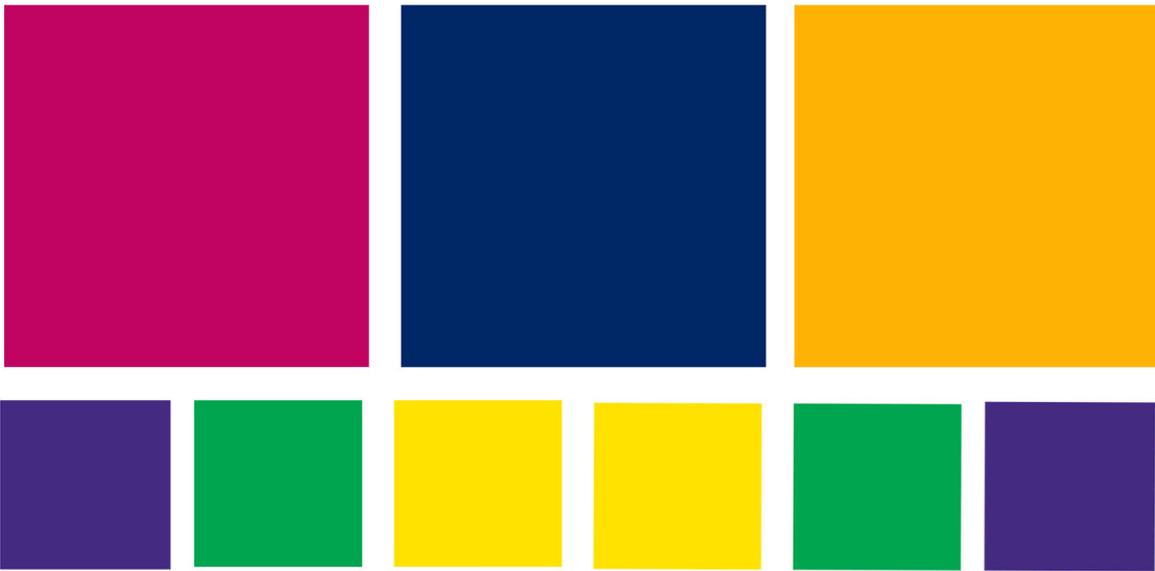


Synthetic Biology

Social and Ethical Challenges



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Executive Summary

1. What is Synthetic Biology?

There is no agreed definition of synthetic biology, but it is best understood as the deliberate design of biological systems and living organisms using engineering principles.

2. Something Old, Something New

The technological manipulation of life was first advocated at the turn of the last century and was instrumental in shaping the rise of molecular biology. However, the widespread use of the term has only occurred since the mid-2000s, as the field has emerged owing to the falling cost of gene sequencing and synthesis. The aims of synthetic biology include: 1) the production of minimal living genomes; 2) the design of interchangeable parts that can be assembled into pathways for the fabrication of novel components; 3) the construction of entirely artificial cells; and 4) the creation of synthetic biomolecules.

3. Developing the Field of Synthetic Biology

The field of synthetic biology is still in its infancy, although there has been a rapid rise in research activity. Public funding has come largely from the US with major investment from the Departments of Defense and Energy. In addition, commercial and charitable interest has come mostly from wealthy individuals and venture capital, with much of this investment being made in companies founded by leading academics. The EU's New and Emerging Science and Technology (NEST) programme has provided early stage funding for 18 synthetic biology research and policy projects. In the UK a series of Networks in Synthetic Biology have recently been funded by BBSRC and the Engineering and Physical Sciences Research Council (EPSRC), with additional support from the Arts and Humanities Research Council (AHRC) and the Economic and Social Research Council (ESRC)¹.

4. Synthetics, or Synbioethics: The rise of concerns about Synthetic Biology

Many parallels have been drawn between the early development of recombinant DNA technology in the 1970s and synthetic biology. A number of key ethical and social issues raised by the technology have been debated, including:

5. Uncontrolled Release

One of the main aims of synthetic biology is the creation of novel genetically modified organisms (GMOs), which may have utility in the production of energy and bioremediation. However, such a prospect raises concerns about their accidental release into the environment, as by their very nature such biological machines could evolve, proliferate and produce unexpected interactions that might alter the ecosystem. A number of measures are being proposed or adopted to ensure adequate biological control, including: engineering bacteria to be dependent on nutrients with limited availability; and integration of self-destruct mechanisms that are triggered should the population density become too great.

