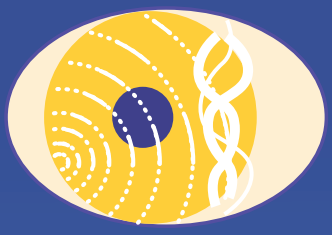


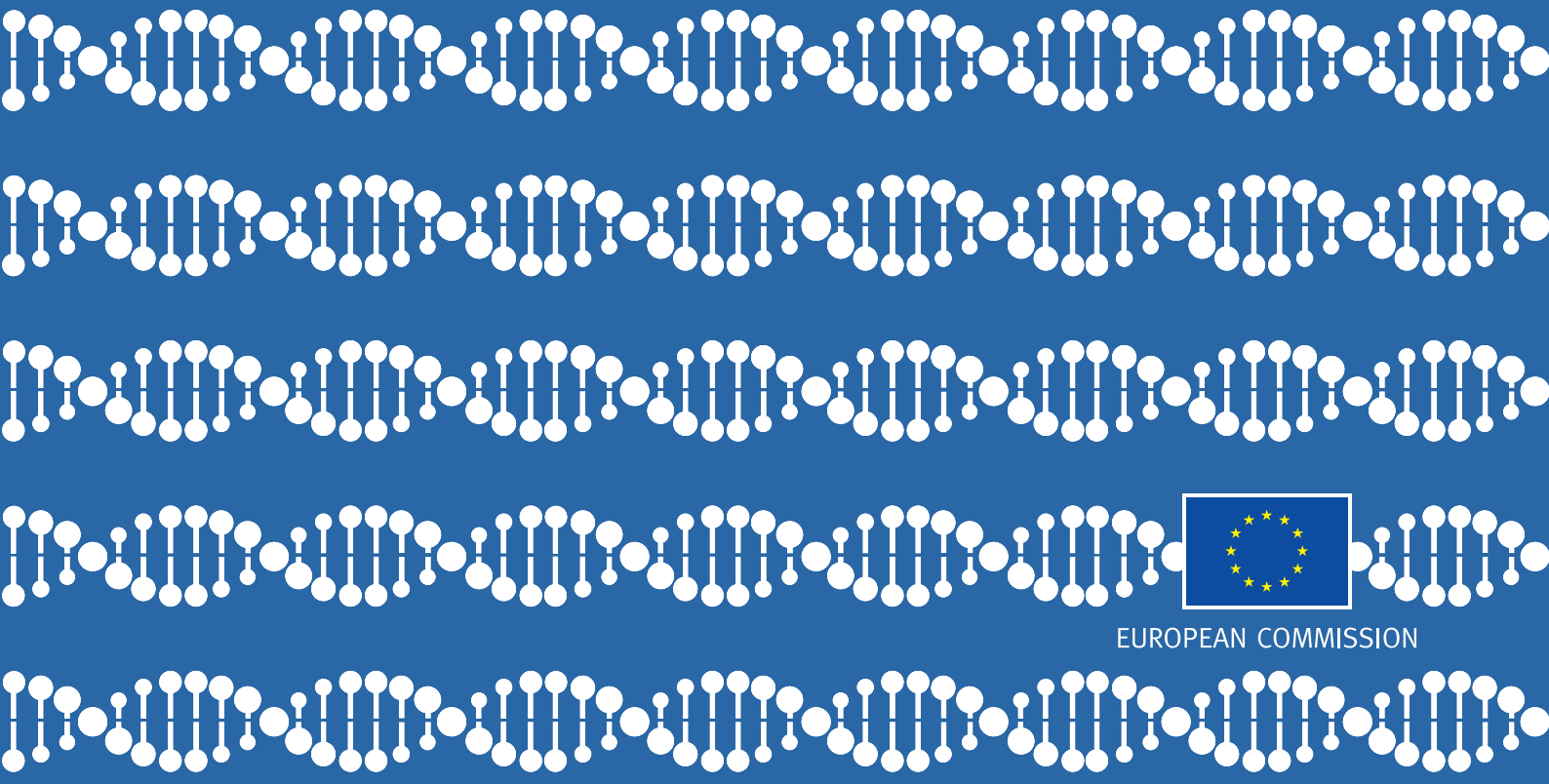
The European Group
on Ethics in Science
and New Technologies
to the European Commission

