outside the laboratory, such as novel amino acids, and thereby controlled in the event of release.

The timing of deliberate release of synthesized organisms into the environment and the need to analyze risks prior to release raises special concern. We must proceed carefully, particularly when the probability or magnitude of risks are high or highly uncertain, because biological organisms may evolve or change after release.[43] Generally, the paradigm for risk assessment throughout the scientific community and oversight agencies is to evaluate a new organism in terms of known relatives and to set containment rules or environmental risk mitigation strategies based on the applicable rules for the known relative (see p. 83). This approach appears to have worked effectively and enabled risk assessors to modify methods as science has evolved.[44] Prudent vigilance is required to ensure that this strategy of comparison to known relatives, when they exist, remains effective as synthetic biology advances.

Recommendation 7: Risk Assessment Prior to Field Release

Reasonable risk assessment should be carried out, under the National Environmental Policy Act or other applicable law, prior to field release of research organisms or commercial products involving synthetic biology technology. This assessment should include, as appropriate, plans for staging introduction or release from contained laboratory settings. Exceptions in limited cases could be considered, for example, in emergency circumstances or following a finding of substantial equivalence to approved products. The gap analysis described in Recommendation 5 should determine whether field release without any risk assessment is permissible and, if so, when.

This recommendation is not intended to suggest that a National Environmental Policy Act-style risks evaluation must be conducted in all cases. As noted, there are numerous models and strategies employed across the government for risk assessment, for example, through FDA's premarket and post-market processes, EPA's Toxic Substances Control Act processes, and others. The goal of this recommendation is to ensure that for any field release there is adequate

consideration of risk. Through the suggested inter-agency process, the government may find that for some products—for example, first-generation fruits or vegetables developed with synthetic biology instead of traditional recombinant methods—there is no material need to establish formal risk assessment and premarket approval if not required already under existing law. Because of the uncertainty surrounding this novel technology and the great potential it presents for confusion and public fear, Recommendations 5 directs the government to affirmatively examine current policies for field release, to ensure that they are adequate, and to disclose to the public the results of this review.

The Commission's deliberations also highlighted the degree to which synthetic biology is an international enterprise. From student competitions to commercial gene synthesis companies, the synthetic biology community is an interactive global network. Oversight and regulatory mechanisms should adopt an analogous approach, so that the United States is involved in regular discussions with other national and transnational organizations, together seeking coordination and consistency when possible. These interactions should foster international collaboration as well as provide opportunities for the United States to learn from the positive and negative experiences of other countries similarly striving to promote the safe development of this field. International cooperation to create, maintain, enforce, and periodically update universal safety standards is essential.

Recommendation 8: International Coordination and Dialogue

Recognizing that international coordination is essential for safety and security, the government should act to ensure ongoing dialogue about emerging technologies such as synthetic biology. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, through the Department of State and other relevant agencies such as the Department of Health and Human Services and the Department of Homeland Security, should continue and expand efforts to collaborate with international governments, the World Health Organization, and other appropriate parties, including international bioethics organizations, to promote ongoing dialogue about emerging technologies such as synthetic biology as the field progresses.

Creating a Culture of Responsible Stewardship

Responsible conduct of synthetic biology research, like all areas of biological research, rests heavily on the behavior of individual scientists. Federal oversight can guide the development of a culture of responsibility and accountability, but it also must be fostered at the local level. Ethical as well as biosafety and biosecurity standards are translated into practice at the laboratory level—and by the institutions that sponsor that laboratory science.[45] As an example, programs focused on homeland and transportation security embrace the message, "if you see something, say something." The same is true for laboratory science. It is at the individual or laboratory level where accidents will occur, material handling and transport issues will be noted, physical security will be enforced, and potential dual use intentions will most likely be detected.

Creating a culture of responsibility in the synthetic biology community could do more to promote responsible stewardship in synthetic biology than any other single strategy. For example, ethics education is required for most federally funded investigators conducting research with human subjects or laboratory animals.[46] Similarly, researchers working with select agents must undergo training in biosafety and biosecurity before having access to select agents and pathogens.[47] Researchers working with recombinant DNA in institutions that receive federal funds for such research know they must undergo review by an institutional biosafety committee (IBC) prior to beginning work.[48] These agreements between scientists and the public are the terms—the social contract, one might say—for conducting "risky" science, and they are well understood by most of the biological and biomedical research community.

Federal funding for engineering research, in contrast to clinical research, generally does not include a requirement for ethics training. Recently, the National Science Foundation began conditioning some research awards on agreements that institutions mentor funded postdoctoral research fellows and implement plans for "appropriate training and oversight in the responsible and ethical conduct of research. . . ."[49] Other federal research sponsors lack even these modest requirements. There is an urgent need more generally for

careful consideration of the education and training necessary to promote ethical conduct in engineering research and practice.

There are new actors in the world of synthetic biology, namely engineers, chemists, materials scientists, computer modelers, and others who practice outside of conventional biological research settings.[50] These groups may not be familiar with the standards for ethics and responsible stewardship that are commonplace for those working in biomedical research. This poses a new challenge regarding the need to educate and inform synthetic biologists in all communities about their responsibilities and obligations, particularly with regard to biosafety and biosecurity.

Recommendation 9: Ethics Education

Because synthetic biology and related research cross traditional disciplinary boundaries, ethics education similar or superior to the training required today in the medical and clinical research communities should be developed and required for all researchers and student-investigators outside the medical setting, including in engineering and materials science. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, in consultation with the National Academy of Sciences, the National Academy of Engineering, the scientific community, and the public, should convene a panel to consider appropriate and meaningful training requirements and models. This review should be completed within 18 months and the results made public.

Collectively, these recommendations are designed to balance enthusiasm for the potential benefits of synthetic biology with the vigilance required to minimize the risks associated with research in this field and its applications. Through technological and regulatory mechanisms, a spirit of international collaboration, and researcher education, the scientific and policy communities can work together to be responsible stewards for humankind, other species, and our shared environment.

Weighing Moral Objections

The Commission's discussion of synthetic biology thus far has focused on efforts to identify and assess the risks and potential benefits of research and development activities. Significant challenges exist for the scientific and regulatory communities in these areas, and these recommendations aim to strengthen systems to promote activity in this field while protecting against risks. There is a second category of concerns regarding synthetic biology, one that is largely independent of specific risk-benefit analyses related to proposed applications or research directions. These are concerns that synthetic biology is intrinsically objectionable from a moral perspective and should therefore not be allowed to proceed.[51] The term "intrinsically objectionable" is used to express the idea that an activity or practice is "bad in itself." The suggestion of some critics, moreover, is that no amount of vigilance, safeguards, or similar mechanisms could justify the transgression by synthetic biology of an important moral barrier.

Intrinsic objections have led to direct policy consequences in other areas of biomedical science and technology, most notably the restrictions on research related to human reproductive cloning and embryonic stem cell research. These types of concerns have had a long and important place in bioethical discussions and debates. Intrinsic objections to synthetic biology raise important issues deserving ongoing consideration as part of comprehensive efforts to assure that this field progresses within appropriate ethical boundaries.

The Commission learned of several possible intrinsic objections to synthetic biology during its deliberations.[52] In one formulation, synthetic biology is thought to conflict with essential concepts of human agency and life, "promoting a grandiosity about human powers or dismissiveness about the specialness of life."[53] The tools of synthetic biology and the technological capabilities they provide may, according to some critics, accentuate humankind's temptation to hubris, suggesting an expansive, even limitless, ability to shape life and the future. Related to this criticism is the suggestion that advances in synthetic biology demonstrate that life is "nothing more than the sum of its parts" and that there is nothing "unique and unknowable about

life itself."[54] Contrasting synthetic biology with genetic engineering, medical ethicists Joachim Boldt and Oliver Müller write,

> [S]ynthetic biology does not soften edges, but creates life forms that are meant not to have any edges from the start. It does not add value to an existing organism; it brings into existence something that counts as valuable from our point of view. Seen from the perspective of synthetic biology, nature is a blank space to be filled with whatever we wish.[55]

Boldt and Müller argue that the transition from genetic engineering to synthetic biology marks a profound shift from the manipulation of existing species to the creation of new forms of life, a shift having considerable ethical significance. They note that the metaphors commonly used in synthetic biology which describe organisms as physical artifacts—"BioBricks," living machines, hardware and software—"may in the (very) long run lead to a weakening of society's respect for higher forms of life that are usually regarded as worthy of protection."[56]

Other commentators note that some of the potential products of synthetic biology "might fail to fit comfortably into our intuitive dichotomy between the living and the non-living."[57] For example, bacterial "bio-factories" are a potential application of synthetic biology that invokes yet another metaphor describing organisms in terms of physical artifacts. These bio-factories would possess many characteristics regularly associated with life, including a nucleic acid genome and the ability to reproduce. They would also possess features commonly associated with machines—such as modular construction and a rational design developed for specific applications.[58] Some critics of synthetic biology suggest that this amalgam of characteristics, even in single-celled organisms, could adversely affect how we understand and treat other forms of life generally, not simply those produced through synthetic biology.

Another related objection to synthetic biology is that it fails to show adequate respect for nature and the environment.[59] These critics distinguish the products of synthetic biology as unnatural in ways that other interactions between humans and nature are not.[60] Philosopher Christopher Preston writes that genomes assembled through synthetic biology "depart from a core principle

of Darwinian natural selection—descent through modification."[61] He argues that synthetic biology may therefore constitute a "moral 'line in the sand.'"

Civil society organizations such as the ETC Group also express concern about the overall impact of synthetic biology on biodiversity, ecosystems, and food and energy supplies worldwide.[62] These critiques combine intrinsic moral objections to the very nature of the enterprise of synthetic biology with reservations regarding its consequences and the specific harms that may result from continued research in the field. Biodiversity, for example, could be adversely affected by unpredictable outcomes of unintentional or deliberate release of synthetic organisms. Additional harms to biodiversity could result from potential applications of synthetic biology that aim to convert "low-value" forests and agricultural products into feedstocks for energy-producing processes.[63]

Concern for the continued flourishing of plant and animal species derives from the unique ability of humans to serve as responsible stewards of nature (see pp. 25-27). It also acknowledges the complex relationships that exist among species in ecosystems. Unintended consequences could result from potential synthetic biology applications that involve new or modified species in nature or novel uses for existing species.

Concerns for biodiversity are not restricted to wholesale threats to species. The potential of synthetic biology to enhance, add, or remove genes (and, therefore, proteins and their functions) within organisms highlights the potential effects of synthetic biology on genetic and genomic diversity. These impacts potentially extend also to genetic diversity among humans. Gene therapy trials using recombinant DNA in humans are already underway. However, genetic manipulation, as described above, is proceeding in limited and carefully controlled ways to potentially improve human health. The Commission is aware of no active or planned research programs involving synthetic biology applied to human genomes, which are vastly larger and more poorly understood than the bacterial genomes studied thus far.

Throughout its deliberations, the Commission took special efforts to learn the views of major faith-based communities, including those of Christianity, Judaism, and Islam. In other contexts, religious groups have expressed clear

and unqualified opposition to specific scientific activities based on intrinsic arguments, such as the position of the Catholic Church on human embryonic stem cell research. Similar opposition to synthetic biology has not been voiced thus far. Following the publication of the Venter Institute's paper, an official from the Catholic Church praised the development as "a further mark of man's great intelligence, which is God's gift enabling man to better know the created world and therefore to better order it."[64] The statement encouraged continued synthetic biology research, provided that the research proceeded responsibly and did not undercut the sanctity of life.

The Commission did not hear or identify any specific objections to current research efforts in synthetic biology based on the views of organized religions. In response to claims by some commentators that the Venter Institute's research demonstrates that life is merely a manipulable series of chemical reactions without any unknowable mystery or value, the Commission heard compelling rebuttals from several faith-based thinkers and others, including many scientists. Among them, it heard that absolutely nothing accomplished in synthetic biology by way of synthesizing the genome of a self-replicating bacterial cell from its component parts—which is the most striking and specific technical achievement of the Venter Institute team—demonstrates that life is without mystery or value that goes beyond the assembly of its parts. The mystery of life is amply great, as both religious and secular minds can appreciate, to survive even the most masterful scientific feats.[65]

As a scholar from the Christian tradition commented to the Commission during its deliberations,

> The mystery of existence from a Christian theological standpoint is that anything is rather than nothing, that there is something rather than nothing. That life is possible. The dynamism and the energy of matter and being itself are taken as an expression of the very vitality of God. And neither wonder nor mystery it seems to me are vitiated by the fact that we have figured out the biomechanical and bioelectrical and biochemical mechanisms thereof.[66]

Although contemporary synthetic biology is occasionally described as "creating life," (see pp. 155-157) this, as a factual matter, has not happened. The field currently is capable of significant but quite limited technical achievements. Potential developments that would raise further intrinsic concerns—the synthesis of genomes for a higher order or complex species, for example—are not currently possible. There is widespread agreement that this will remain the case for the foreseeable future. Synthetic biology is currently capable of manipulation and duplication of genomes of single-celled organisms. The creation of novel, complex organisms *de novo*, the focus of some opposition to synthetic biology on intrinsic grounds, is a far more difficult technical achievement. The Commission does not find it to be an inevitable consequence of recent and ongoing research activities in synthetic biology.

After careful deliberation, the Commission was not persuaded by concerns that synthetic biology fails to respect the proper relationship between humans and nature. It was reminded during its deliberations of the challenges of defining "nature" or "natural" in this context, particularly in light of humans' long history interacting with and affecting other species, humankind, and the environment.[67] Damaging consequences have resulted from some of this past activity. The Commission believes, however, that opposition to synthetic biology at present on such grounds alone does not adequately reflect the relationship of this technology to previous scientific activities and the current limited capabilities of the field.

These varied concerns are quite valuable, however, in calling attention to fundamental, challenging questions regarding how to best understand interactions among humans, technology, and nature beyond the limited context of synthetic biology. To what extent and in what valuable ways are the many different kinds of life on earth more than the sum of their standardized and non-standardized biological parts? Such discussions and the related attention they direct toward potential objections to synthetic biology will surely continue as the field matures, as well they should. The question relevant to the Commission's present review of synthetic biology is whether this field brings unique concerns that are so novel or serious that special restrictions are warranted at this time. Based on its deliberations, the Commission has concluded that special restrictions are not needed, but that prudent vigilance

can and should be exercised. As this field develops and our ability to engineer higher-order genomes using synthetic biology grows, other deliberative bodies ought to revisit this conclusion. In so doing, it will be critical that future objections are widely sought, clearly defined, and carefully considered within their appropriate context.

Recommendation 10: Ongoing Evaluation of Objections

Discussions of moral objections to synthetic biology should be revisited periodically as research in the field advances in novel directions. Reassessment of concerns regarding the implications of synthetic biology for humans, other species, nature, and the environment should track the ongoing development of the field. An iterative, deliberative process, as described in Recommendation 14, allows for the careful consideration of moral objections to synthetic biology, particularly if fundamental changes occur in the capabilities of this science and its applications.

Intellectual Freedom and Responsibility

Democracies depend on intellectual freedom coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways. Sustained and dedicated creative intellectual exploration begets much of our scientific and technological progress. A robust public policy regarding the responsible conduct of science must promote the creative spirit of scientists and unambiguously protect their intellectual freedom. At the same time, responsible science should reject the technological imperative: the mere fact that something new can be done does not mean that it ought to be done.

Society as a whole has a stake in what scientists and engineers do. In turn, scientists and engineers should recognize the potential impact of their research on those who will experience both its benefits and burdens and their responsibility to those who provide the means, directly or indirectly, for their research. As a corollary to the principle of intellectual freedom and responsibility, the Commission endorses a principle of regulatory parsimony, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good.

The section on responsible stewardship stressed the importance of regulatory parsimony, recommending limiting regulation to that which is necessary to promote public safety and security, public beneficence, and justice and fairness. In its discussion of democratic deliberation (see pp. 152-155), the Commission recognizes the important part that all citizens can serve in working together for the common good. Responsible stewardship and democratic deliberation are two important components of a framework that promotes intellectual freedom coupled with responsibility. This section examines the central role of this principle in supporting the development of synthetic biology and other emerging technologies.

Intellectual freedom lies at the heart of America's scientific enterprise. Such freedom facilitates the innovation and industry that have fueled its success. History is rife with examples in which ingenuity, hard work, and unfettered creativity have yielded extraordinary, sometimes unexpected, scientific

advances for the betterment of society as a whole. From Benjamin Franklin studying electricity with a kite in a raincloud, to the Wright Brothers testing different aerodynamic control systems and building the first successful airplane, students learn every day about the value of intellectual and scientific freedom and exploration.