¹ http://www.bbsrc.ac.uk/funding/opportunities/2007/synthetic_biology.html

6. Bioterrorism

The ability of synthetic biology to produce known, modified or new microorganisms designed to be hostile to humans is a major concern, and has been demonstrated by the synthesis of the polio virus and the pandemic Spanish Flu virus of 1918. A major issue in this respect is the ready availability and poor control over commercial DNA synthesis. Furthermore, in the future 'garage biology' (synthetic biology at home) may be established as a hobby. However, most concern arises from state-level biological warfare programmes. A number of proposals have been made by both scientific groups and government agencies to address the dual use (military/civilian) nature of synthetic genomics, including: controls over commercial DNA synthesis and public research; and considering the impact of synthetic biology on international bioweapons conventions. As yet there is no policy consensus on these issues. Furthermore, there is an ongoing debate about whether improved biosecurity measures should be achieved through professional self-regulation or formal statutory oversight.

7. Patenting and the Creation of Monopolies

The drive to create a microorganism that can turn biomass into fuels such as ethanol or hydrogen is a major focus of research, which has prompted a concern that patenting may lead to the creation of commercial monopolies or inhibit basic research. In response, there have been moves to develop an open-source movement (based on so called BioBricks) involving creation of a 'commons' that will facilitate open scientific research.

8. Trade and Global Justice

Perhaps the biggest success in synthetic biology to date has been in the production of terpenoids for the manufacture of the antimalarial medicine artemisinin, a drug that holds significant promise for worldwide malaria victims. However, there are concerns that synthetic artemisinin would ensure that no local production of natural *Artemisia* could be sustained in developing countries, thereby maintaining the discrepancy of wealth and health between rich and poor nations.

9. Creating Artificial Life

One of the most potent promises of synthetic biology is the creation of 'artificial life'. This has provoked fears about scientists 'playing God' and raises philosophical and religious concerns about the nature of life and the process of creation. It has been suggested that a stable definition of 'life' is impossible and that synthetic biologists are confused over what life is, where it begins and particularly, how complex it must be. In response a number of scientists have proposed a modified version of Turing's test for life imitation. However, it is unclear whether these moves to undermine lay concepts of life will ameliorate deeper fears about the blurring of the boundary between the artificial and the natural world.

10. Conclusion and Recommendations

Synthetic biology should be understood in terms of both well established traditions within molecular biology and as an emerging field in its own right. Whilst concerns should be contextualised in this historical approach, it is important to recognise that something new and important is happening. In part this represents a growing confidence in the scientific community to undertake the project of engineering life, but it also marks the maturity of a series of powerful technologies, which may be converging with other developments in computing, materials science and

nanotechnology. However, whilst rapid scientific progress is possible, it must be recognised that translating this knowledge into real world applications is often a slow process requiring significant investment.

1. It is vital to recognise the importance of maintaining public legitimacy and support. In order to achieve this, scientific research must not get too far ahead of public attitudes and potential applications should demonstrate clear social benefits. Furthermore, the potential benefits of the technology must not be overhyped for this risks both creating excessive public anxiety and unrealistic hopes.
2. The scientific community must take, and be seen to be taking, a lead in debating the implications of their research and engaging with broader society around the issues raised by synthetic biology.
3. Partnership with civil society groups, social scientists and ethicists should be pursued as a highly effective way of understanding critical issues, engaging with publics and winning support for emerging scientific fields. Experiments in upstream engagement and public consultation should be undertaken to provide a valuable channel for helping negotiate the boundaries of what is socially acceptable science.
4. A robust governance framework must be in place before the applications of synthetic biology are realised. This will require a thorough review of existing controls and regulations, and the development of new measures, particularly relating to biosafety, environmental release and biosecurity.

Research agencies, such as the BBSRC, have an important role, not only in terms of funding the best science, but also in steering and shaping the field. Thus research can be undertaken in a way that ensures ongoing public support and realises the potential social and economic benefits of these powerful technologies, whilst controlling risks in a way that reassures both the public and the scientific community.