Ethics of synthetic biology

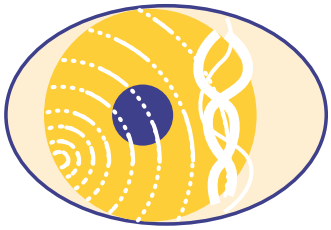
Opinion No

25

Brussels, 17 November 2009



EUROPEAN COMMISSION



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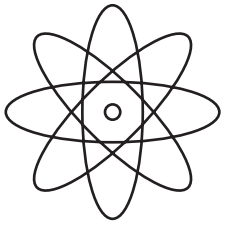

Brussels, 17 November 2009

Chief Editor
Maurizio SALVI

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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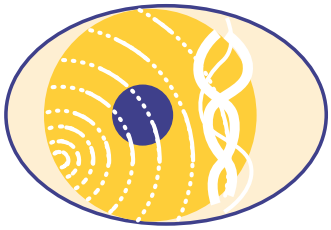

European Group
on Ethics in Science
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to the European Commission

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.

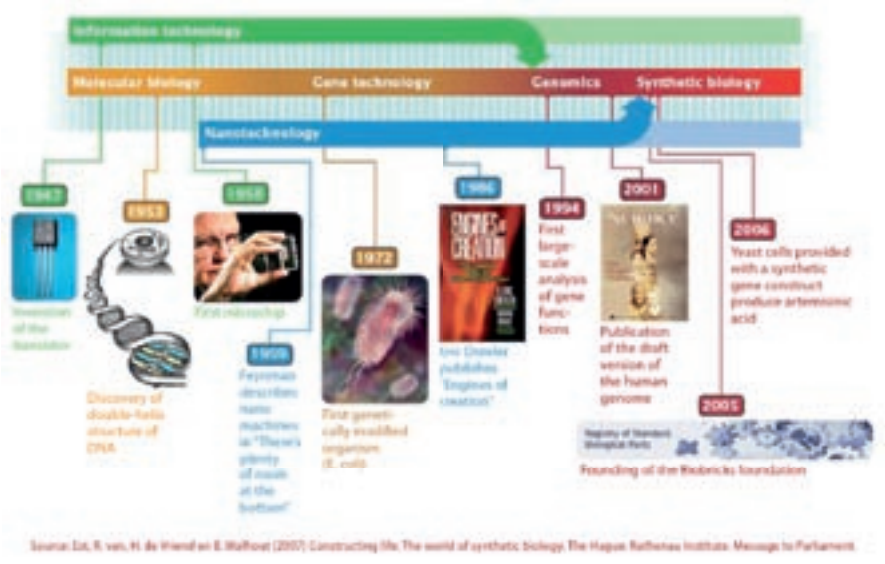
([39]) Such an approach has been used since before the time of Aristotle, and, in a more formal way, by Descartes, G. Galilei and Newton.

([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.

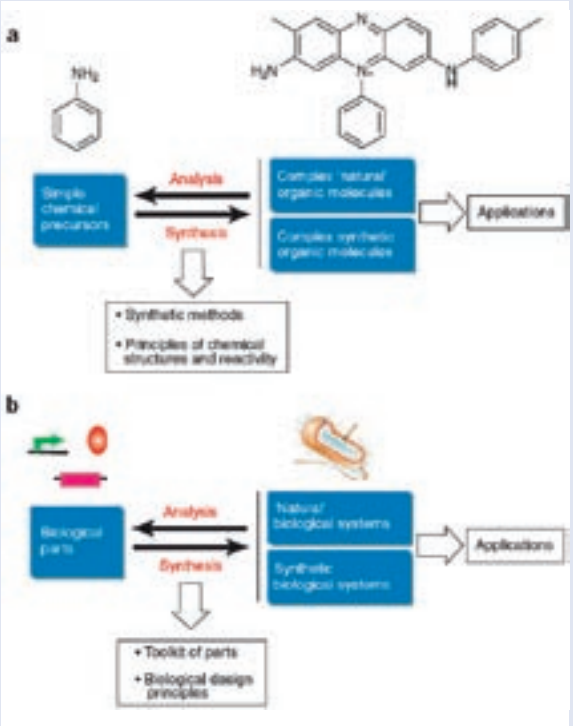


Figure 1. a) Analysis and synthesis in organic chemistry; b) Analysis and synthesis in synthetic biology ([49]).