Scottish scientist Alexander Fleming famously discovered the antibiotic penicillin by chance in 1928 after observing an area on a mold-contaminated Petri dish where bacteria did not grow. David Hewlett and William Packard started in their backyard garage an electronics revolution that continues to the present, working in the 1930s in what is now described as the "birthplace of Silicon Valley." And the Internet, with its vast reach today, began as a simple idea to share data among U.S. Defense Department researchers in the 1960s. These examples show that the precise outcomes of open scientific exploration and discourse cannot always be predicted, but the value they deliver as the engine of progress, in science and in society overall, is unparalleled.

Intellectual freedom and responsibility can be understood in two senses. First is the special institutional attribute—academic freedom and responsibility—that pertains to the "academy" (broadly speaking, universities and the scholars and researchers whose professional standing carries with it the rights and responsibilities of academic freedom). Some research involving synthetic biology today occurs in this setting, which includes unique institutional structures to promote the responsibility that accompanies intellectual freedom. Second is the right of all individuals to freedom of inquiry. The DIY research communities and other private researchers are exercising such freedom but without the institutional norms and procedures designed to assure responsibility, although these groups often develop their own mechanisms intended to do so.

In academic communities, intellectual freedom is essential. The ability to explore ideas openly and freely—even controversial or unpopular ideas—is fundamental to the mission of education and research. "The common good depends upon the free search for truth and its free exposition," according to one widely endorsed statement on academic freedom.[68] Academic freedom is not to be confused with license; it protects neither socially irresponsible behavior (the abuse of one's academic office) nor research that poses risks to

individuals or institutions without adequate safeguards. Its limitations notwithstanding, the free exchange of ideas is essential to both academic inquiry and to the overall health of societies, and is recognized to be vital in the United States and other modern democracies. Protecting this core freedom—while meeting the corresponding responsibilities—is among the foremost concerns of academic communities.

Certain regulatory and norm-based constraints on academic and intellectual freedom in academic and other settings ensure that scientists act responsibly to protect others. In academic science, universities and other institutions accept the responsibility to abide by safety and security measures in laboratory research. These institutions, government, and most industry research programs employ extensive quality assurance and control processes that satisfy both external mandates and internal needs. In non-academic settings, like some DIY synthetic biology communities, recognition and acceptance of such processes are less common. In some cases, practitioners unaffiliated with an institution are simply unaware of applicable or reasonable restrictions governing scientific research methods intended to promote security and safety.[69]

Research Oversight Policies and Practices

Citizens and their leaders should have a voice in deciding the conditions and direction of research efforts, especially, though not exclusively, when public funds are used. Likewise, scientists have a responsibility to ensure that they use public monies wisely and act in ways consistent with public trust. Recognizing this responsibility, scientists at the early stages of the genetic engineering revolution came together to develop what remains a substantially self-regulated system to protect against physical risks in genetic research. At the historic Asilomar Conference on Recombinant DNA in 1975, scientists developed a set of principles that required containment measures to be an essential consideration in experimental design and that "the effectiveness of the containment should match, as closely as possible, the estimated risk."[70] Although the scientists recognized that it might be difficult to predict the level of risk for any particular experiment given the novel character of the research, the guidelines established graded containment strategies and categorized expected areas of inquiry, setting minimum levels of containment

within the graded system. Like atomic scientists before them, the scientists who participated at Asilomar recognized that the uncertain nature of the risks associated with their efforts demanded that they act cautiously and with utmost attention to the public interest. They agreed to defer types of research that could not be carried out at that time with sufficient safeguards.

Building on this framework, scientists both in and outside government developed a shared culture of responsibility to assure safe conduct of research in the largely uncharted world of genetic engineering. In the 35 years since Asilomar, the then-nascent field of genetic engineering research has flourished. Its safety continues to be governed by a dynamic process of active engagement among scientists in academia, government, and the private sector.

Synthetic biology today finds itself in a position similar to the field of genetic engineering in 1975. Some urge extreme caution and prohibition until safety is proven, and others are perhaps too sanguine, dismissing all efforts that might limit intellectual freedom and scientific exploration. As mentioned in the sections on responsible stewardship and democratic deliberation, the Commission finds neither of these approaches appropriate. The principle of intellectual freedom and responsibility leads us to the conclusion that restrictions on research, whether by self-regulation among scientists or by government intervention, should limit the free pursuit of knowledge only when the perceived risk is too great to proceed without limit. Restrictions can prevent research harms but also can impede innovation and progress that may itself reduce harms.

In 2009, NIH recommended that synthetic biology research should be overseen at this time in the same manner as more traditional genetic engineering research. The Commission agrees. The *NIH Guidelines for Recombinant DNA Research* (the *NIH Guidelines*), discussed in Chapter 4, establish safety conditions based on the risk profile of the end product, for example, a genetically modified virus strain, rather than the techniques used to make it. Risks are assessed and safety precautions imposed based on risks, but research is not limited or restricted in the absence of realistic and identified concerns. This framework is time-tested, familiar to most researchers, and consistent with the principle of intellectual freedom and responsibility.

A moratorium at this time on synthetic biology research generally or in particular areas would inappropriately limit intellectual freedom. Instead, the scientific community—in academia, government and the private sector—should continue to work together to evaluate and respond to known and potential risks of synthetic biology as this science evolves.

Recommendation 11: Fostering Responsibility and Accountability

The government should support a continued culture of individual and corporate responsibility and self-regulation by the research community, including institutional monitoring, enhanced watchfulness, and application of the *NIH Guidelines for Recombinant DNA Research.* As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate, and re-evaluate periodically, the effectiveness of current research oversight mechanisms and determine what, if any, additional steps should be taken to foster accountability at the institutional level without unduly limiting intellectual freedom. Academic and private institutions, the public, the National Institutes of Health, and other federal funders of synthetic biology research should be engaged in this process. An initial assessment should be completed within 18 months and the results made public.

This activity may best be undertaken through the coordinated approach chosen to implement Recommendation 4. The Office of Science and Technology Policy or another Executive Branch office could also direct this review. The responsible office must be empowered to bring together all relevant agencies and departments and assure effective engagement with outside groups.

The notion of "enhanced watchfulness" requires the scientific community to recognize the varied risks associated with synthetic biology and develop internal processes to identify and respond to potential threats rapidly and effectively. Enhanced watchfulness reflects a relationship among scientists, citizens, and policy makers built on trust and mutual respect. To earn and preserve public trust, the research community should actively engage in continuing efforts to promote the safe development of synthetic biology and to recognize potential threats before they cause harm.

A culture of responsibility is particularly effective in university settings where academic freedom is an institutionalized right but not an unrestricted license. The responsibilities attendant to this freedom are implemented through practical mechanisms that nurture and support the culture of responsibility. Compliance with the *NIH Guidelines*, for example, is assured through a series of internal checks and balances from the investigator through to local oversight committees (e.g., IBCs) and the institutional signing official responsible for assuring that the institution meets all terms and conditions of research funding.

Researchers in institutions outside the university setting also have an incentive to limit risks and frequently have systems in place to support and sustain the culture of responsibility. Biotechnology companies staffed with scientists trained in academia and accustomed to working with oversight committees like IBCs often volunteer to comply with the *NIH Guidelines* and other standards developed through consensus of the scientific community.[71] Researchers in government agencies are also familiar with IBC review and the *NIH Guidelines*, and often are required to comply with them (see pp. 89-90).

Nurturing this same culture among DIY investigators or others outside of institutional settings is more challenging. The global expansion of DIY synthetic biology raises fears about biosafety and biosecurity. The open access environment underpinning many DIY efforts, as well as the increasing affordability and availability of synthetic biology tools through private gene synthesis companies and others, generates understandable concern about the ongoing effectiveness of self-regulation and the culture of responsibility standard. In partial response, the FBI expanded efforts in the last few years to partner with industry and actively engage the DIY community on safety concerns and risk mitigation strategies.[72]

The principle of intellectual freedom and responsibility, when responsibility is exercised largely by individual rather than institutional actors, requires the government to be particularly vigilant, although perhaps no more limiting of research efforts. To exercise the appropriate level of oversight, the government will need to monitor the growth and capacity of researchers outside of institutional settings. This effort may require the government to expand current

oversight or engagement activities with these non-institutional researchers. NIH or the Department of Energy, for example, could be charged to sponsor education programs and workshops that bring together these groups. They could fund training grants or related programs to promote responsibility among this community.

Recommendation 12: Periodic Assessment of Security and Safety Risks

Risks to security and safety can vary depending on the setting in which research occurs. Activities in institutional settings, may, though certainly do not always, pose lower risks than those in non-institutional settings. At this time, the risks posed by synthetic biology activities in both settings appear to be appropriately managed. As the field progresses, however, the government should continue to assess specific security and safety risks of synthetic biology research activities in both institutional and non-institutional settings including, but not limited to, the "do-it-yourself" community. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, working with the Department of Homeland Security, the Federal Bureau of Investigation and others, should undertake and periodically update this assessment. An initial review should be completed within 18 months and the results made public to the extent permitted by law.

As above, this activity could be undertaken by a central office implementing Recommendation 4, but it need not be, provided that the implementing office has sufficient authority to accomplish this charge. The analysis recommended here should identify efforts to bring the non-institutional communities into the ongoing culture of responsibility and local accountability that currently exists in many institutional settings.

This recommendation acknowledges that the norms of safe and responsible conduct that have evolved over time for many researchers in institutional settings may not be understood or followed by those new to the field or outside of these settings, but it is not a call for specific restraints upon the DIY community at this time. Synthetic biology is occasionally critiqued as scientists "playing God," (see pp. 155-157), but a more general concern is ensuring that all scientists, particularly DIY scientists, reject a culture of *play* and adopt a

culture of *responsibility* as it relates how they view their own research in a field fraught with risks to themselves, the public, and the environment.

It is important to note that there is presently no serious risk of completely novel organisms being constructed in non-institutional settings such as the DIY community. The research result announced by the Venter Institute in May 2010 was a significant technical achievement, but the synthesis of a self-replicating bacterial cell with a synthetic genome required nearly 15 years of work by a large team of highly experienced scientists and an estimated $40 million in research expenditures. The Commission's deliberations revealed that this combination of technical and financial resources and scientific expertise is not currently available in the DIY community. The potential synthesis of completely novel organisms presents additional, still unresolved technical challenges even for research groups working in institutional settings. While there are known risks related to near-term activities by the DIY community, such as the growth of potentially pathogenic organisms using conventional methods or inadequate waste disposal practices, the risks associated with this group using synthetic biology techniques to create novel organisms are presently quite low.

This recommendation echoes recent conclusions of the NSABB, which also considered issues of education and outreach to all practitioners of synthetic biology and ways to effectively promote a culture of responsibility.[73] Scrutiny is required to assure that DIY scientists have an adequate understanding of necessary constraints to protect public safety and security, but at present the Commission sees no need to impose unique limits on this group.

Assessing Oversight and Export Controls

The culture of responsibility depends, at least in part, on voluntary compliance with the *NIH Guidelines* in institutions without federal research funding, such as private companies. Accordingly, the Commission recommends that the government undertake an ongoing process of review to monitor risks and effectiveness of current oversight systems in these settings and in contexts such as the DIY community.

However, certain risks—generally involving national security—often warrant additional protections. One of the primary concerns about the risks posed by synthetic biology is its dual use potential, defined as the possibility that it will yield information or technologies capable of being misused, thereby endangering public health or national security. The threat of malevolent use of scientific knowledge is not new; however, the global, collaborative, and electronically linked nature of modern biological sciences, such as synthetic biology, complicates efforts to control scientific information and material exchanges across borders.

Where uncertainty exists regarding the danger of specific genetic sequences that potentially code for harmful substances, sequence providers should strive to ensure that customers and end-users have legitimate purposes for their use. Adherence to the government's voluntary *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* will aid these efforts.[74] Scientists and laboratory technicians should ensure that containment and other safety precautions are in place. The scientific community should take steps to carefully manage both scientific and social risks associated with synthetic biology as this field grows.

Chapter 4 briefly describes the current system of export controls and other measures designed to reduce concerns about malevolent use arising from information exchange. Policy makers in this area face complex challenges. Completely free exchange of data and materials might endanger public safety, but unilateral action to limit exchange could damage American research efforts in synthetic biology if U.S. scientists and students are excluded from full collaboration in the international community. An additional complication for export control efforts in synthetic biology is that much of the "currency" of the field are the sequences of genetic data that are often available in public databases or could be distributed easily and without detection.

Several recent advisory groups have recommended ongoing discussions among research universities, industry, and government on this topic. The National Research Council's 2007 report, *Science and Security in a Post 9/11 World*, expressly calls for more dialogue on export controls. The NSABB in 2010 also recommended expanded outreach and education strategies "that address

dual use research and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology."[75] The Commission agrees that scientists should be actively engaged in these debates.

Recommendation 13: Oversight Controls

If the reviews called for in Recommendation 12 identify significant unmanaged security or safety concerns, the government should consider making compliance with certain oversight or reporting measures mandatory for all researchers, including those in both institutional and non-institutional settings, regardless of funding sources. It may also consider revising the Department of Commerce's export controls. Any such change should be undertaken only after consultation with the scientific, academic, and research communities and relevant science and regulatory agencies such as the National Institutes of Health, the Department of Homeland Security, and the Environmental Protection Agency. Export controls should not unduly restrain the free exchange of information and materials among members of the international scientific community.

Democratic Deliberation

The principle of democratic deliberation reflects an approach to collaborative decision making that embraces respectful debate of opposing views and active participation by citizens. At the core of democratic deliberation is an ongoing, public exchange of ideas, particularly regarding the many topics—in science and elsewhere—in which competing views are advocated, often passionately. A process of active deliberation and justification promotes an atmosphere for debate and decision making that looks for common ground wherever possible, and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests. With careful attention to the processes through which decisions are reached and justified, democratic deliberation promotes outcomes that are inclusive, thoughtfully considered, and respectful of competing views.

Biotechnology has the potential to affect everyone, and opportunities for the public to participate in discussion and deliberation about emerging technologies such as synthetic biology are critical. The principle of democratic deliberation highlights the importance of robust public participation in both the development and implementation of specific policies as well as in a broader, ongoing national conversation about science, technology, society, and values.

In its examination of synthetic biology, the Commission saw encouraging examples of ways in which the public has been invited to learn about this emerging field and to share its perspectives. It learned of groups of citizens coming together, sharing their mutual interest and expertise in synthetic biology—biologists and engineers, teachers and students, professionals and amateurs, from nations around the world. These activities provide an important foundation for expanded efforts regarding public engagement and public education that are not only valuable but essential. This section highlights examples of how citizens are already shaping the present and future of synthetic biology and notes several opportunities for how these efforts can be enhanced and strengthened.

Promoting an Ongoing Public Dialogue

Many groups in addition to this Commission have studied and reported on issues related to synthetic biology in the past several years, including U.S. and international government agencies, professional societies, commercial and industry groups, and private organizations. As the Commission did throughout its deliberations, virtually all of these groups consulted broadly among those with interest and expertise regarding the potential impact of synthetic biology on science and society. The Commission commends these efforts, as they embody a belief that policy regarding synthetic biology is best developed when informed by open and ongoing discussions among a diverse group of stakeholders. Policymaking bodies involved in regulation and oversight of synthetic biology are encouraged to continue to actively solicit input from the public regarding their work, ensure that those views receive thoughtful consideration, and make available and accessible to the public the eventual decisions that are reached and the reasoning for them. Public deliberation is particularly valuable while the field is still young, as there is a unique opportunity to shape its development in ways most likely to promote the public good while assuring safety and security.

The Commission understands that not all policymaking activities in this area can be fully transparent to the public, such as those related to some aspects of biosecurity or involving trade secrets in certain commercial applications of synthetic biology. Concerns about biosecurity and proprietary interests ought not, however, justify excessive secrecy such that the development of science and the participation of the public are unduly compromised. Nor should these necessary limitations preclude those with advisory or decision-making responsibilities from viewing the public as active partners in their work. In addition to being a valuable source of good ideas, public participation frequently fosters the perceived political legitimacy of the policies and practices that are ultimately chosen.