Synthetic Biology: social and ethical challenges

Synthetic biology is an exciting multidisciplinary field that promises many benefits, whilst at the same time raising important social and ethical issues. Yet although it is a rapidly emerging field, it must be stressed that work on synthetic biology is still at a very early stage with relatively few UK researchers choosing to call themselves synthetic biologists and no dedicated funding stream supporting these activities. However, this looks set to change in the near future, with funding agencies such as the BBSRC, EPSRC and the Medical Research Council (MRC) playing a key role in creating this new area of investigation. This report has been commissioned as part of the activities of a BBSRC Strategy Panel working group that has been considering the main social and ethical issues that might be of concern to the public as regards synthetic biology. It is hoped that it will help inform debate in both the scientific community and the wider public more generally, so that some of the sensitive issues that might arise as the field advances can be taken into account at an early stage.

This report therefore aims to briefly review the main social and ethical issues raised in public debates about synthetic biology. In particular, it draws on media reports, academic publications and grey literature mostly published in the last five years. The first two sections provide some definitions of synthetic biology and summarise the central areas of scientific research. This is followed by a description of how the science and technology has developed in recent years, the emergence of public debate about its implications and the policy response to these concerns in a number of key areas. Finally, some reflections on the lessons that might be learnt from the earlier debates over genetic engineering and recommendations for policy are offered in the conclusion.

1. What is Synthetic Biology?

Synthetic biologists have been debating their neologism for years. Rob Carlson, an early advocate of the subject, recalls the various appellations of 'Intentional Biology', 'Constructive Biology', 'Natural Engineering', 'Synthetic Genomics' and 'Biological Engineering'². Quoting '*Making Sense of Life*' by Evelyn Fox Keller in his forthcoming book '*Learning to Fly: the past, present and future of Biological Technology*' Carlson suggests that the term 'Synthetic Biology' has been in use for over a century and as such its continued employ is somewhat inevitable³. Though some of these varied terms are deployed simultaneously, it does appear from reviews of the literature that 'Synthetic Biology' is becoming the dominant term describing this new field.

What seems to be at stake in this struggle for nomenclature is not only the establishment of a disjunction, the drawing up of boundaries for a new field, but also the weight of social implications and public (mis)understandings of what it promises to achieve. Indeed, due to internal fears over possible incitement of anti-recombinant-DNA riots the proposed title of Steven Benner's 1988 conference in Switzerland, 'Redesigning Life', had to be renamed [Ball 2004]. There seems to be a fear that the single word *synthetic* connotes negative images of monstrous life forms let loose by maniacal scientists. However, it is certain that whilst terminology plays a role in perception, the fears for and about synthetic biology will not be allayed by simply changing its name.

² Rob Carlson's Blog http://synthesis.typepad.com/synthesis/2006/05/synthetic_biolo_1.html

³ Pages from his book available at: <http://www.biologyistechnology.com/>

Whatever umbrella term is placed over the research the goals are broadly similar and can be summarised thus:

[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 characterized 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 ⁴

However, a questionnaire from SYN BIOLOGY⁵ indicates that key stakeholders in the field can't agree on exactly what synthetic biology is [SYN BIOLOGY 2006], but at heart synthetic biology is the deliberate design of biological systems and living organisms using engineering principles. This idea has a long history that can be traced to the foundation of modern biology at the outset of the 20th century.

2. Something Old, Something New

The scientifically compelling idea of the technological manipulation of life was first advocated by Jacques Loeb at the turn of the last century. In particular, he elaborated a materialistic and mechanistic view of living things which would allow them to be engineered [Pauly, 1987]. This 'engineering principle' in biology directly influenced many of the early leaders in genetics, including both Morgan and Muller, the latter testifying that after he read Loeb's work in 1911, his major scientific goal was to control evolution [Ibid., p177]. This objective played a key role in Muller's search for a means of artificially creating mutations and eventually led him to successfully experiment with X-rays [Ibid., p179]. Muller's work was fundamentally important as it was the first demonstration that heredity could be artificially manipulated by means other than selective breeding.