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-

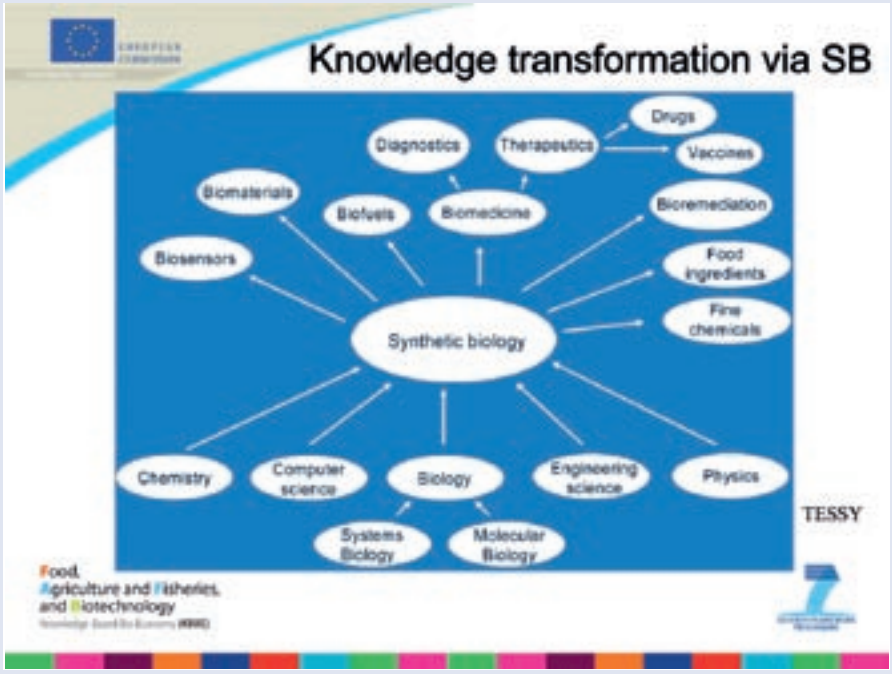
([49]) http://www.nature.com/nchembio/journal/v3/n9/pdf/nchembio0907-521.pdf.

([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

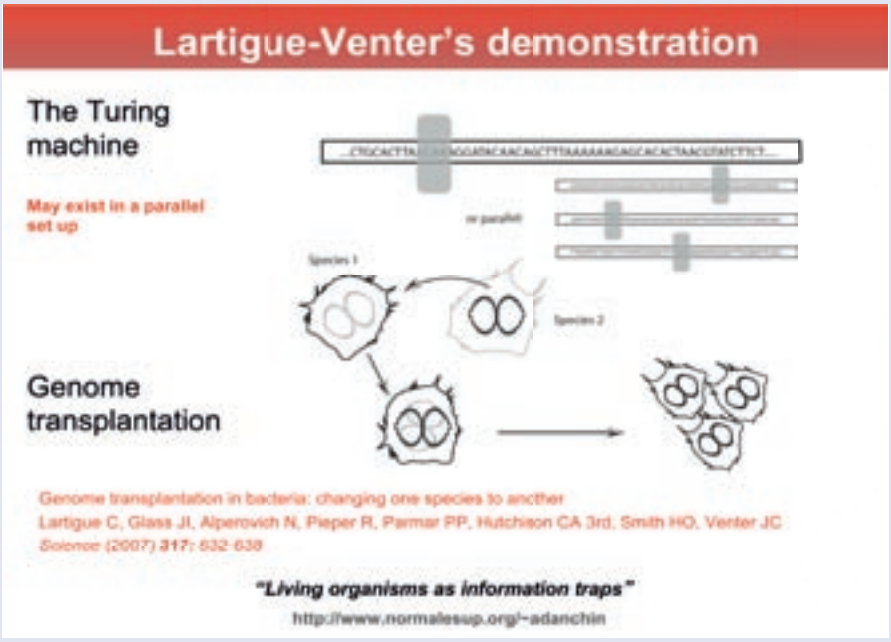
The conceptual basis underlying many modern approaches to biology is a reductionist view, which accepts that biological phenomena are expressions of chemical-physical processes. There are numerous examples of this paradigm, including Monod (1967), Eigen (1975) and Watson (1998). According to this view, 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.