A recent survey of public attitudes regarding synthetic biology found that nearly two-thirds of respondents supported continued development of the field, including additional research on its possible effects on humans and the environment.[76] There was a strong correlation between self-reported awareness of

synthetic biology and support for ongoing research, as 80 percent of those who had heard a lot about the field believed it should move forward, compared to only 52 percent of those who had heard nothing about it. Overall, 73 percent of those surveyed reported having heard "just a little" or "nothing at all" about synthetic biology. These data indicate both the need for broader public engagement regarding synthetic biology and the positive impact of such efforts on public support for novel and otherwise unfamiliar technologies.

In many areas of biomedical research, public engagement is an important component of study design and a means to ensure public support. A notable example of this practice is the Framingham Heart Study and its Ethics Advisory Board. The study, which began in 1948, is a federally funded project based in Framingham, Massachusetts that aims to identify and understand the risk factors for heart disease by observing entire families and populations over time. The Framingham Ethics Advisory Board is comprised largely of past and present study participants as well as local clergy and physicians. It serves as a forum for community deliberations and a vehicle to advise the researchers on design and oversight issues.[77]

The development of the NIH policy on Genome-Wide Association Studies demonstrates another type of proactive public engagement to build public understanding and support. In connection with building a large-scale, central database of individual genotype and phenotype information for secondary research studies, NIH published requests for public comment during the policy development process and held meetings with members of the public prior to finalizing its policy.[78] In another example, community engagement is required by law for certain research projects in which individual informed consent is not feasible, such as research conducted in emergency settings.[79] Increasingly, community engagement or consultation is a prerequisite for research with particular populations, such as Native Americans, or research requiring the use of high-containment facilities to control dangerous pathogens.

Other groups have noted the potential value of public engagement specifically for synthetic biology and related topics. In its April 2010 report on synthetic biology, NSABB recommended outreach and education directed toward participating scientific communities, while also stating that more active

engagement of the general public could lead to a better collective understanding of synthetic biology.[80]

An active, dynamic exchange between citizens and government need not be confined to regulatory and legislative processes. During its deliberations the Commission learned of several initiatives in which government agencies such as the FBI are in regular dialogue with members of the synthetic biology community.[81] These activities provide opportunities for citizens and their government to learn from each other, exchange ideas, share concerns, and work collaboratively toward fostering a safe, productive environment in which synthetic biology can develop.

Government bioethics commissions such as this one can be part of national and international conversations regarding synthetic biology and other emerging technologies.[82] While by no means a substitute for robust, ongoing exchanges between citizens and policy makers, the Commission's deliberations on this matter sought to provide an inclusive forum for discussion, with the hope that its recommendations will be a catalyst for future deliberations.

The Commission's interest in democratic deliberation calls for a national and international dialogue on synthetic biology and its implications, a conversation that bridges specific research initiatives and considers how the field as a whole can best move forward safely and beneficially. The Public Engagement with Research Team of the Research Councils UK is one example of an approach that promotes sustained interactions among researchers, students, and the public on major themes related to research and innovation.[83]

Recommendation 14: Scientific, Religious, and Civic Engagement

Scientists, policy makers, and religious, secular, and civil society groups are encouraged to maintain an ongoing exchange regarding their views on synthetic biology and related emerging technologies, sharing their perspectives with the public and with policy makers. Scientists and policy makers in turn should respectfully take into account all perspectives relevant to synthetic biology.

Democratic deliberation encourages respect for a wide range of reasonable perspectives. Positions based directly on personal revelations—whether divine or secular in nature—are unlikely to be accessible to most citizens. However, by carefully attending to the concerns raised by religious traditions, a respectful dialogue can develop that can often lead to positions that are accessible, independent of their source.[84] While the Commission did not observe significant religious concerns related to synthetic biology at this time (see pp. 137-138), the field is young, and future developments may prompt new concerns, underscoring the importance of ongoing deliberation that is responsive to changing circumstances in science and society.

Striving for Accuracy and Understanding

For effective public deliberation on potentially contentious topics such as synthetic biology, participants should endeavor to express their views in ways that are accessible to others. In part, this means striving to convey one's own views and those of others accurately and with as much mutual understanding as possible. Throughout its deliberations, the Commission was impressed by the quality of discourse on synthetic biology from those working in and around the field. It did observe, however, that the media sometimes described synthetic biology in ways more provocative than accurate. This observation may not be surprising to some, but it makes the development of ongoing deliberative forums on science all the more essential to enhancing public understanding.

In the days immediately following the May 20, 2010, announcement of the creation of the first self-replicating cell containing an entirely synthetic genome, some press accounts worldwide declared, "Scientists have created the world's first synthetic life form."[85] Subsequent coverage attempted to place this work in context, particularly regarding whether it could properly be described as truly creating synthetic or artificial life. In its deliberations, the Commission heard that while the May 20 announcement marked a significant technical achievement in demonstrating that a relatively large genome could be accurately synthesized and substituted for another, it did not amount to the "creation of life"[86] (see Chapters 2 and 3 for further discussion).

While this interpretation of the research appears to be widely held among the scientific community, public perceptions of synthetic biology may have been influenced by initial news of "creating life." This language may excite public interest in a potentially transformative field, but it can serve a useful purpose only if it is followed by careful and robust deliberation informed by an accurate understanding of the current state of synthetic biology and the uncertainty regarding its potential benefits and risks. This example illustrates the considerable opportunities and challenges facing science journalists today to excite public interest and convey accurate understanding of developments in science and technology.

Discussions about synthetic biology and related technologies often raise objections that scientists are "playing God." The Commission's deliberations with representatives of a range of religious communities found this language to be unhelpful at best, misleading at worst. It learned that secular critics of the field are more likely to use the phrase "playing God" than are religious groups. While religious thinkers suggested caution regarding the human tendency toward hubris, none expressed concern that synthetic biologists were "playing God."[87] The provocative nature of this phrase does more to obscure rather than to illuminate those important moral concerns regarding synthetic biology that deserve serious consideration (see pp. 135-140).

Recommendation 15: Information Accuracy

When discussing synthetic biology, individuals and deliberative forums should strive to employ clear and accurate language. The use of sensationalist buzzwords and phrases such as "creating life" or "playing God" may initially increase attention to the underlying science and its implications for society, but ultimately such words impede ongoing understanding of both the scientific and ethical issues at the core of public debates on these topics. To further promote public education and discourse, a mechanism should be created, ideally overseen by a private organization, to fact-check the variety of claims relevant to advances in synthetic biology.

Public deliberation about synthetic biology can be hindered both by imprecise language such as "creating life" or "playing God" as well as by scientific claims that fail to convey accurately to the public the current state of the field, the implications of research results, and the limits of scientists' present knowledge and abilities. The fact-check mechanism recommended here is intended to address these concerns by providing an independent venue where scientific claims related to synthetic biology or other emerging technologies are evaluated by impartial, qualified experts. The results of these analyses would be readily accessible to the public, likely through a website. The Commission envisions a program analogous to FactCheck.org, a project that monitors the accuracy of statements made about U.S. politics.[88] It would be interactive, inviting the public to suggest claims for review by project staff, and funded by private sources without real or perceived conflicts of interest.

Improving Scientific and Ethical Literacy

Meaningful citizen participation in deliberations regarding synthetic biology requires familiarity with general concepts in science and particular aspects of this developing field. Collectively, these tools are referred to as "scientific literacy."[89] The National Academy of Sciences has defined scientific literacy as "the knowledge and understanding of scientific concepts and processes required for personal decision making, participation in civic and cultural affairs, and economic productivity."[90]

Making science accessible to the public requires creativity and innovation in public education. The Commission was pleased to learn that in synthetic biology several groups have launched commendable efforts to educate the public about this emerging field. These groups include the Synthetic Biology Project of the Woodrow Wilson International Center for Scholars and the Synthetic Biology Engineering Research Center, which is funded in part by the National Science Foundation.[91] Through online resources, curricula for teachers and students, and events such as the International Genetically Engineered Machine (iGEM) competition (see p. 46), these and other groups are developing innovative programs to increase the public's understanding of synthetic biology.

Public education efforts addressing synthetic biology need to be part of our Nation's expanded attention to an increasingly urgent need to enhance scientific literacy, broadly understood. Scientific literacy must go hand-in-hand with improved ethical literacy, meaning an understanding of moral concepts, traditions, and controversies concerning the responsibilities and rights of individuals and communities toward one another.

Recommendation 16: Public Education

Educational activities related to synthetic biology should be expanded and directed to diverse populations of students at all levels, civil society organizations, communities, and other groups. These activities are most effective when encouraged and supported by various sources, not only government, but also private foundations and grassroots scientific and civic organizations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, with input from the scientific community, the public, and relevant private organizations, should identify and widely disseminate strategies to promote overall scientific and ethical literacy, particularly as related to synthetic biology, among all age groups.

This effort could be led by EOP or the relevant science agencies such as NIH or DOE in collaboration with the Department of Education. This group should consider the feasibility of including public education components or the development of school curriculum modules in research funding agreements. These activities could be linked to specific projects or organized at the institutional level among recipients of federal research support. It should also examine other models to promote and enhance scientific and ethical literacy, including activities directed by private organizations or developed by private groups in partnership with the government. The Synthetic Biology Project of the Woodrow Wilson Center may serve as one such model.

Scientific research and public education about science are best approached as mutually related, even mutually dependent, endeavors. The iGEM competition, for example, combines hands-on student exposure to research tools and practices with education on many issues—science, safety, and policy—related to synthetic biology. The Commission commends programs throughout the

scientific community that include educational programs as components of ongoing research projects. One illustrative example is Project BioEYES, which provides classroom-based learning opportunities for students in grades K-12 through the use of live zebrafish.[92] With active participation from scientists committed to making science accessible to young people, over 18,000 students in Philadelphia, Baltimore, and South Bend have encountered science in innovative ways. In particular, this project and others similarly directed to under-resourced schools seek to make science available to all students, particularly those who might otherwise lack access to cutting-edge scientific resources and expertise.

In 1999, the National Bioethics Advisory Commission noted that the need for expanded education is "not simply…the provision of information with the aim of adding to the net store of knowledge by any one person or group; rather, education refers to the ongoing effort to inform, challenge, and engage."[93] Engaging citizens—and particularly young people—in challenging science curricula regarding synthetic biology and other emerging technologies as well as many other issues lies at the intersection of science and citizenship. In light of our Nation's dependence on socially responsible scientific innovation for economic progress and individual well-being, the urgency of expanding effective science and ethics education cannot be exaggerated.

Fostering Grassroots Collaborations

As noted, democratic deliberation is based on ongoing interaction among citizens on topics of common interest. For an emerging technology such as synthetic biology, many of these dialogues will be among scientists or other interested citizens and policy makers or regulators. Such interactions are vital to a democracy, but they are not sufficient. Exchanges among individuals and groups of citizens are also important. In particular, grassroots collaborations have been established around synthetic biology. Groups such as DIYbio are loosely organized networks of self-described "citizen scientists" coming together because of a common interest in the tools, methods, and applications of synthetic biology, rather than shared professional affiliations or policy responsibilities. In this way, the "do-it-yourself" community embodies a "do-it-together" ethos.[94]

These kinds of collaborations are commendable; they strengthen notions of citizenship and community at the core of a democracy. They demonstrate that science and its oversight do not belong exclusively to experts, highly trained professionals, or government officials. Science is a shared resource, affecting and belonging to all citizens.

Through democratic deliberation, questions raised by the emerging science of synthetic biology can be explored and evaluated on an ongoing basis in a manner that welcomes the respectful exchange of opposing views. This deliberation is best positioned to succeed when it includes a diverse set of accessible arguments built upon a foundation of public understanding and engagement with science and technology. In this way, democratic deliberation advocates for an inclusive view of synthetic biology and its oversight. A community-oriented perspective strengthens efforts to ensure that this science develops in ways that will be acceptable to the majority of the population. This perspective also complements activities intended to promote justice and fairness in the development of synthetic biology and its applications.

Justice and Fairness

The principle of justice and fairness relates to the distribution of benefits and burdens across society. Emerging technologies like synthetic biology, for good or ill, affect all persons. Society as a whole has a claim toward reasonable efforts on the part of both individuals and institutions to avoid unjust distributions of the benefits, burdens, and risks that such technologies bring. This same claim extends internationally to all those who may be affected—positively or negatively—by synthetic biology and its applications.

In calling attention to justice and fairness, the Commission highlights the importance of considering not simply *what* the benefits and risks of synthetic biology are, but *to whom and to what* those benefits and risks are directed. Its examination of synthetic biology discussed strategies intended to realize potential benefits and minimize risks by means of thorough, inclusive deliberative processes. These benefits and risks can be specified; they are not abstract concepts. They have the potential to directly and significantly affect individuals and entire populations, species, and environments. The principle of justice and fairness encourages a proactive sensitivity to the distribution of these outcomes.

Justice and fairness are concepts with closely related but distinct meetings. Many definitions exist, but justice is generally the broader concept of the two. One type of justice, distributive justice, refers to concern for the equitable allocation of goods and evils in a society. Fairness provides one specification of justice, as in philosopher John Rawls's principles of equal liberty and equal opportunity among members of communities as two of the primary attributes of "justice as fairness."[95] In its work, the Commission refers to the principles of justice and fairness collectively to refer broadly to concern for how benefits and burdens ought to be shared among communities and nations.

Some of the most exciting potential current applications of synthetic biology involve products with the potential to address major challenges in global health and welfare. Semi-synthetic artemisinin (see p. 65), for example, could offer a valuable treatment for malaria around the globe. Synthetic biofuels could be particularly valuable in nations where energy deficits hinder development and

economic growth. There is great value in striving to pursue these and other applications and to ensure, if successful, that they reach those individuals and communities who would most benefit from them.

As it advances, synthetic biology may also pose a spectrum of risks to human health, other species, ecosystems, and national security (see Chapter 3). The likelihood and severity of most of these risks are difficult to predict at this time, but part of the work of oversight activities, broadly speaking, is to assess where the risks and harms of synthetic biology are most likely to be experienced, if at all, and act to prevent or minimize any adverse impacts. Research-related risks, potential environmental exposures, and social and economic displacement can be unavoidable hazards of science and technology, but these burdens should not fall disproportionately on any particular individual or group. Of great concern are those individuals and groups whose political, economic, or other status makes them particularly vulnerable.

Sensitivity to the fair distribution of the risks and benefits of synthetic biology, like other biotechnologies, is appropriate regardless of the source of funding. Yet fair distribution of the benefits of synthetic biology is an especially important consideration for government-funded research. Government support provides both benefits and obligations. Benefits include the creation of a safe and secure research environment as well as direct funding for particular projects. These benefits come with a corresponding responsibility for beneficiaries to do their part to ensure that return on these investments is justly distributed across society. Concern for justice and fairness should be a central consideration of all aspects of the planning and implementation of research in synthetic biology and its applications.

Just Distribution of Risks, Burdens, and Potential Benefits

With any technological advance come burdens and risks. These burdens can arise both in the research and development process and from the eventual introduction of new technologies and products into the marketplace. Frequently, the risks are unknown or of uncertain magnitude at the early stages

of development of a field. Ongoing and recurring risk assessment is often required to fully understand and respond appropriately.

Chapter 3 discusses the potential benefits and risks of synthetic biology as it is understood today. One set of risks relates to the conduct of synthetic biology research. These include risks to laboratory workers and personnel, risks to research subjects, and risks related to the unintentional or deliberate release of experimental agents into the environment. In the United States, numerous oversight systems are in place to guard against potential harms that may result from these types of risks (see Chapter 4). These include provisions designed to prevent physical harm to workers, study subjects, and the public generally.

For study subjects, specific mechanisms are in place to ensure that volunteers are fully informed about, and agree to accept, the possible risks or harms they may face before they begin. Oversight bodies assess research risks in light of potential benefits to individuals, and in some cases, communities, prior to approval. Many believe also that research should be responsive to the needs of the entire population being studied or affected by the research activities.[96]

Evaluation of research proposals and ongoing review should include consideration of possible environmental exposures or social disruption. These considerations are particularly relevant for synthetic biology. Clinical and observational research in this field is relatively limited at present, but harmful environmental effects or unintended consequences on human health loom as major sources of concern and public anxiety. These concerns need not be addressed by institutional review boards, which are commonly understood to be prohibited by federal regulation from considering such effects beyond their relevance to the protection of human subjects directly participating in the research.[97] To address the uncertain or potentially unique risks that may arise from synthetic biology in light of its extraordinary potential to manipulate and manage living systems, special consideration and safety reviews may be needed. In addition to concerns about possible environmental exposures or social disruption, consideration must also be given to potential hazards to the public posed by synthetic biology consumer products, including medicines.