The aim of engineering life was also instrumental in shaping the development of what became known as molecular biology during the 1930s. A key factor in the emergence of this new science and the realisation of what Kay has called the 'molecular vision of life' was the role of the Rockefeller Foundation in sponsoring a very large programme of research into the physical and chemical basis of life [Kay, 1993]. Before the war the Foundation was the largest source of funding for basic research in biology, with Federal government support only becoming significant after 1945. Between 1932-1959 it invested over \$25 million in molecular biology in the USA [Ibid., p6].

The concept of living things as having machine-like properties that can be deliberately altered became institutionalised in the rise of post-war molecular biology and was clearly articulated by pioneer researchers such as Monod, Rostand and Tatum. Despite this, it was only in 1974 that the Polish geneticist Waclaw Szybalski introduced the term "synthetic biology" at the birth of the recombinant DNA era:

⁴ Video available at: http://webcast.berkeley.edu/event_details.php?webcastid=15766

⁵ One of the programmes funded by NEST – more detail can be found below.

Let me now comment on the question "what next". 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 the unlimited expansion potential and hardly any limitations to building "new better control circuits" and finally other "synthetic" organisms, like a "new better mouse". ... I am not concerned that we will run out of exciting and novel ideas, ... in the synthetic biology, in general. [Szybalski, 1974].

However, the widespread use of the term synthetic biology has only occurred since the mid-2000s. The reasons for this are complex, but the resurgence of interest in the idea of using engineering principles to create artificial life is largely down to the falling cost of gene sequencing and synthesis following the completion of the human genome project and the development of high speed automation. In this sense, advances in the speed and scale of existing technologies, rather than the arrival of new ones, have enabled the realisation of one of the longest held promises of modern biology.

2.1 The Scope of Synthetic Biology

Research within synthetic biology can be explored through one of two approaches: top-down, or bottom-up. The top-down approach attempts to eliminate the problem of natural complexity by removing it, e.g. by stripping a genome of all genetic material that is not absolutely essential for replication and functionality. The bottom-up approach uses naturally occurring organisms that appear to have little complexity and adds the required functions by engineering them into the existing genome. There are a number of major areas of research that constitute the field of synthetic biology. These can crudely be broken down under the following headings: making minimal genomes; designing modular components; pathway engineering; expanding the genetic pool; production of artificial cells; and creation of synthetic biomolecules.

a) Minimal Genomes

The production of minimal genome microbes entails experiments designed to determine the smallest number of genes required for a bacterium to survive and follows the top-down approach to synthetic biology. Craig Venter's team at the Institute for Genomic Research began to experiment with the bacterium *Mycoplasma genitalium* in the 1990s. This research built on a survey of the *M. genitalium* genome using random sequencing [Peterson 1993] and resulted in the estimation of a gene complement of 470 coding regions for such things as DNA repair, energy metabolism and other essential processes [Fraser et al 1995]. This figure was reduced to 386 essential genes by 2005⁶. The production of minimal living genomes is undertaken to produce a 'chassis' that can have other synthetic pathways added [ETC 2007], thereby enabling various products to be made from the same basic organism. It is hoped that these basic cells could be utilised for such things as producing efficient fuel alternatives or as a means to slow climate change. Though the basic science involved in the production of these minimal genomes, predominantly gene knockout technology, has been utilised for some time, the outcome of such experimentation in the production of minimal genomes is relatively new. Furthermore, the development

⁶ <http://genomicsgsl.energy.gov/pubs/2005abstracts/html/file42.shtml>

of those minimal genome microbes into working systems for the production of fuels or clean up of environmental contaminants is still at a very early stage.

b) Modular Components, Pathway Engineering and the Expanded Gene Pool

Whereas other disciplines in biology are seen to struggle with modelling and describing the complexity of systems, the engineering perspective strips the system to its bare bones and then develops a 'limited number of well characterized, standardized objects' [Pleiss 2006], which can be modelled using present computing capacity. These standardized objects, or interchangeable parts [Benner and Sismour 2005], represent a top-down approach to synthetic biology and can be built from first principles, in a hierarchical manner, into complex systems, in which each component and its interactions are known. This predictability means that at every level in the hierarchy in a system the details of how the components are constructed from parts is irrelevant. Thereby the abstraction of design and fabrication can be accomplished, meaning that complex machines can be developed from a small number of basic modular elements⁷.