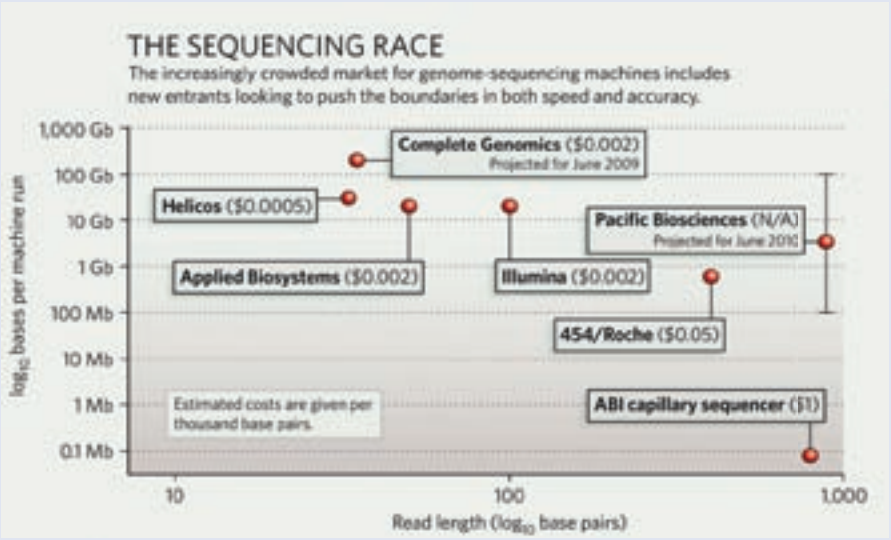
Some of the basic disciplines of modern biology such as biochemistry and molecular biology are based on a reductionist approach. The hope was that by deconstructing the systems and understanding individual parts of the system in great detail it would be possible to reconstruct pathways, cell systems 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.





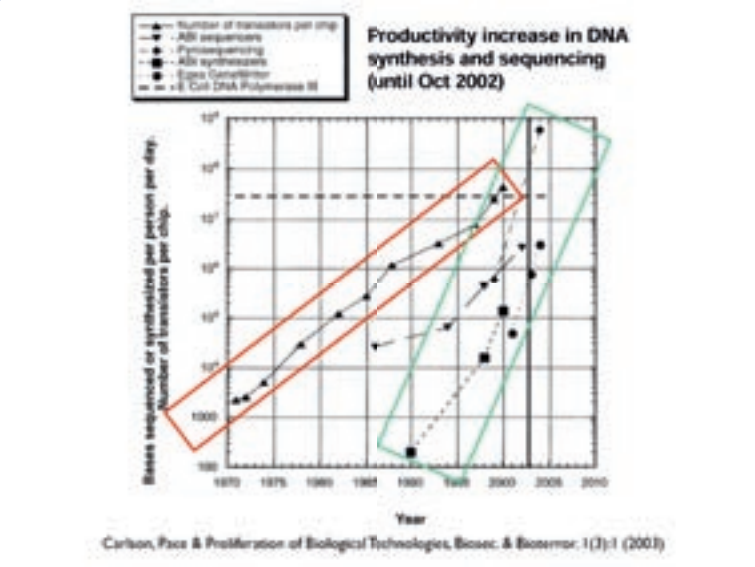
http://www.nature.com/news/2009/090206/pdf/news.2009.86.pdf