Recommendation 17: Risks in Research

Risks in research should not be unfairly or unnecessarily borne by certain individuals, subgroups, or populations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should lead an interagency evaluation of current requirements and alternative models to identify mechanisms that ensure that the risks of research in synthetic biology, including for human subjects and other affected parties, are not unfairly or unnecessarily distributed. Relevant scientific, academic, and research communities, including those in the private sector, should be consulted. This review should be completed within 18 months and the results made public.

Attention to these concerns is particularly relevant when those participating directly in research or likely to be affected by research activities do not share the nationality, culture, economic status, or political power of those conducting the research.

The introduction of new technologies may also lead to increased risk of harmful environmental exposures in specific locations, and the principles of justice and fairness require vigilant attention to these environmental risks. The arrival of new products or applications of synthetic biology should not compel any particular population to "shoulder a disproportionate burden of the negative human health and environmental impacts of pollution or other environmental hazards."[98] All citizens ought to "enjoy the same degree of protection from environmental and health hazards."[99] Accordingly, the Commission makes the following recommendation as a means to expand attention to the relative burden that some communities or individuals may bear regarding the potentially adverse effects and risks of new technologies.

Recommendation 18: Risks and Benefits in Commercial Production and Distribution

Risks to communities and the environment should not be unfairly distributed. Manufacturers and others seeking to use synthetic biology for commercial activities should ensure that risks and potential benefits to communities and the environment are assessed and managed so that the most

serious risks, including long-term impacts, are not unfairly or unnecessarily borne by certain individuals, subgroups, or populations. These efforts should also aim to ensure that the important advances that may result from this research reach those individuals and populations who could most benefit from them. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate current statutory mandates or regulatory requirements for distribution of risks and benefits and consider developing guidance materials and voluntary recommendations to assist manufacturers as appropriate.

There is considerable enthusiasm among advocates of synthetic biology for the varied benefits that this emerging field may yield for individuals and communities. Some critics have expressed concern, however, that synthetic biology will only exacerbate existing disparities with regard to health, welfare, and socioeconomic status.[100] Similar concerns are often voiced in response to other new technologies.

Much of the optimism surrounding synthetic biology stems directly from its potential to address some of the longstanding, significant problems associated with these disparities. Synthetic biology offers potential applications that may be particularly beneficial to less advantaged populations, including improved quality and access to vaccines against infectious diseases, medications, and fuel sources. A just society recognizes the value of establishing incentives to create new knowledge and to translate it into vibrant markets in ways intended to distribute benefits widely. As new tools arrive and mature, it will be important to identify strategies to responsibly ensure that communities and nations who may most immediately benefit are empowered to do so. Doing so will require ongoing review of how intellectual property and licensing arrangements can best be structured to promote both scientific innovation and the public good (see pp. 119-122).

Stakeholders should work collaboratively, aiming to ensure that advances made possible by synthetic biology reach those who could benefit from them, particularly less advantaged populations. Attention to the just distribution of potential benefits is most effective when continually examined in concert with research and development activities. It encourages an awareness of the

full "life cycle" of a new application of synthetic biology, from initial research through potential global implementation. This holistic perspective recognizes that decisions made even in early stages of development may have consequences—technological, economic, or practical—that can affect the eventual implementation of potential research products positively or negatively. The ongoing development of semi-synthetic artemisinin is an example of a research program that reflects an appreciation for the challenges and importance of ensuring wide access to possible products.[101] Research and development activities throughout synthetic biology would be well served by similar appreciation of the relationships among current activities, potential future implementation concerns, and the concepts of justice and fairness.

[1] Although current levels of public and private investment in synthetic biology are not available, according to the Woodrow Wilson Center, the U.S. Government has spent approximately $430 million on research related to synthetic biology since 2005. By comparison, the European Union and three individual European countries—The Netherlands, U.K., and Germany—spent approximately $160 million during that same period. See: Woodrow Wilson International Center for Scholars. (2010). *Trends in Synthetic Biology Research Funding in the United States and Europe, June 2010, Research Brief 1.* Available at: http://www.synbioproject.org/library/publications/archive/researchfunding/. A few companies' combined spending already far exceeds those public investments. (*See, e.g.*, Dimond, P. (2010). Analysis & Insight: Synthetic biology—the devil is in the financial details. *Genetic Engineering and Biotechnology News* (July 13, 2010). Available at: http://www.genengnews.com/analysis-and-insight/synthetic-biology-the-devil-is-in-the-financial-details/77899331/.)

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[11] *See* Secretary's Advisory Committee on Genetics, Health, and Society. (2010). *Revised Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*. Available at: http:// oba.od.nih.gov/oba/SACGHS/SACGHS%20Patents%20Report%20Approved%202-5-20010.pdf; see also, National Research Council (2006). *Reaping the Benefits of Genomic and Proteomic Research*. Washington, D.C.: National Academies Press.

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64 BBC Monitoring Europe. *Vatican Dismisses Synthetic Cell's Life-Giving Dimension, Lauds Science Research*. May 25, 2010. Translation of Gian Guido Vecchi. *Cautela in Vaticano 'È un ottimo motore ma non è la vita.'* Available at: http://archiviostorico.corriere.it/2010/maggio/22/Cautela_Vaticano_ottimo_motore_non_co_9_100522032.shtml.

65 Wheeler, S.E., Martha Ashby Carr Professor of Christian Ethics, Wesley Theological Seminary. (2010). Contributions of Christian Thought to Assessments of Synthetic Biology. Presentation to the Presidential Commission for the Study of Bioethical Issues, September 13, 2010. Available at: http://www.bioethics.gov/transcripts/synthetic-biology/091310/philosophical-and-theological-perspectives.html.

66 Ibid.

67 Buchanan, A., op cit.; See also Lustig, B.A., Brody, B.A., and G.P. McKenny (eds.). (2008). *Altering Nature. Vol. I: Concepts of 'Nature' and 'The Natural' in Biotechnology Debates*. New York: Springer Publishing.

68 American Association of University Professors. (1940). *Statement of Principles on Academic Freedom and Tenure*. Available at: http://www.aaup.org/AAUP/pubsres/policydocs/contents/1940statement.htm. Consider also the discussion by Supreme Court Chief Justice Warren, in *Sweezey v. New Hampshire*, 354 U.S. 234 (1957), defending the academic freedom of a faculty member and recognizing the importance of new knowledge to civilization: "No field of education is so thoroughly comprehended by man that new discoveries cannot yet be made…Scholarship cannot flourish in an atmosphere of suspicion and distrust. Teachers and students must always remain free to inquire, to study and to evaluate, to gain new maturity and understanding; otherwise our civilization will stagnate and die." *Sweezey v. New Hampshire*, 354 U.S. 234, 250 (1957).

69 *See* You, E.H., Supervisory Special Agent, Federal Bureau of Investigation. (2010). FBI Perspective: Addressing Synthetic Biology and Biosecurity. Federal Oversight of Synthetic Biology. Presentation to the Presidential Commission for the Study of Bioethical Issues, July 9, 2010. Available at: http://www.bioethics.gov/transcripts/synthetic-biology/070910/federal-oversight-of-synthetic-biology.html.

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71 *See, e.g.*, DHHS. (2009). *Biosafety in Microbiological and Biomedical Laboratories, 5th Edition*. Available at: www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf.

72 *See* You, E.H., op cit.

73 NSABB, op cit.; Patterson, A., op cit.

74 DHHS/NIH. (2009). *NIH Guidelines for Research Involving Recombinant DNA Molecules*. Available at: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html.

75 NSABB, op cit., p.13.

76 Hart Research Associates, Synthetic Biology Project, Woodrow Wilson International Center for Scholars. (2010). *Awareness & Impressions of Synthetic Biology: A Report of Findings Based on a National Survey among Adults*. Available at: http://www.synbioproject.org/process/assets/files/6451/_draft/hart_revised_.pdf.

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[79] *See, e.g.*, Office of Human Research Protections. (2010) *Emergency Research Informed Consent Requirements*. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm.

[80] NSABB, op cit..

[81] You, E.H., op cit.

[82] The charter of the President's Council on Bioethics instructed it "to provide a forum for a national discussion of bioethical issues." See Kass, L. (2005). Reflections on public bioethics: A view from the trenches. *Kennedy Institute of Ethics Journal* 15(3):221-250; The National Bioethics Advisory Commission frequently recommended ongoing review and assessment of the topics it studied, with its reports contributing to such a process. *See, e.g.*, National Bioethics Advisory Commission. (1999). *Ethical Issues in Stem Cell Research*. Available at: http://bioethics.georgetown.edu/nbac/pubs.html.

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[85] *See, e.g.*, Sample, I. (2010). Craig Venter Creates Synthetic Life Form. *Guardian*. 20 May 2010. Available at: http://www.guardian.co.uk/science/2010/may/20/craig-venter-synthetic-life-form.

[86] Brenner, S., Senior Distinguished Fellow of the Crick-Jacobs Center, The Salk Institute. (2010). Reflections for the Future. Presentation to the Presidential Commission for the Study of Bioethical Issues, September 14, 2010. Available at: http://www.bioethics.gov/transcripts/synthetic-biology/091410/reflections-for-the-future.html.

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[88] FactCheck.org. Available at: http://factcheck.org/.

[89] The National Science Education Standards provides the following definition: "Scientific literacy means that a person can ask, find, or determine answers to questions derived from curiosity about everyday experiences. It means that a person has the ability to describe, explain, and predict natural phenomena. Scientific literacy entails being able to read with understanding articles about science in the popular press and to engage in social conversation about the validity of the conclusions. Scientific literacy implies that a person can identify scientific issues underlying national and local decisions and express positions that are scientifically and technologically informed. A literate citizen should be able to evaluate the quality of scientific information on the basis of its source and the methods used to generate it." National Committee on Science Education Standards and Assessment, National Research Council. (1996). *National Science Education Standards*. Washington, DC: National Academies Press, p.22.

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[92] For additional information, *see* BioEYES. *What is BioEYES?* Available at: http://www.bioeyes.org/.

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APPENDIX
Guest Speakers

Bonnie L. Bassler, Ph.D.
Howard Hughes Medical Institute Investigator; Squibb Professor, Department of Molecular Biology, Princeton University; President, American Society for Microbiology

Jason Bobe, M.S.I.S.
Director of Community, Personal Genome Project, Harvard Medical School; Co-Founder, DIYbio.org

Sydney Brenner, M.D., D.Phil.
Senior Distinguished Fellow of the Crick-Jacobs Center, The Salk Institute

Allen Buchanan, Ph.D.
James B. Duke Professor of Philosophy; Investigator, Institute for Genome Sciences and Policy, Duke University; Distinguished Research Associate, Uehiro Centre for Practical Ethics, University of Oxford

Arthur L. Caplan, Ph.D.
Emmanuel and Robert Hart Director, Center for Bioethics; Sydney D. Caplan Professor of Bioethics, School of Medicine, University of Pennsylvania

Alexander M. Capron, LL.B.
University Professor; Scott H. Bice Chair in Healthcare Law, Policy and Ethics; Professor of Law, Keck School of Medicine; Co-Director, Pacific Center for Health Policy and Ethics, University of Southern California

Robert Carlson, Ph.D.
Principal, Biodesic

George Church, Ph.D.
Professor of Genetics, Harvard Medical School

James J. Collins, Ph.D.
University Professor; William F. Warren Distinguished Professor; Professor of Biomedical Engineering; Co-Director, Center for BioDynamics, Boston University; Investigator, Howard Hughes Medical Institute

Drew Endy, Ph.D.
Terman Fellow & Assistant Professor of Bioengineering, Stanford University; Director, BIOFAB: International Open Facility Advancing Biotechnology; President, The BioBricks Foundation

Ruth R. Faden, Ph.D.
Director, Johns Hopkins Berman Institute of Bioethics; Philip Franklin Wagley Professor of Biomedical Ethics; Professor, Department of Health Policy and Management, Bloomberg School of Public Health; Professor, Department of Medicine, Johns Hopkins University

Gregory Kaebnick, Ph.D.
Research Scholar, The Hastings Center; Editor, The Hastings Center Report

Nancy M.P. King, J.D.
Professor, Department of Social Sciences and Health Policy, Wake Forest University School of Medicine; Co-Director, Wake Forest University Center for Bioethics, Health, and Society

Ingrid Mattson, Ph.D.
Director, Macdonald Center for the Study of Islam and Christian-Muslim Relations; Director, Islamic Chaplaincy Program; Professor of Islamic Studies and Christian-Muslim Relations, Hartford Seminary; President, Islamic Society of North America

Jonathan D. Moreno, Ph.D.
David and Lyn Silfen University Professor; Professor, History and Sociology of Science; Professor, Philosophy; Professor of Medical Ethics, School of Medicine, University of Pennsylvania

Thomas H. Murray, Ph.D.
President, The Hastings Center

Bryan G. Norton, Ph.D.
Distinguished Professor of Philosophy, School of Public Policy, Georgia Institute of Technology

Amy Patterson, M.D.
Acting Director, Office of Science Policy; Director, Office of Biotechnology Activities, National Institutes of Health

Kristala L.J. Prather, Ph.D.
Assistant Professor, Department of Chemical Engineering, Massachusetts Institute of Technology

Arti K. Rai, J.D.
Elvin R. Latty Professor of Law, Duke University School of Law; Member, Institute for Genome Science and Policy, Duke University

David Rejeski
Director, Science and Technology Innovation Program, Woodrow Wilson International Center for Scholars

David A. Relman, M.D.
Thomas M. and Joan C. Merigan Professor of Medicine; Chief, Division of Infectious Diseases, Department of Medicine; Professor, Department of Microbiology and Immunology, Stanford University School of Medicine; Chief of Infectious Diseases, Veterans Administration Palo Alto Health Care System; Chair, Working Group on Synthetic Biology, National Science Advisory Board for Biosecurity

Randy D. Rettberg, M.S.
Director, iGEM and MIT Registry of Standard Biological Parts; Principal Research Engineer, Department of Biological Engineering, and Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology

Michael Rodemeyer, J.D.
Lecturer, Department of Science, Technology & Society, School of Engineering and Applied Science, University of Virginia

Markus Schmidt, Ph.D.
Co-founder, Organisation for International Dialogue and Conflict Management, Vienna, Austria

Allison Snow, Ph.D.
Professor, Department of Evolution, Ecology and Organismal Biology, Ohio State University

Ashley J. Stevens, D.Phil.
Special Assistant to the Vice President of Research, Office of Technology Development; Senior Research Associate, Institute for Technology Entrepreneurship and Commercialization, Boston University; President, Association of University Technology Managers

Damon A. Terrill, J.D., M.A.
Senior Vice President and General Counsel for International Legal and Regulatory Affairs, Integrated DNA Technologies; Member, International Gene Synthesis Consortium

Jim Thomas
Programme Manager, ETC Group

J. Craig Venter, Ph.D.
Founder and President, J. Craig Venter Institute

Ralf Wagner, Ph.D.
Chief Executive Officer and Chief Science Officer, Geneart AG; Professor and Chief, Molecular Microbiology and Gene Therapy, Institute of Medical Microbiology & Hygiene University of Regensburg; Member, International Gene Synthesis Consortium

David B. Weiner, Ph.D.
Professor, Department of Pathology and Laboratory Medicine; Chair, Therapy and Vaccines Program, CAMB, University of Pennsylvania; Chair, Scientific Advisory Board, Inovio Pharmaceuticals

Ron Weiss, Ph.D.
Associate Professor, Department of Biological Engineering and Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology

Sondra E. Wheeler, Ph.D.
Martha Ashby Carr Professor of Christian Ethics, Wesley Theological Seminary

Hugh Whittall
Director, Nuffield Council on Bioethics

Paul Root Wolpe, Ph.D.
Asa Griggs Candler Professor of Bioethics; Director, Center for Ethics, Emory University

Edward H. You
Supervisory Special Agent, Federal Bureau of Investigation, Weapons of Mass Destruction Directorate, Countermeasures Unit I, Bioterrorism Prevention Program

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Commission présidentielle américaine sur les questions éthiques associées à la biologie de synthèse

Décembre 2010

Traduction en français des dix-huit recommandations

Rapport de la commission présidentielle américaine sur les questions éthiques associées à la biologie de synthèse (2010)

les dix-huit recommandations

Recommandation 1 : Évaluation du financement public et publication

Le gouvernement fédéral devrait faire procéder, par une instance centrale telle que le Bureau exécutif du Président (*Executive Office of the President*), à une évaluation coordonnée du financement public actuel des activités de biologie de synthèse, ainsi que des fonds publics affectés aux financement des techniques de recherche pour l'évaluation et la maîtrise des risques et de l'étude des questions éthiques et sociales soulevées par la biologie de synthèse. Il conviendrait de réaliser cette évaluation dans un délai de 18 mois et d'en publier les résultats.

Recommandation 2 : Appui à une recherche scientifique prometteuse

L'intérêt général devrait primer dans toute décision d'investir des fonds publics dans la biologie de synthèse, plutôt que dans d'autres activités scientifiques. Il conviendrait que les Instituts nationaux de la santé (NIH), le ministère de l'Énergie et d'autres administrations fédérales poursuivent leur travail d'évaluation des propositions de recherche, en recourant à des procédures d'examen mutuel et à d'autres instances de réflexion spécialement créées pour garantir que cette recherche scientifique, la plus prometteuse qui soit, soit menée dans l'intérêt de la collectivité.

Recommandation 3 : L'innovation par l'échange

La biologie de synthèse n'en est qu'aux tout premiers stades de son développement et il convient d'encourager l'innovation. Dans le cadre de l'approche coordonnée visée à la Recommandation 4, le Bureau exécutif du Président devrait piloter un projet visant à déterminer si la politique d'attribution de licences et les pratiques d'échange actuelles sont suffisantes pour garantir l'accessibilité des résultats de la recherche fondamentale en biologie de synthèse et promouvoir ainsi l'innovation et, dans le cas contraire, s'il y a lieu de prendre d'autres mesures ou d'améliorer ces pratiques. Cette évaluation devrait être conduite avec la participation des

Instituts nationaux de la santé, des autres administrations de financement de la recherche en biologie de synthèse, notamment le ministère de l'Énergie et la NASA (National Aeronautics and Space Administration), l'Office des brevets (USPTO), et de l'industrie, des universités et des associations de la société civile. Il conviendrait de réaliser cette évaluation dans un délai de 18 mois et d'en publier les résultats.

Recommandation 4 : Une approche coordonnée de la biologie de synthèse

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À ce stade, la Commission ne voit pas la nécessité de créer des instances supplémentaires, ni de soumettre à une supervision les organismes s'occupant spécifiquement de biologie de synthèse. En lieu et place, la Commission recommande au Bureau exécutif du Président de mettre au point, en concertation avec les autres administrations fédérales concernées, une approche claire, précise et coordonnée de la recherche et du développement en biologie de synthèse au niveau de toute l'administration. Il conviendrait d'identifier un mécanisme ou un organe chargé de :

- mobiliser les ressources existantes en assurant une évaluation continue et coordonnée des progrès de la biologie de synthèse ;

- veiller à ce que les spécifications réglementaires soient cohérentes et non contradictoires ;

- informer régulièrement et en temps utile les citoyens des résultats de la recherche. Les autres activités de cet organe ou mécanisme de coordination sont décrites dans d'autres recommandations.

Recommandation 5 : Évaluation des analyses de risques et des carences dans l'analyse des risques liés à la dissémination volontaire dans l'environnement

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Compte tenu de la difficulté d'analyser les risques face à l'incertitude – en particulier les risques d'événements à faible probabilité et à fort impact potentiel dans un domaine en émergence – des évaluations continues seront nécessaires au fur et à mesure des avancées. Les procédures réglementaires devraient être évaluées et actualisées autant que nécessaire pour que les autorités de réglementation disposent des bonnes informations. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait réunir une instance interinstitutionnelle pour discuter des activités d'évaluation des risques, des

raisons d'être des différences d'approche et des stratégies pour une plus grande harmonisation dans toute l'administration. Cette instance devrait également pointer les éventuelles lacunes dans les méthodes actuelles d'évaluation des risques afférents à la dissémination d'organismes synthétiques dans l'environnement. Il conviendrait de réaliser ces évaluations dans un délai de 18 mois et d'en publier les résultats.

Recommandation 6 : Suivi, confinement et contrôle

À ce stade précoce de développement, le potentiel de nuisance, par la prolifération accidentelle d'organismes ou d'autres matériaux bioactifs issus de la biologie de synthèse dans l'environnement, nécessite de mettre en place des protections et un suivi. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait diriger un processus d'évaluation continue de la capacité d'organismes synthétiques à se multiplier dans l'environnement naturel et identifier, autant que nécessaire, des mécanismes fiables de confinement et de contrôle. Ainsi, des « gènes suicides », ou d'autres mécanismes déclencheurs d'autodestruction, pourraient être envisagés pour limiter leur durée de vie. Une autre solution consisterait à rendre dépendants les organismes produits, pour leur nutrition, de substances absentes en dehors du laboratoire, telles que de nouveaux acides aminés, et donc contrôlables en cas de dissémination accidentelle.

Recommandation 7 : Analyse des risques préalable à la dissémination volontaire dans l'environnement

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Il conviendrait d'effectuer une analyse raisonnable des risques, en vertu de la loi relative à la protection de l'environnement (*National Environmental Policy Act*) ou de toute autre législation, préalablement à la dissémination dans l'environnement d'organismes issus de la recherche ou de produits commerciaux utilisant les technologies de la biologie de synthèse. Cette analyse devrait prévoir, si besoin est, des plans pour l'introduction ou la dissémination des substances confinées en laboratoire. Des dérogations pourraient être envisagées dans certains cas précis, notamment en cas d'urgence ou après la découverte d'une équivalence substantielle avec des produits agréés. L'analyse de carences visée à la Recommandation 5 devrait déterminer si une dissémination dans l'environnement non précédée d'une évaluation des risques peut être autorisée et, dans l'affirmative, dans quelles conditions.

Recommandation 8 : Coordination internationale et dialogue

Reconnaissant le caractère primordial de la coordination internationale pour la sécurité et la sûreté, le gouvernement devrait faire en sorte d'assurer un dialogue permanent sur les technologies émergentes telles que la biologie de synthèse. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait, par l'entremise du Département d'État et des autres administrations concernées, notamment le ministère de la Santé et des Services sociaux (DHHS) et le ministère de la Sécurité intérieure, poursuivre et développer ses initiatives de collaboration avec les autorités internationales, l'Organisation mondiale de la santé et d'autres parties intéressées, y compris avec les organisations internationales de bioéthique, pour favoriser un dialogue permanent sur les technologies émergentes telles que la biologie de synthèse, à mesure que la recherche avance.

Recommandation 9 : Éducation à l'éthique

Parce que la biologie de synthèse et les travaux de recherche en la matière transcendent les frontières interdisciplinaires traditionnelles, il conviendrait de développer une éducation à l'éthique d'un niveau semblable, voire supérieur, à la formation demandée aujourd'hui dans la recherche médicale et clinique et de l'exiger de tous les chercheurs et étudiants-chercheurs en dehors de la médecine, y compris dans le domaine des sciences de l'ingénieur et des matériaux. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait, en concertation avec l'Académie des sciences (National Academy of Sciences), l'Académie des métiers de l'ingénieur (National Academy of Engineering), la communauté scientifique et les citoyens, constituer un groupe de travail pour examiner les critères et les modèles appropriés et intéressants pour cette formation. Il conviendrait de réaliser cette évaluation dans un délai de 18 mois et d'en publier les résultats.

Recommandation 10 : Examen continu des objections

Il conviendrait de revoir régulièrement le débat sur les objections d'ordre moral à la biologie de synthèse au fur et à mesure que la recherche dans ce domaine avance dans des directions nouvelles. Le réexamen des préoccupations exprimées quant aux implications de la biologie de synthèse pour les hommes, les autres espèces, la nature et l'environnement, devrait suivre les

avancées de la recherche. Un processus itératif de réflexion du type visé à la Recommandation 14 permet d'examiner attentivement les objections d'ordre moral opposées à la biologie de synthèse, en particulier si des changements fondamentaux interviennent dans les possibilités de cette science et de ses applications.

Recommandation 11 : Promouvoir la responsabilité et la transparence

Le gouvernement devrait favoriser une culture permanente de la responsabilité et de l'autorégulation individuelles et collectives chez les chercheurs, ce qui inclurait un contrôle institutionnel, une vigilance renforcée et l'application des lignes directrices des Instituts nationaux de la santé relatives à la recombinaison de l'ADN (*National Institutes of Health Guidelines for Recombinant DNA Research).* Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait évaluer, et réévaluer à intervalles réguliers, l'efficacité des mécanismes actuels de surveillance de la recherche et examiner si des mesures supplémentaires, le cas échéant, devraient être prises pour promouvoir la responsabilité sans restreindre inconsidérément la liberté intellectuelle. Les instituts universitaires et privés, les citoyens, les Instituts nationaux de la santé et les autres administrations fédérales finançant la recherche en biologie de synthèse devraient être associés à ce processus. Il conviendrait de réaliser une première évaluation dans un délai de 18 mois et d'en publier les résultats.

Recommandation 12 : Évaluation périodique des risques pour la sécurité et la sûreté

Les risques pour la sûreté et la sécurité peuvent être différents en fonction du contexte des activités de recherche. Les activités de recherche pratiquées dans un environnement institutionnel sont susceptibles de comporter moins de risques que dans un environnement non institutionnel – même si certainement, tel n'est pas toujours le cas. Il semble que les risques présentés par la biologie de synthèse soient correctement gérés à ce jour dans les deux types d'environnement. Toutefois, au fur et à mesure que la recherche progresse, le gouvernement devrait continuer d'évaluer les risques spécifiques pour la sûreté et la sécurité des activités de recherche en biologie de synthèse dans les deux environnements, institutionnels et non institutionnels, y compris, mais pas seulement, dans la communauté des biologistes amateurs (« DIYBio »). Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait, en coopération avec le ministère de la Sécurité intérieure, le FBI (*Federal Bureau of Investigation*) et d'autres administrations,

réaliser cette évaluation et l'actualiser à intervalles réguliers. Il conviendrait de réaliser une première évaluation dans un délai de 18 mois et d'en publier les résultats, pour autant que le permette la législation.

Recommandation 13 : Contrôle de suivi

Si les mesures d'évaluation préconisées à la Recommandation 12 révèlent un manquement dans la gestion de risques majeurs pour la sûreté et la sécurité, le gouvernement devrait envisager d'imposer à l'ensemble des chercheurs, institutionnels ou non institutionnels et sans considération de leurs sources de financement, de se soumettre à certaines mesures de supervision ou à des obligations d'information. Le gouvernement pourrait également envisager de revoir les contrôles à l'exportation prévus par le ministère du Commerce extérieur. De tels changements ne devraient intervenir qu'après avoir consulté les milieux scientifiques et universitaires, les chercheurs, les institutions scientifiques et autorités réglementaires concernées, notamment les Instituts nationaux de la santé, le ministère de la Sécurité intérieure et l'Agence de protection de l'environnement (EPA). Les contrôles à l'exportation ne devraient pas restreindre inutilement la liberté d'échanger des informations et des matériaux entre les membres de la communauté scientifique internationale.

Recommandation 14 : Engagement des communautés scientifiques, laïques et civiles

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Les scientifiques, les politiques, les religieux, les laïcs et la société civile sont invités à s'engager dans un processus continu d'échange de vues sur la biologie de synthèse et sur les technologies émergentes correspondantes, en partageant leurs conceptions avec les citoyens et les décideurs. Les scientifiques et les décideurs seraient tenus, pour leur part, de respecter pleinement l'ensemble des points de vue sur la biologie de synthèse.

Recommandation 15 : Précision de l'information

Il conviendrait que dans leurs discussions sur la biologie de synthèse, les individus comme les forums de réflexion s'efforcent d'employer un langage clair et précis. Si dans un premier temps, l'emploi d'un vocabulaire dans l'ère du temps et d'expressions en quête de sensationnel comme « création de nouvelles formes de vie » ou « jouer à Dieu » peut braquer les projecteurs sur la science sous-jacente et sur ses implications pour la société, il peut en

définitive être un obstacle à une compréhension constante des enjeux à la fois scientifiques et éthiques au cœur du débat public sur ces sujets. Pour promouvoir encore l'éducation et le débat citoyens, il conviendrait d'instaurer un mécanisme, placé sous la supervision d'une organisation privée dans l'idéal, pour assurer la vérification factuelle des informations faisant état d'avancées en biologie de synthèse.

Recommandation 16 : Éducation des citoyens

Il conviendrait de développer des activités d'éducation à la biologie de synthèse à l'intention de divers publics d'étudiants de tous niveaux, des organisations de la société civile, des citoyens ordinaires et de divers groupes. Ces activités ont une efficacité optimale lorsqu'elles bénéficient des encouragements et de l'appui non seulement du gouvernement, mais aussi de fondations privées et associations scientifiques et civiques. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait, avec la participation de la communauté scientifique, des citoyens et des organisations privées concernées, recenser et faire connaître les stratégies permettant de favoriser l'acquisition d'une culture scientifique et éthique générale, et plus particulièrement en biologie de synthèse, dans toutes les catégories d'âge.

Recommandation 17 : Les risques de la recherche

Certains individus, sous-groupes ou populations n'ont pas à supporter injustement ou inutilement les risques de la recherche. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait piloter une évaluation interinstitutionnelle des critères actuels et des modèles possibles pour identifier des mécanismes garants d'une répartition des risques liés à la recherche en biologie de synthèse, pour l'homme et pour toute autre partie concernée, qui ne soit pas injuste ou inutile. Les milieux scientifiques et universitaires et les chercheurs, y compris ceux du secteur privé, devraient être consultés à cet égard. Il conviendrait de réaliser cette évaluation dans un délai de 18 mois et d'en publier les résultats.

Recommandation 18 : Risques et avantages de la production et de la distribution commerciales

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La répartition des risques pour les populations locales et l'environnement ne doit pas être injuste. Les acteurs économiques cherchant à utiliser la biologie de synthèse à des fins commerciales devraient veiller à ce que les risques et les avantages potentiels en découlant pour les populations locales et l'environnement soient évalués et gérés de telle façon que certains individus, sous-groupes ou populations n'aient pas à en supporter injustement ou inutilement les risques les plus graves et leurs incidences à long terme. Leur action devrait viser à ce que les avancées majeures de la recherche soient dirigées vers les individus et les populations les plus à même d'en tirer le meilleur bénéfice. Dans le cadre de l'approche coordonnée préconisée à la Recommandation 4, le Bureau exécutif du Président devrait évaluer les obligations légales actuelles ou les prescriptions réglementaires applicables à la répartition des risques et des avantages et envisager d'élaborer des orientations et des recommandations volontaires pour aider, si besoin est, les fabricants.

Articles

Toward interoperable bioscience data

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To make full use of research data, the bioscience community needs to adopt technologies and reward mechanisms that support interoperability and promote the growth of an open 'data commoning' culture. Here we describe the prerequisites for data commoning and present an established and growing ecosystem of solutions using the shared 'Investigation-Study-Assay' framework to support that vision.

To tackle complex scientific questions, experimental datasets from different sources often need to be harmonized in regard to structure, formatting and annotation so as to open their content to (integrative) analysis. Vast swathes of bioscience data remain locked in esoteric formats, are described using nonstandard terminology, lack sufficient contextual information or simply are never shared due to the perceived cost or futility of the exercise. This loss of value continues to engender standardization initiatives and drives the ongoing conversation about the encouragement of data sharing through appropriate reward mechanisms.

Minimum reporting guidelines, terminologies and formats (hereafter referred to generally as reporting standards) are increasingly used in the structuring and curation of datasets, enabling data sharing to varying degrees. However, the mountain of frameworks needed to support data sharing between communities inhibits the development of tools for data management, reuse and integration. Here we describe a way in which a group of data producers and consumers work within an invisible metadata framework that enables the coordinated use of reporting standards by service providers and circumvents many of the problems caused by data diversity. The same framework enables researchers, bioinformaticians and data managers to operate within an open data commons.

A full list of author affiliations appears at the end of the paper.

From reusable data to reproducible research

Shared, annotated research data and methods offer new discovery opportunities and prevent unnecessary repetition of work. Although funding agencies, journals and community initiatives encourage good data stewardship and sharing through the use of community reporting standards, data sharing remains challenging[1–3]. More significant coordination has occurred in the food and drug regulatory arena[4] and in commercial science, where investments in procedures and tools that integrate external sources with internal data now enhance decision-making processes[5].