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

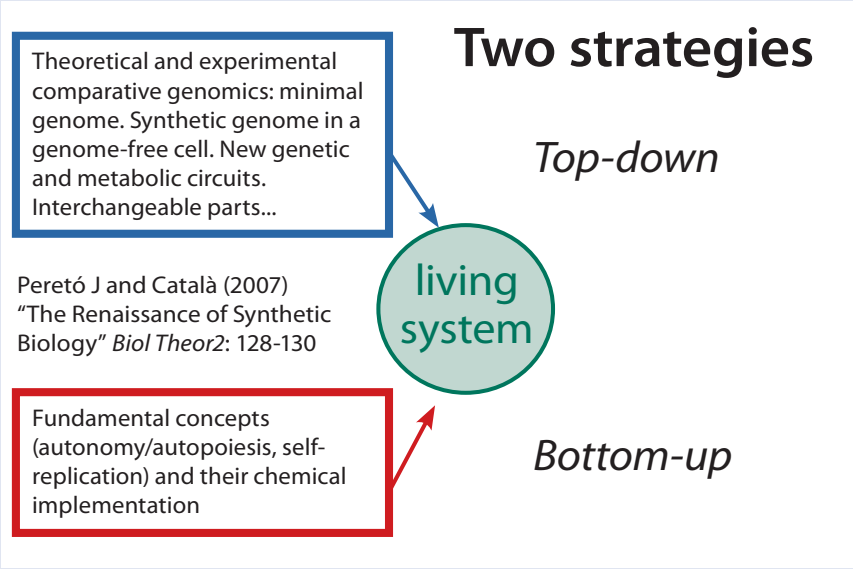
Synthetic biology models are informative tools for the design of engineered biological systems to better predict system behaviour prior to fabrication. Because of the intentional nature of manufacturing synthetic biology products, modelling is a key factor allowing

([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.).

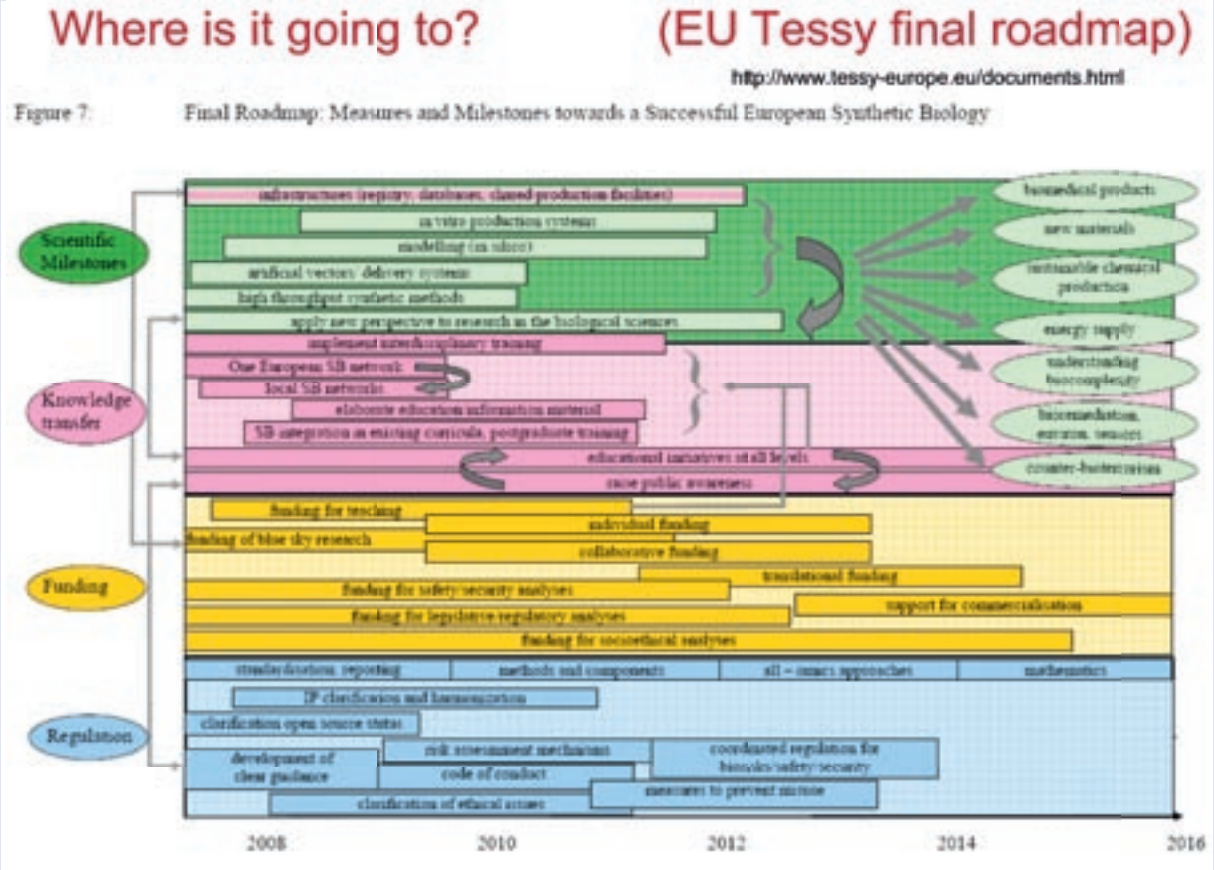
With some exceptions European national agencies and programmes are not yet very active ([84]). Europe has, so far, been relatively slow to embrace the potential opportunities from synthetic biology, despite the substantial pool of expertise which could be tapped to contribute towards an effective EU 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