Funding agency 'encouragement' has normally taken the form of top-down data sharing policies. Increasingly, however, funding agencies are also requiring specific data management, preservation and sharing plans in grant applications and are monitoring adherence[6]. Such an approach requires researchers to follow or develop best practices collaboratively. These practices are also emerging organically through the provision of independent databases, tools and curators, driven by advocates of the sharing of both pre- and post-publication data[7,8]. To build an interoperable open data ecosystem will require leveraging all of these positive efforts and further increasing community buy-in.

Time to leap outside the box

Overall, most stakeholder groups accept the principles of data sharing, but in practice, achieving compliance is challenging, especially when new technologies or combinations of technologies are employed. The current wealth of domain-specific reporting standards provides proof of stakeholders' engagement with standardization and sharing, but the use of combinations of technologies presents challenges[9,10]. Descriptions of investigations of biological systems in which source material has been subject to several kinds of analyses (for example, genomic sequencing, protein-protein interaction assays and the measurement of metabolite concentrations) are particularly challenging to share as coherent units of research because of the diversity of reporting standards with which the parts must be formally represented. Equally, most repositories are designed for specific assay types, necessitating the fragmentation of complex datasets[11–15].

One way forward is to establish reciprocal data exchange between major repositories, but budgetary constraints limit such activities[15,16], and a crop of differing methodologies still imposes barriers[11,12].

Researchers acting as data consumers also face challenges when the component parts of an investigation are scattered across databases. Fragmented datasets can only be reassembled by those equipped to navigate the various reporting guidelines, terminologies and formats involved[17]. Cross-cutting, topic-specific reference datasets have been assembled, but predominantly by large initiatives (such as Sage Commons) and programs (such as ENCODE or the US National Institutes of Health–National Institute of Allergy and Infectious Diseases' Bioinformatics Resource Centers (BRCs)). These limitations fuel the indifference researchers feel about investing significant effort to share their data[18].

As the main facilitators of data sharing, major public repositories are evolving to support the structure and detail increasingly present in complex, multipart datasets (such as the US National Center for Biotechnology Information's BioSample system). By importing data from external files under their own schemata, databases provide badly needed integration. The speed of this evolution is dependent on access to highly skilled biocurators able to generate and validate complex annotations, increasing the pressure on data producers to quality check data before submission[19].

ISA commons: a part of the data-commoning revolution

New solutions are required that deliver economies of scale in data capture and inherently support data integration, rendering the process of data capture and annotation scalable in the face of the current 'data bonanza'. Here we refer to efforts toward such positive solutions as 'data commoning'. **Box 1** presents an exemplar ecosystem of data curation and sharing solutions from groups working together to create a cross-domain data sharing vision of the future. These collaborative groups are, in essence, on the path to building a data commons, serving an increasingly diverse set of domains including environmental health, environmental genomics, metabolomics, (meta)genomics, proteomics, stem cell discovery, systems biology, transcriptomics and toxicogenomics, but also communities working to characterize nucleic acid structures and to build a library of cellular signatures. This emerging commons depends on its participants' use of the metadata categories 'Investigation' (the project context), 'Study' (a unit of research) and 'Assay' (analytical measurement). This so-called ISA framework is the backbone upon which the discovery, exchange and informed integration of data sets articulate with one another.

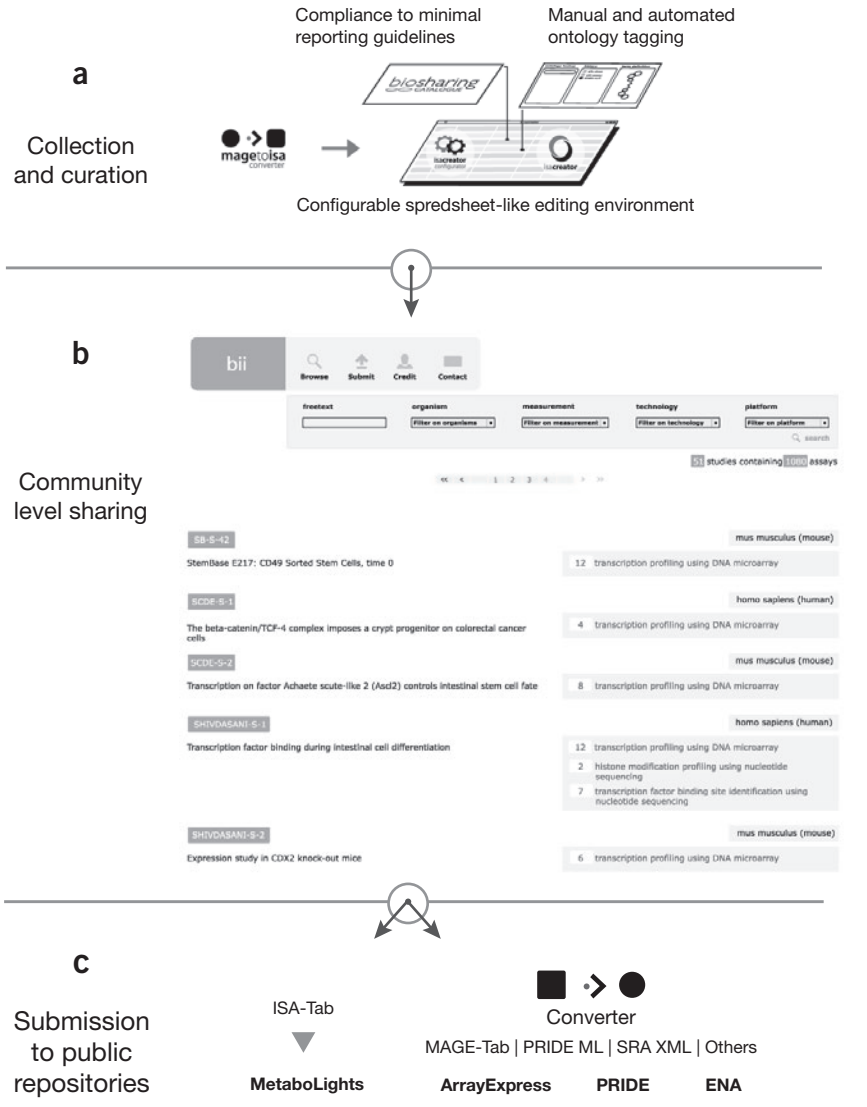

Figure 1 The ISA framework in action in the stem cell–based system of the Harvard Stem Cell Institute (HSCI). The data management workflow of the HSCI's Stem Cell Discovery Engine (SCDE) system, powered by the ISA framework. (**a**) Curators use the ISAconfigurator and ISAcreator software modules to consistently curate a variety of internally generated stem cell-based genomics profiles according to community-developed minimum information guidelines and terminologies; published transcriptomics-based studies are also collected via the MAGEtoISA module, then curated and enriched for consistency. (**b**) Consistently represented investigations are loaded in the BioInvestigation Index (BII) component that stores and serves the (public and private) data sets to the HSCI and wider community. (**c**) Upon publication, investigations are directly submitted to those public repositories using ISA-Tab format, or converted to/from other supported formats via the ISAconverter.

At the heart of the ISA framework is the extensible, hierarchical 'ISA-Tab' file format[20] that can be used alone or as a template for a variety of spreadsheet-based formats for data sharing[21]. ISA-Tab was developed by mapping a number of public repositories' submission formats onto one structure for representing experimental metadata, leveraging common elements while keeping data files external in their native or community-specific formats. ISA-Tab offers the chance for both project-specific and public repositories to adopt a common file format for representing experimental metadata, increasing the flow of richly described investigations into the public domain.

The modular ISA software suite, which implements the ISA-Tab format, acts to

BOX 1 EXAMPLES OF THE GROWING ECOSYSTEM OF ISA COMMONS PARTICIPANTS

To better understand the utility of the ISA framework, we present here a series of brief case studies in which one or more of its elements have been embedded in open-source systems that facilitate standards-compliant collection, curation, management, distribution and reuse of data within a community. Other emerging systems include MeRy-B and the Biomedical Information Research Network (BIRN) BioScholar Knowledge Management system, the Harvard Medical School Library of Integrated Network–based Cellular Signatures (LINCS) effort and ArrayTrack at the Center for Bioinformatics of the US Food and Drug Administration (FDA), along with internal systems at the Leibniz Institute of Plant Biochemistry, the Microbial Inventory Research Across Diverse Aquatic Long Term Ecological Research Sites (MIRADA LTERs), the International Census of Marine Microbes (ICoMM), the Environmental Microbiology activities at the Argonne National Laboratory, the Bioplatforms Australia consortium and the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia. Furthermore, ISA-Tab is used to facilitate the sharing of chemical and enzymatic structure-probing data in the Single Nucleotide Resolution Nucleic Acid Structure Mapping (SNRNASM) annotation guidelines. An instance of selected ISA software components is also being integrated as part of an extended workflow for a microarray gene expression resource at The Novartis Institutes for BioMedical Research (NIBR) to facilitate research aimed at drug discovery and development.

GigaScience. Now the world's largest sequencing center, BGI (formerly known as the Beijing Genomics Institute) is centrally involved in many large international sequencing projects. To speed the review, publication and sharing of large-scale data sets, BGI has launched GigaScience, a combined database and journal using BGI's cloud computing and server infrastructure. GigaScience will use the ISA Infrastructure to capture many kinds of study and assay metadata along with relationships between data set components. Through implementation of DataCite's Digital Object Identifiers (DOIs), data sets will be fully trackable and citable, supporting the awarding of credit to data producers.

HSCI Blood Genomics Repository. The Harvard Stem Cell Institute (HSCI) Blood Genomics Repository holds hematopoietic (blood) stem cell data from HSCI Blood program researchers studying the molecular and cellular characteristics and pathways involved in hematopoietic stem cell self-renewal. The repository comprises heavily curated data from gene expression, epigenetic modification and transcription factor–binding studies using various technologies and platforms, and it is made available in the form of ISA-compatible files.

HSCI Stem Cell Discovery Engine. The Stem Cell Discovery Engine (SCDE) is a manually curated public resource with a focus on cancer, powered by the ISA software suite and hosted by the HSCI. SCDE handles the submission, integration, visualization and dissemination of high-throughput studies and provides linked molecular analysis through Galaxy to experimental metadata. Data sets selected for inclusion are annotated using public resources and then expertly curated to ensure accuracy, consistency, compliance with relevant reporting requirements and appropriate use of terminologies.

MetaboLights. The MetaboLights resource will include the first public cross-species, cross-application database at the European Bioinformatics Institute (EBI) accepting metabolite structures and other data from metabolomic experiments. A curated reference layer with spectroscopic, chemical and biological information about metabolites will be developed to enhance submitted data. The project uses the ISA infrastructure and will publish customized templates for capturing study information, and assays using nuclear magnetic resonance and mass spectrometry, using common terminologies.

NERC EnvBase. The UK Natural Environmental Research Council's (NERC) Environmental Bioinformatics Centre (NEBC) collects and catalogs data sets from environmental and functional genomics investigations by the NERC research community and their international collaborators. Using the ISA infrastructure, the NEBC's data catalog, EnvBase, has recently been expanded to hold and serve investigations curated to meet community-developed standards requirements—in particular, standards developed and maintained by Genomic Standards Consortium (GSC) relevant to metagenomic investigations. The collection of experimental metadata at source is facilitated by the deployment of the editor component on a Bio-Linux platform.

NIEHS Center for Environmental Health. The National Institute of Environmental Health Sciences' Center for Environmental Health at Harvard works to preserve a diverse array of data from environmental research, population-, patient- and laboratory-based studies, and published data sets imported from other databases. The ISA infrastructure serves as the base for this institutional repository and will also serve as a 'resource locator', allowing new investigators to quickly identify collaborators and available preliminary data from historical studies, reducing redundancy.

Nutritional Phenotype Database. The Nutritional Phenotype Database (dbNP) facilitates the sharing of large-scale laboratory clinical intervention and observation studies relating to food intake between Dutch research groups and with international consortia. Their harmonization of study description, following the ISA approach, allows cross-experiment comparisons and facilitates the querying of data at the biological outcome level (for example, by pathway).

SEEK. The SEEK is a web-based registry and repository for systems biology data, models and experiments. Originally developed for SysMO, a pan-European consortium studying dynamic molecular processes in microorganisms, it has since been adopted to handle data sets from other large systems biology projects. The SEEK 'experimental contexts' follow the ISA approach for conversion to other formats.

SIDR. The Standards-based Infrastructure with Distributed Resources (SIDR) works to collect, preserve and disseminate genomics and functional genomics data sets from a variety of French National Centre for Scientific Research's groups. The various experiment types are structured following the ISA approach, identified with DOIs, and also provided in several formats. Part of a broader approach, SIDR aims to address complex issues in systems biology and is being customized for the translational medicine domain.

(i) regularize local collection and management of experimental metadata, (ii) reduce the adoption barrier for using community minimum reporting guidelines and terminologies through customizable configuration, (iii) facilitate consistent curation at source and (iv) support direct submission to a growing number of public repositories, both in ISA-Tab format (such as MetaboLights and the other systems shown in **Box 1**) and through conversion to other supported formats[12–14]. An example of the ISA framework in action is illustrated by the Harvard Stem Cell Institute (HCSI)'s Stem Cell Discovery Engine (SCDE)[22] and shown in **Figure 1**.

Without community-level harmonization and interoperability, many community projects risk becoming data silos, aggravating the problem. Using the shared, metadata-focused ISA framework, it is now possible to aggregate investigations in community 'staging posts', merge them in various combinations, perform meta-analyses and more straightforwardly submit to public repositories. Furthermore, simplifying the integration of bioscience data can only speed systems biology research[23] and improve the ability of the R&D community to utilize shared data[24].

The growing number of communities using the ISA framework adds credibility to this metadata-focused data sharing vision. Taking this a step further, **Figure 2** shows how these communities' systems—a mix of public and internal tools that use ISA software components or, minimally, the ISA-Tab format—will progressively interrelate to build the 'ISA commons'. Activities are already underway under the auspices of the World Wide Web Consortium (W3C) Semantic Web for Health Care and Life Sciences Interest Group (HCLSIG)'s Scientific Discourse task force to generate serialized ISA-Tab metadata in compliance with the recommendations of the international Linked Data community[25]. Semantic integration of bioscience data with the wider corpus of human knowledge then becomes more straightforward.

BioSharing: standard cooperating procedures

It is widely acknowledged that unlocking shared data promises to accelerate discovery, but this process requires new models for the way we collaborate[1–3,5,6,17,18,26]. But reporting standards often have different levels of maturity, and inevitably, duplication of effort. Communication between standards initiatives is pivotal to ensure that a common or at least complementary set of standards exists and is widely used by the academic and commercial sectors to maximize the utility of shared data. Building on the effort of the Minimum Information for Biological and Biomedical Investigations (MIBBI) portal[10], the BioSharing initiative works to strengthen collaborations between researchers, funders, industry and journals and to discourage redundant (if unintentional) competition between standards-generating groups[27]. The BioSharing catalog maps the landscape of standards and the systems implementing them, and it also works to build graphs of complementarities in scope and functionality. In time and after consultation, a set of criteria for assessing the usability and popularity of standards will be implemented to maximize their adoption and use to assist the

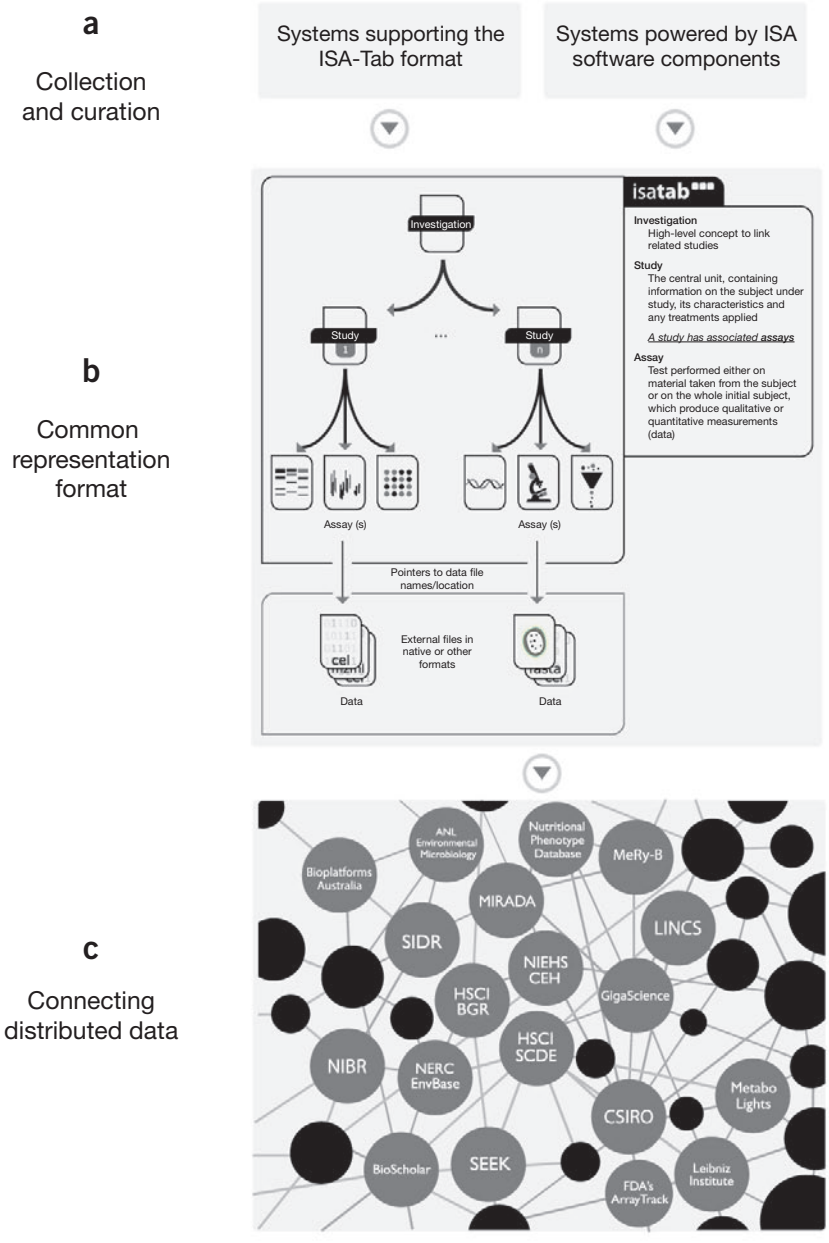

Figure 2 Building the 'ISA commons', a growing ecosystem of resources that work to provide a data commons. (**a**) Data sets of interest to each community are collected and curated. (**b**) Capture systems, either powered by the ISA software suite or supporting the hierarchical ISA-Tab structure, deliver a common representation of experimental content that transcends individual domains. (**c**) To achieve broader data integration, the next step is to explore the growing Linked Data universe. The European Innovative Medicines Initiative (IMI) Open PHACTS project, for example, will use semantic web approaches to make existing knowledge available for linking, querying and where possible, reasoning. This project will benefit greatly from study descriptions that draw on the ISA model to connect quantified information held in semantic triple stores to data from actual experiments performed. As a result, the project will connect public and private datasets to genomics resources, enabling the combination of existing and new experimental data.

virtuous data cycle—from generation to standardization through publication to subsequent sharing and reuse.

The research community requires solutions that accommodate the current 'wealth' of standards and resources, but hides it from users, thereby simplifying their efforts to meet (or ideally, exceed) applicable reporting requirements. Although ongoing activities hold promise, they are a drop in the ocean compared to the daunting challenges ahead: for example, the integration of clinical and biological data in translational medicine[28] and the establishment of mechanisms to support credit for data sharing, which would benefit data producers for making their data accessible (for example, refs. 29,30).

Nonetheless, the vision of data sharing through a 'commons' is entirely technologically possible; communities simply need agree on the largely organizational changes required. The continued collaborative development and uptake of standard frameworks, and the emergence of compliant tools and interoperable data sets such as we have described, illustrates the potential of the horizontal, synergistic approach that is data commoning. Such horizontal integration transcends individual life science domains and assay- or technology-focused communities.

A growing movement

The ISA commons is a growing exemplar ecosystem of data curation and sharing solutions built on a common metadata tracking framework, providing tools and resources to create and manage large, heterogeneous data sets in a coherent manner, and allowing users of (parts of) data sets to 'connect the metadata dots'. We are open to coordinating efforts with other data commons working on similar and related aspects of the same problem, who we invite to adopt and contribute to the further evolution of the ISA framework—the results of years of effort to agree to a basic *lingua franca* for the standards community.

We urge new communities interested in breaching the boundary of their own biodomain to join the growing ISA network and the BioSharing initiative, thereby contributing to the realization of this data-sharing vision: to empower ever more scientists to take data management and sharing into their own hands, using community standards while remaining blissfully unaware of the underlying complexities of the implementation of those standards.

Note: The views presented in this article do not necessarily reflect those of the US Food and Drug Administration.

URLs. BGI, http://en.genomics.cn/; BioLinux, http://nebc.nerc.ac.uk/tools/bio-linux; Bioplatforms Australia, http://bioplatforms.com.au/; CSIRO, http://www.bioinformatics.csiro.au; **BioSharing**, http://biosharing.org/; BIRN BioScholar Knowledge Management system, http://bmkeg.isi.edu/; DataCite's DOIs, http://www.datacite.org/; dbNP, http://www.dbnp.org/; ENCODE, http://encodeproject.org/ENCODE/dataStandards.html; Galaxy, http://galaxy.psu.edu/; GSC, http://gensc.org/; GigaScience, www.gigasciencejournal.com/; HSCI's SCDE, http://discovery.hsci.harvard.edu/; HSCI's Blood Genomics Repository, http://bloodprogram.hsci.harvard.edu/; ICoMM, http://icomm.mbl.edu/; IMI Open PHACTS, http://www.openphacts.org/; **ISA Commons**, http://www.isacommons.org/; **ISA software suite and ISA-Tab**, http://www.isa-tools.org/; Leibniz Institute of Plant Biochemistry, http://www.ipb-halle.de/en/research/stress-and-developmental-biology/research/bioinformatics-mass-spectrometry/research-projects; LINCS, http://lincs.hms.harvard.edu/; Linked Data, http://linkeddata.org/; MeRy-B, http://www.cbib.u-bordeaux2.fr/MERYB/index.php; http://listserver.ebi.ac.uk/mailman/listinfo/metabolights/; MIRADA LTERs, http://amarallab.mbl.edu/mirada/mirada.html/; NIEHS' Center for Environmental Health, http://www.hsph.harvard.edu/research/niehs; NCBI's BioSample, http://www.ncbi.nlm.nih.gov/biosample; NERC EnvBase, http://bii.nwl.ac.uk/; NIBR, http://www.nibr.com/; NIH-NIAID's BRCs (Bioinformatics Resource Centers), http://www.niaid.nih.gov/labsandresources/resources/brc; Sage Commons, http://sagebase.org/commons/; SEEK, http://www.sysmo-db.org/; SIDR, http://sidr-dr.inist.fr/; SNRNASM, http://snrnasm.bio.unc.edu/; SysMO, http://www.sysmo.net/; http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/NCTRCentersofExcellence/ucm078990.htm/; W3C HCLSIG Scientific Discourse task force, http://www.w3.org/wiki/HCLSIG/SWANSIOC.

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AUTHOR CONTRIBUTIONS

S.-A.S. and P.R.-S. designed and led the development of the ISA framework and the BioSharing catalogue. D.F. and S.-A.S. are the cofunders of the BioSharing initiative. E.M. is the lead engineer of the ISA framework and, with P.R.-S., of the BioSharing site. C.T. coordinates the MIBBI portal. W.H. conceived SCDE and the role of an ISA approach to integration and within its stem cell systems, W.H., O.H., B.C., S.J.H.S. and K.B. contributed to the development of the ISA framework and worked on the SCDE. W.T. and H.F. contributed to the development of the ISA framework and strategies to integrate it with the FDA's ArrayTrack tool. S.N. contributed to the development of the ISA framework and developed workflows to integrate it with lab equipment. L.A.-Z. worked toward the implementation of ISA for the MIRADA-LTERS and ICoMM data sets. T.B. developed the NERC Environmental Bioinformatics Center (NEBC) EnvBase catalogue. G.B. worked toward the implementation of ISA for the BIRN BioScholar Knowledge Management system. T.C. leads the W3C working subgroup on Scientific Discourse; S.D. led the development of the Harvard Stem Cell Institute (HSCI) Blood Genomics repository, and M.E. worked on the integration of ISA-Tab into the system. L.-A.C. assisted the ISA developers to make use of the DataCite Metadata Store to mint Digital Object Identifiers (DOIs). J.C. and C.E.S. worked toward the implementation of ISA for use with HMS LINCS data. A.d.D. and D.J. worked toward the implementation of ISA for the MeRy-B knowledgebase. S.E. and S.L. worked on the integration of the ISA framework into the *GigaScience* and BGI database infrastructure. C.T.E. worked toward the implementation of ISA in the dbNP database and provided links to the Open PHACTS project. J.G. worked toward the implementation of ISA at the Argonne National Laboratory. C.G. and K.W. worked on the implementation of ISA-Tab in the SEEK platform. J.K. led the CarcinoGENOMICS project under which the ISA framework was first funded and developed. K.H., P.d.M. and C.S. developed the MetaboLights, powered by the ISA framework. A.L. led the implementation of the ISA-Tab in the SNRNASM annotation guidelines. S.M. and D.R. worked toward the integration of selected ISA software components as part of an extended workflow at NIBR. M.R. headed the development of the SIDR repository and the implementation of the ISA-Tab format. A.M. worked toward the implementation of ISA at CSIRO. C.A.S. worked toward the implementation of ISA at Bioplatforms Australia.
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Neurobiologiste et neurologue

La France peut-elle manquer le train de la bioéconomie ?

Les sciences du vivant sont en train de bouleverser nos modes de vie plus encore que les technologies de l'information et de la communication, et en alliance étroite avec elles. Depuis la définition que nous avons de l'individu jusqu'aux principes même de nos équilibres économiques, ce mouvement de fond est si puissant qu'il en devient à la fois naturel et invisible.

Regardez si vous les avez encore ces numéros des magazines de fin d'année qui reviennent sur les grands moments de 2011. Vous y trouverez des révolutions politiques, des catastrophes naturelles, des crises financières, mais rien sur le séquençage d'ADN à très haut débit ou l'imagerie cérébrale de nos modes de pensée, les avancées scientifiques n'étant considérées que lorsqu'elles revêtent un caractère de mystère quasi métaphysique comme la quête du boson de Higgs. Et pourtant, que de découvertes fascinantes, étonnantes, porteuses d'espoir, dans le champ des sciences de la vie. Et ces avancées donnent naissance à un monde nouveau.

Nous ne sommes encore qu'au début des retombées économiques et sociales des connaissances acquises en sciences de la vie. Par exemple depuis la seconde guerre mondiale la connaissance des hormones sexuelles et de leurs mécanismes de contrôle chez la femme a donné lieu à une première révolution avec la dissociation entre sexualité et procréation. Beaucoup a déjà été écrit sur les conséquences sociologiques de cette révolution. Peu, sauf sous l'angle démographique, a été analysé en termes économiques. Puis le développement de ces connaissances a permis l'émergence des techniques de fécondation in vitro, dissociant fertilité et procréation. L'impact de cette seconde révolution a été beaucoup analysé sur notre conception de l'être humain et a été l'un des thèmes majeurs du champ de la bioéthique. Ce domaine s'étend rapidement,

après la procréation médicalement assistée, donc l'origine d'une vie humaine, il touche les questions de la fin de vie, et bientôt celles de l'intimité individuelle par les avancées des neurosciences. Mais ici encore les implications économiques de ces connaissances sont peu commentées malgré le bouleversement qu'elles vont entraîner avec l'émergence d'un domaine majeur : la bioéconomie.

Les connaissances du vivant vont en effet changer notre conception de la santé, humaine ou animale, et notre environnement. Et de façon inédite et intéressante ce double mouvement va se faire d'une façon intégrée, c'est-à-dire à partir des mêmes connaissances et des mêmes technologies : les biotechnologies. Ce qui va être nouveau également sera la rapidité du passage de la recherche académique à des applications à grande échelle, avec intégration d'autres domaines de la science et de la technologie comme les nanotechnologies et les technologies de l'information et de la communication, c'est la révolution de la convergence. Prenons un exemple avec la biologie de système, champ scientifique nouveau qui essaie d'associer en un ensemble cohérent les multiples résultats obtenus dans différents laboratoires sur telle ou telle molécule particulière. Cette approche scientifique essaie de comprendre de façon intégrée comment fonctionne le réseau d'un ensemble de molécules, par exemple au sein d'une cellule. Les modèles qui sont produits prédisent un certain fonctionnement de la cellule dans une condition particulière. Ce qui peut être testé au laboratoire. Son développement le plus spectaculaire est la biologie de synthèse qui permet par l'assemblage de briques du vivant de simuler les modèles obtenus et de tenter de les corriger. Les applications potentielles sont immenses, par exemple en santé humaine dans le domaine du cancer ou celui des maladies génétiques. Mais ces mêmes connaissances et ces mêmes programmes vont également servir à transformer des cellules vivantes en micro-usines à produire des sucres ou des alcools qui seront les biocarburants du futur. Ces mêmes connaissances peuvent aussi transformer des bactéries en pompes à métaux lourds pour dépolluer les sols industriels ou encore transformer des algues en puits à carbone pour essayer de capter du CO2. L'étendue des domaines économiques potentiellement concernés à conduit à définir le concept de bioéconomie, par exemple dans le rapport *Bioeconomy to 2030* de l'Organisation pour la Coopération et le Développement Economique (OCDE, 2009).

Plus du quart de la richesse d'un pays sera consacré bientôt à la bioéconomie. Inutile pour cela d'être grand prophète sachant que le seul domaine de la santé humaine représente aujourd'hui 12% du PIB américain et que la seule industrie du médicament a engendré pour 2011 un chiffre d'affaire mondial de 880 milliards de dollars avec en tête des ventes des besoins qui ne sont malheureusement pas près de baisser comme le cancer et les maladies mentales. Un marché du médicament en forte reprise (+5%) malgré la crise et sans couvrir aujourd'hui les immenses besoins des pays du Sud (maladies infectieuses) ou offrir de traitement pour les maladies neurodégénératives associées à l'allongement de la vie (Alzheimer).

Si nous analysons pour commencer ce domaine qui concerne chacun d'entre-nous très particulièrement, la santé, on observe que le médicament n'est que la

partie émergée de l'iceberg du coût d'une pathologie. Prenons par exemple les maladies qui affectent le cerveau, qu'elles soient neurologiques comme la sclérose en plaques, première cause de handicap chez les jeunes, ou psychiatriques, comme la schizophrénie ou les dépressions graves. Nous allons trouver ici des maladies banales et fréquentes comme la migraine, ou graves comme les accidents cérébrovascuaires, seconde cause de mortalité après les arrêts cardiaques. Une récente étude européenne (Gustavsson A, et al., Eur Neuropsychopharmacol. 2011 Oct;21(10):718-79) évalue le coût des maladies du cerveau pour les 514 millions d'habitants de l'Union Européenne à 798 milliards d'euros en 2010. Ce coût suit une croissance rapide puisqu'il a doublé depuis l'évaluation de 2004. Il est composé pour 37% de dépenses médicales directes, pour 23% de dépenses non médicales liées au handicap ou à la maladie et enfin pour 40% des pertes d'activité du patient ou de son entourage. Le médicament ou le procédé de soin n'est donc que l'une des parties de la bioéconomie. Avec de meilleures connaissances des conditions de développement de la maladie, la prévention et le dépistage, dans le jargon biologique on parle de recherche ou de surveillance de biomarqueurs, vont devenir des champs économiques important, touchant peu ou prou toute la population. Inversement, les modes de prise en charge de la maladie vont changer nos modes de vie, avec des technologies comme la télémédecine, la présence de capteurs de paramètres biologiques intégrés à nos vêtements, des maisons de plus en plus "intelligentes" et adaptées à leurs occupants malades ou potentiellement malades....