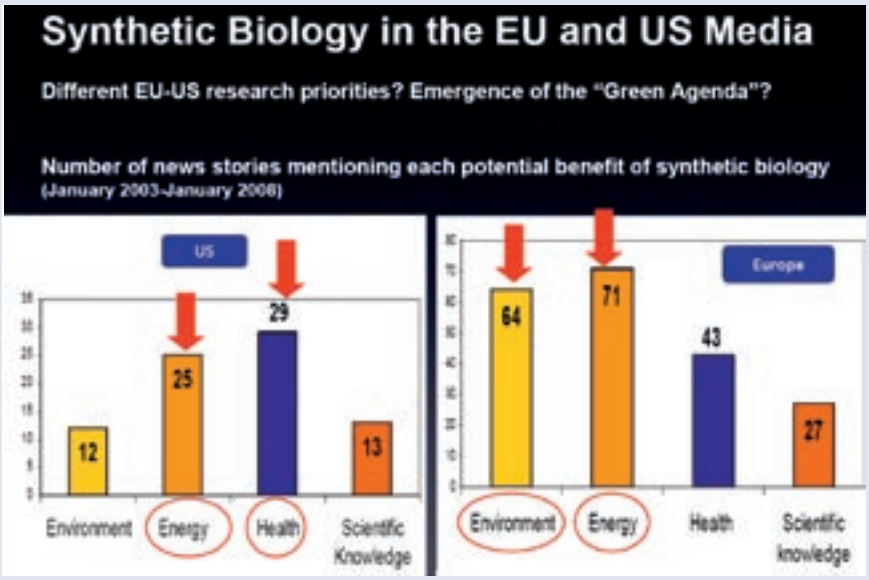
([148]) Nature Editorial (2006) Policing ourselves *Nature* 441: 383.

([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.

([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.

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])

([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.

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Emmanuel Agius

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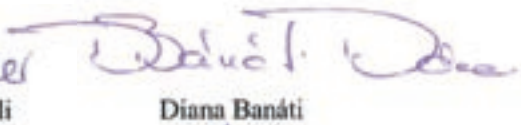


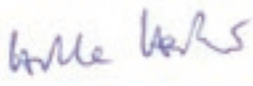
Diana Banáti

Anne Cambon-Thomsen

Rafael Capurro

Inez de Beaufort

Josef Glasa



Hille Haker

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Paula Martinho da Silva

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Pere Puigdomenech-Rosell

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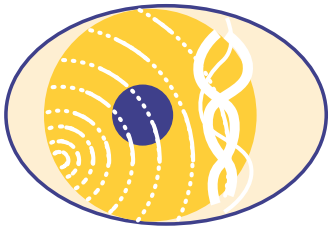

Groupe européen d'éthique
des sciences et des nouvelles
technologies auprès
de la Commission européenne

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.

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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.

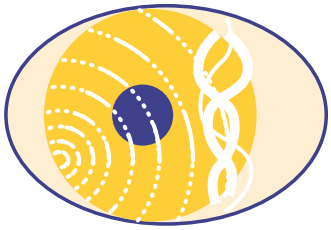
Recommandation n° 25: Le GEE demande à l'UE de financer de manière appropriée la recherche interdisciplinaire portant sur les aspects suivants de la biologie synthétique:

- *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.