Face à de tels enjeux, crise économique ou pas, des pays comme les USA se sont résolument engagés dans l'aventure de la bioéconomie, l'année 2011 se terminant favorablement pour les Instituts Nationaux de la Santé (NIH) qui se voient accorder un budget de 30,7 milliards de dollars pour 2012. Un des points clé de l'analyse de ce budget en progression dans un contexte de limitation drastique des dépenses publiques est le développement d'une démarche de transfert rapide des connaissances fondamentales vers leurs application : de la paillasse du laboratoire académique au développement biotechnologique et industriel. Pour les USA, la nouvelle frontière c'est le vivant. Quelques pays européens comme la Grande-Bretagne ont décidé de ne pas manquer ce rendez-vous. Le Sud-est asiatique et la Chine se sont déjà placés. Dans tous ces pays la biologie est réellement une priorité de recherche et représente environ la moitié des investissements. Ce n'est pas aujourd'hui le cas en France, loin s'en faut. Priorité de nos gouvernants au tournant du millénaire, la biologie ne représente aujourd'hui pas plus du quart de la recherche publique, avec dans la période récente quelques rares effets d'annonce et peu de concrétisation. Mais la biologie n'est pas la seule mal lotie dans notre pays. Dommage car la célèbre phrase de Sully devrait être aujourd'hui "biologie et biotechnologie seront les mamelles de la France." De fait nous disposons d'une agriculture parmi les plus solides et d'une infrastructure de soins permettant le transfert rapide de la recherche vers la clinique humaine. Mais les signes avant-coureurs des grands périls sont là. Nous disposons de jeunes bien formés au niveau secondaire, mais qui s'engagent de moins en moins dans les filières scientifiques. Notre industrie pharmaceutique s'étiole et le premier secteur qu'elle abandonne est sa recherche. Notre secteur des biotechnologies peine à

se développer. Pourquoi la santé est-elle toujours vue ici comme une charge de dépenses et non comme une source potentielle de richesse ? Pourquoi le développement d'une agriculture moderne est-il perçu comme un viol des traditions et non comme un élan vers l'avenir ?

La bioéconomie sera confrontée à de nombreux challenges, son acceptabilité n'étant pas le moindre péril. Sans aborder ici la question des cellules souches embryonnaires humaines qui restent aujourd'hui du domaine de la recherche scientifique, l'exemple évident de la difficulté est apparu avec les organismes génétiquement modifiés (OGM) utilisés en agriculture. Dans certains pays, Amérique du Nord ou du Sud, mais également Espagne, l'utilisation de graines génétiquement modifiées n'a pas suscité de réaction. Au contraire le rejet a été violent en France. La recherche fondamentale en biologie n'est pas ici réellement en cause, même si malheureusement des installations de l'Institut National de la Recherche Agronomique (INRA) ont été détruites par quelques ignorants, la recherche étant le seul moyen de savoir un jour si ces OGM présentent ou non un risque pour notre santé ou pour notre environnement. C'est le modèle économique sous-jacent aux OGM qui a été attaqué. La bioéconomie est donc également un enjeu démocratique majeur. D'où l'urgence de comprendre, connaître et débattre pour assumer notre développement futur et ne pas se contenter de voir cette nouvelle révolution industrielle et sociétale se dérouler sans nous.

Glossaire

GLOSSAIRE[1]

Acides aminés

Les acides aminés sont des molécules qui entrent dans la composition des protéines grâce à des liaisons que l'on appelle peptidiques. On compte 20 acides aminés naturels.

Acides nucléiques

Ce sont des macromolécules, c'est-à-dire de grosses molécules relativement complexes, formées d'une longue chaîne de monomères – les nucléotides. La première fonction des acides nucléiques est le stockage et la transmission de l'information génétique. On trouve deux types d'acides nucléiques dans les organismes vivants : l'acide désoxyribonucléique (ADN) et l'acide ribonucléique (ARN).

ADN

Signifie acide désoxyribonucléique. Il représente le matériel génétique de tous les organismes cellulaires. Dans les cellules, l'information emmagasinée dans l'ADN contrôle les activités cellulaires grâce à sa transcription en ARN.

Il existe dans l'ADN quatre bases azotées différentes – c'est-à-dire des petites molécules chimiques cycliques de nature relativement simple. Ces bases sont appelées : adénine, thymine, guanine et cytosine. Ces bases, associées au sucre désoxyribose, sont enchaînées au long du polymère linéaire d'ADN, leur ordre (séquence) étant porteur de l'information génétique. Deux de ces brins, enroulés l'un autour de l'autre en directions opposées, constitue ce qu'on appelle la double hélice d'ADN.

ADN polymérase

Enzyme capable de répliquer l'ADN.

ADN recombinant

Molécules combinant des séquences d'ADN dérivées de plusieurs sources.

ARN

Signifie acide ribonucléique. L'ARN est un polymère. L'ARN diffère de l'ADN par l'usage du sucre ribose plutôt que désoxyribose. Il est constitué de trois bases azotées identiques à celles de l' ADN : adénine, guanine, cytosine. Seule la thymine est remplacée par l'uracile. Ces bases, associées au sucre ribose, sont enchaînées au long du polymère linéaire d'ARN. Leur ordre est déterminé par la séquence d'ADN qui lui sert de modèle au cours du processus dit de transcription.

[1] *Sources principales : Gérald Karp, « Biologie cellulaire et moléculaire », 2010 et Michel Morange, « Histoire de la biologie moléculaire », 2003*

ARN messager (ARNm)	La découverte de l'ARNm en 1961 est due à François Jacob et Jacques Monod. Un ARN messager est un ARN qui lui-même code une protéine. Une molécule d'ADN peut servir de modèle pour la synthèse de nombreuses molécules d'ARN qui serviront chacune de modèle pour produire un grand nombre de chaînes polypeptidiques ou protéines.
ARN de transfert (ARNt)	Les ARNt constituent une classe d'ARN nécessaire à la synthèse des protéines, processus dit de "traduction". Ce sont les adaptateurs entre l'information codée dans les nucléotides de l'ARN messager et l'alphabet formé d'acides aminés d'un polypeptide.
ATP (adénosine triphosphate)	Molécule servant de source d'énergie à de nombreux processus cellulaires et qui est l'un des précurseurs de l'ARN.
Bactériophage	Virus capable d'infecter les bactéries.
Bases azotées	Molécules faisant partie des nucléotides, qui sont eux-mêmes des éléments de l'ADN et de l'ARN. Les bases azotées présentes dans l'ADN sont : l'adénine, la cytosine, la guanine et la thymine. Dans l'ARN, l'uracile remplace la thymine.
Bioconversion	Transformation de la matière organique (comme les déchets) en autres matières organiques ou en sources d'énergie (par exemple le méthane) à l'aide d'un procédé, comme la fermentation, faisant appel à des organismes vivants. On compte parmi les bioconversions : la combustion, la distillation alcoolique, la fermentation méthanogène, les plantes à hydrocarbures, la chimiurgie (ensemble des opérations chimiques qui transforment la biomasse en énergie directement utilisable).
Biofilm	Population de micro-organismes intimement associés à des surfaces vivantes ou minérales par l'intermédiaire d'une substance muqueuse composée de polymères biologiques (sucres, protéines, ADN, acides humiques). Ils sont présents partout : sur le tronc des arbres ou les galets du fond d'une rivière, mais aussi de la coque des bateaux, à l'intérieur des tuyauteries de distribution d'eau ou des radiateurs de chauffage central et même dans notre bouche et sur nos gencives où ils forment la plaque dentaire.

Biomasse	Ensemble des organismes vivants sur les continents et dans les océans, qu'ils soient des micro-organismes des plantes ou des animaux. Cependant son exploitation énergétique concerne principalement les plantes et les arbres. Les programmes de recherche et de développement visent ainsi à transformer la biomasse lignocellulosique (résidus agricoles et forestiers, cultures dédiées comme les taillis à courte rotation) en biocarburants dits de seconde génération et/ou en bio énergie (chaleur, électricité).
Biopuce	Dispositif miniature permettant d'analyser, en quelques heures, des milliers de séquences ADN ou ARN. Grâce à la biopuce, il est possible de repérer des mutations et de savoir quels gènes répondent à l'action d'une molécule ou sont impliqués dans une maladie.
Bio-remédiation ou **bio dépollution**	Utilisation d'organismes vivants et plus particulièrement de micro-organismes (champignons, bactéries) pour éliminer les polluants toxiques des différents milieux naturels.
Biosécurité ou **sécurité biologique**	D'après une définition de l'Organisation mondiale de la santé, la biosécurité désigne l'ensemble des mesures et de pratiques visant à protéger les personnes et l'environnement des conséquences liées à l'infection, à l'intoxication ou à la dissémination de micro-organismes ou de toxines.
Bio-sûreté ou **sûreté biologique**	D'après une définition de l'Organisation mondiale de la santé, la bio-sûreté désigne l'ensemble des mesures et des pratiques visant à prévenir les risques de pertes, de vol, de détournement ou de mésusage de tout ou partie de micro-organismes ou de toxines dans le but de provoquer une maladie ou le décès d'êtres humains.
Blooms (en français efflorescence algale)	Sont une augmentation relativement rapide de la concentration d'une (ou de quelques) espèce (s) du phytoplancton dans un système aquatique. Cette concentration accrue se traduit généralement par une coloration de l'eau (rouge, brun- jaune ou vert). Ce phénomène peut concerner les eaux douces ou marines et provoquer la suffocation des poissons. Il peut aussi représenter un danger pour l'homme, lorsque les blooms produisent des toxines.

Briques du vivant	D’après le Registry of standard biological parts (Répertoire des composants biologiques standard), les briques du vivant sont une norme désignant les composants interchangeables destinés à construire des systèmes biologiques dans les cellules vivantes. Ces composants sont généralement des segments d'ADN.
Cellules eucaryotes	Cellules contenant un noyau protégeant le matériel héréditaire. Elles constituent les plantes, animaux, levures et champignons.
Cellules procaryotes	Cellules dépourvues de noyau. Ce sont les bactéries, la bactérie *Escherichia coli* étant le procaryote le plus étudié.
Cellules souches embryonnaires (SE)	Cellules isolées à partir de très jeunes embryons des mammifères. À la différence des cellules souches adultes, les cellules SE peuvent être cultivées indéfiniment.
Cellules souches pluripotentes	Cellules SE capables de se différencier dans n’importe quel type de cellule de l’organisme. Dans la plupart des cas, on a isolé les cellules SE à partir d’embryons provenant des cliniques de fertilité.
Chimiotactisme	Désigne l’attraction ou la répulsion d’un organisme unicellulaire par une substance chimique. Par exemple, les bactéries mobiles peuvent réagir à des stimuli, être attirées par des substances nutritives, comme le sucre, les acides aminés, l’oxygène, ou être repoussées par des substances nuisibles.
Chromosome	Structure cellulaire microscopique représentant le support physique des gènes et de l’information génétique. Toujours constitués d’ADN et souvent de protéines, les chromosomes existent dans les cellules de tous les êtres vivants, en nombre variable, spécifique à chaque espèce.
Châssis	Hôte cellulaire organisé pour accueillir un objet biologique de synthèse, comme par exemple, l’ADN synthétisé. Aujourd’hui, on utilise plusieurs châssis naturels d’organismes vivants, dont l’ADN d’origine a été extrait : la bactérie *Escherichia coli*, hôte de nos intestins, la levure, responsable de la fabrication de la bière et du pain, ou le bacille inoffensif *Bacillus subtilis*, qui se trouve en abondance dans le sol.
Circuits génétiques	Ensemble de bio-molécules interagissant entre elles pour réguler l'expression des gènes.

Confinement	Le confinement sert à isoler physiquement les organismes issus de la biologie de synthèse par rapport à l'environnement. Il existe néanmoins deux autres méthodes : le confinement trophique qui consiste à réaliser des organismes synthétiques qui dépendent d'un nutriment que seul le laboratoire peut leur fournir et le confinement sémantique qui consiste à réaliser des organismes synthétiques dont le codage génétique ou le support de l'information génétique sont différents de ceux des organismes naturels, ce qui empêche ainsi toute interférence. Les confinements trophique et sémantique font actuellement l'objet de beaucoup de recherches.
Cytoplasme	Milieu intérieur de la cellule, hors noyau (pour les eucaryotes).
Enzymes	Elles catalysent – c'est-à-dire accélèrent –les réactions chimiques qui se produisent à l'intérieur des cellules vivantes. Elles peuvent accélérer les réactions par un facteur supérieur à 10 milliards. Il existe chez l'homme plus de 10000 enzymes, chacune étant spécifique d'une réaction chimique particulière.
Enzymes de restriction	Enzyme utilisée par les bactéries pour restreindre le développement potentiel de virus.
Escherichia coli	Modèle bactérien utilisé pour étudier le fonctionnement cellulaire
Exons	Parties traduites des gènes qui codent les protéines.
Expression des gènes	Processus par lequel un gène est décodé en un produit final, ARN ou protéine. Dans ce dernier cas, le processus comprend deux étapes. D'abord, la transcription, qui permet d'obtenir une copie du gène présent sur le chromosome sous forme d'un ARN messager (ARNm). Ensuite, la traduction, qui est l'étape durant laquelle cet ARNm est lu par le ribosome, pour obtenir une protéine.
Gène	Segment d'ADN contenant l'information nécessaire à la fabrication d'une biomolécule active, ARN ou protéine. Il est considéré comme unité d'hérédité.
Gènes putatifs	Encore appelés gènes hypothétiques, les gènes putatifs sont des fragments d'ADN considérés comme étant des gènes, en se fondant sur leur séquence. Mais ni leur produit ni leur fonction ne sont connus.

Génie génétique	Ensemble de techniques permettant d'altérer la séquence des fragments d'ADN que l'on a isolés pour modifier soit la protéine pour laquelle ils codent, soit les signaux qui en régulent l'expression.
Génome	Constitué par un ensemble de gènes, il contient l'information génétique propre à chaque espèce d'organisme.
Génotype	Ensemble de la composition génétique d'un individu.
Hétérotrophe	Organisme utilisant les composés organiques comme source de carbone.
Méganucléases	Molécules capables de couper l'ADN à certains endroits spécifiés.
Métabolisme	Ensemble des réactions chimiques qui se déroulent dans la cellule.
Nanogalénique	Utilisation des nanotechnologies par la pharmacie galénique, qui est l'art et la science de préparer, conserver et présenter les médicaments.
Nanomédecine	Désigne la conception, la synthèse et l'utilisation de matériaux, de dispositifs, de techniques à l'échelle nanométrique, afin d'améliorer la compréhension, le diagnostic ou le traitement de maladies.
Nucléotides	Composés organiques constitutifs de l'ADN (ou de l'ARN), ils sont formés d'un sucre – le désoxyribose (ou le ribose) - et d'une base : l'adénine, la thymine, la guanine et la cytosine, notées : A,T,G,C.
Oscillateur	Dispositif imitant un réseau cellulaire en induisant périodiquement la synthèse d'une protéine fluorescente.
Paires de bases	Désignent l'appariement de deux bases azotées situées sur deux brins complémentaires d'ADN ou d'ARN. Cet appariement est effectué par des ponts d'hydrogène. Dans l'ADN, l'adénine (A) s'apparie avec la thymine (T) grâce à deux ponts d'hydrogène. La guanine (G) s'apparie avec la cytosine(C) par trois ponts d'hydrogène. Dans l'ARN, la thymine est remplacée par l'uracile (U).
Panic érigé (Panicum virgatum-switchgrass)	Plante herbacée, dont la répartition naturelle va de l'Amérique du Nord à l'Amérique Centrale. Compte tenu de son rendement et de son potentiel énergétique, le panic érigé fait partie des graminées qui pourraient intégrer la filière de la biomasse.

Phage	*voir* **Bactériophage**.
Plasmides	Molécules d'ADN circulaires portant des gènes de résistance aux antibiotiques et capables de se répliquer de manière autonome dans la cellule bactérienne et dans la levure *Saccharomyces cerevisiae* (levure de bière, levure de boulanger)
Polynucléotides	Macromolécules constituées par l'enchaînement de plusieurs nucléotides.
Portes logiques	En informatique, les portes logiques sont des instructions qui permettent de faire fonctionner un microprocesseur. Par analogie, en biologie, une porte logique assure des fonctions similaires grâce à des interactions entre bio-molécules.
Protéines	Ce sont des macromolécules, c'est-à-dire des molécules de grande taille, formées de plusieurs milliers d'atomes. Les protéines sont fabriquées à partir de 20 acides aminés différents. Chaque protéine est caractérisée par le nombre d'acides aminés qui la composent, la nature de ces acides d'aminés, mais surtout l'ordre dans lequel ils sont enchaînés, ce que l'on appelle la séquence des protéines.
Ribosome	Particules infracellulaires sur lesquelles s'effectue la synthèse des protéines.
Transfection	Introduction d'un ADN étranger dans une cellule d'eucaryote supérieur cultivée *in vitro*.
Vectorisation	Aucun médicament ne peut exercer une activité thérapeutique si la molécule biologiquement active qu'il renferme n'est pas capable de franchir les barrières biologiques qui séparent le site d'administration du site d'action. La vectorisation des médicaments correspond au transport des molécules biologiquement actives jusqu'à leur cible biologique.