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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.

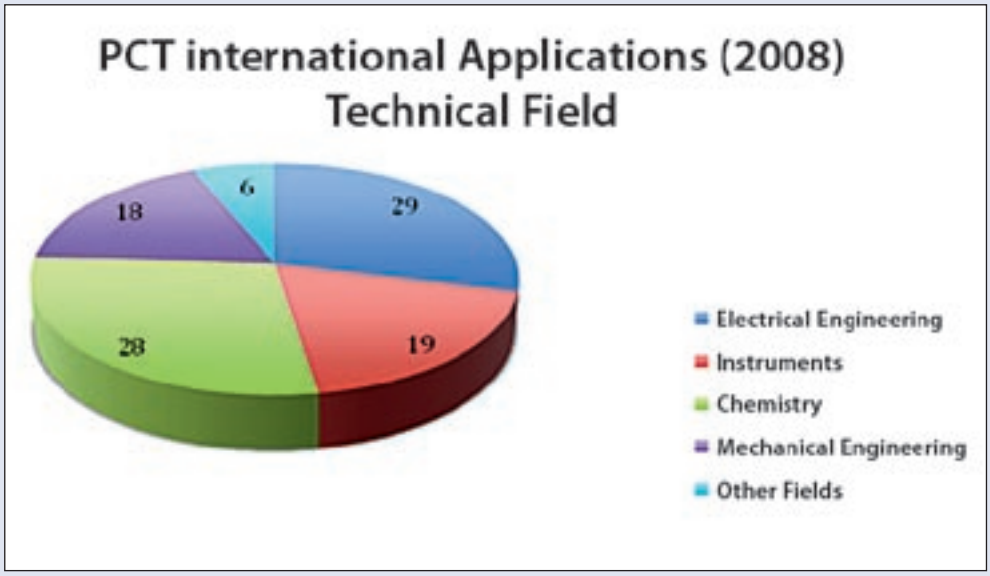
A patent is a limited 'negative' national right given to an inventor for a short period of time (usually 20 years from date of filing) in exchange for a publication of a full specification that allows anyone reading the patent to replicate the invention. In practice descriptions are often published a (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

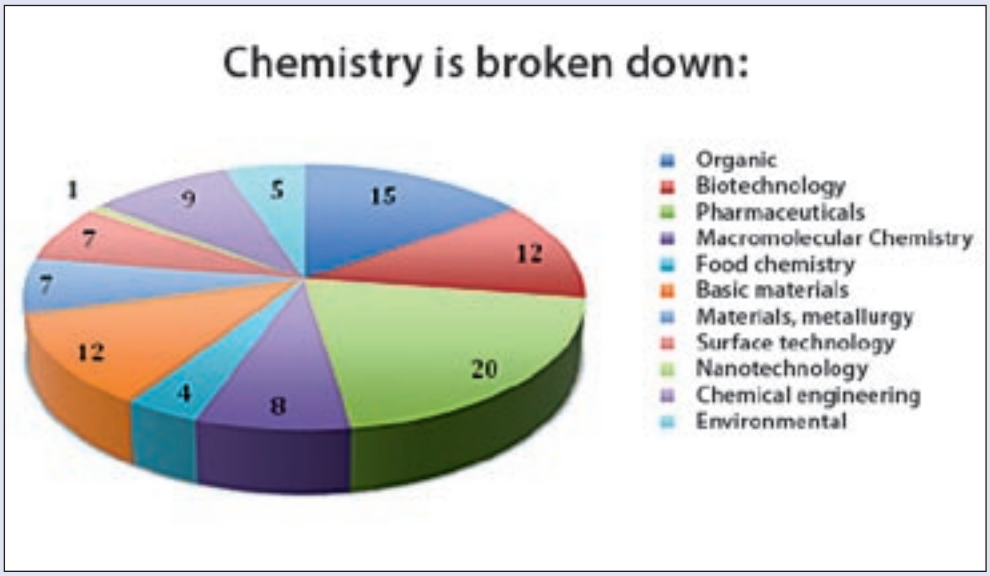
([12]) W. Cohen et al., 'Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector' Working Paper (Pittsburgh: Carnegie-Mellon University 1997).

([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

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([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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