To achieve this engineering abstraction research is intensively focused both on the standardization of these interchangeable parts and the decoupling of complex systems into more manageable components [Endy 2005]. This allows for researchers dispersed across the world to collaborate independently. A registry of these standardized parts is being developed at MIT⁸, where they are increasingly known as BioBricks. MIT also runs an annual international competition for undergraduate students to design a system using BioBricks called iGEM⁹.

Benner and Sismour [2005] outline the two types of interchangeable parts being developed by the synthetic biology community: DNA and proteins. Deoxyribonucleic acid has proven to be an excellent structure for modification since the backbone that supports the base pairs is relatively stable, even when entirely synthetic nucleic acids are added to the sequence. Slight modifications to the DNA polymerase enzyme allow for normal 'reading' of a DNA sequence that contains nucleotides other than AGCT [Benner and Sismour 2005]. The two artificial nucleotides produced by Benner's team are K and X, forming what he calls AEGIS (An Expanded Genetic Information System).

In contrast, the search for protein-based interchangeable parts has proven more difficult. Engineering proteins by modifying the amino acid sequence in a predictable fashion is a highly complex process due to the secondary and tertiary structures that proteins arrange themselves into. Amino acids interact with each other causing the chain to fold and bend into a three dimensional structure that is hard to anticipate from sequence data alone. As such, attempts to engineer interchangeable parts have so far been successful mostly by DNA modification.

The production of pathways made up of these interchangeable parts is the ultimate goal and progress has been made along those lines by the Gate's Foundation-backed Berkeley team. In collaboration with Amyris Biotechnologies they have been developing a synthetic pathway for the production of naturally occurring compounds known as isoprenoids. This is explored further in Section 8 below.

⁷ See: <http://openwetware.org/wiki/Image:AbstractionHierarchy.jpg> for a visual explanation

⁸ The MIT BioBricks Project is a Wiki of standard biological parts that have been designed with standard prefix and suffix sequences such that they can be assembled using well known cloning techniques.

⁹ International Genetically Engineered Machine Competition http://parts.mit.edu/igem07/index.php/Main_Page

c) Artificial Cells

The creation of artificial cells operates through a bottom-up process, as opposed to the top-down strategies so far described [ETC 2007]. Scientists such as Steen Rasmussen, who was awarded a \$5m grant from the Los Alamos National Laboratory, are attempting to build life-like cells from scratch [ETC 2007]. They place three components at the centre of that project: a system of metabolism; an information-storing molecule; and a membrane to hold it together. Rasmussen's team is developing a 'protocell'¹⁰. The protocell is different from naturally occurring cells, or minimal living organisms, perhaps most evidently in the use of Peptide Nucleic Acid (PNA) in place of DNA. PNA uses peptides in place of the DNA sugar-phosphate backbone. Rasmussen's lab is just one of the 13 partners in the PACE (Programmable Artificial Cell Evolution) consortium¹¹. This research network aims to produce self-organising, evolvable, life-like systems to make the next generation of self-repairing computer and robotics technologies and to 'direct all kinds of complex production and remediation on the nanoscale'¹².

d) Synthetic Biomolecules

As earlier indicated the search for interchangeable parts through protein modification has proven complex due to the secondary and tertiary structural features of these molecules. The modification of amino acid sequences after they have been transcribed from genes in the cell can greatly alter the functionality of the sequence, offering some explanation for the observed discrepancy between low gene number and increased complexity in the higher animals. British scientists [van Kasteren et al. 2007] have recently developed a chemical tagging system that utilises established GM techniques (the LacZ reporter enzyme scaffold) to attach post-translation modifications to amino acid sequences, thereby producing proteins that have functions such as detecting mammalian brain inflammation and disease. Other examples of protein modification are detailed in a *Science* perspectives article [Davis 2004], and include such things as the construction of a synthetic mimic of erythropoietin that has a prolonged circulation time in the body [Kochendoerfer et al 2003].

3. Developing the Field of Synthetic Biology

A major conference, Synthetic Biology 1.0 convened at MIT in June 2004 announced the world's first synthetic biology department. The follow-up event Synthetic Biology 2.0 was held at Berkeley in 2006, and SB 3.0 in Zurich 2007¹³. In the UK the major synthetic biology conference BioSysBio was inaugurated in 2007 at the University of Manchester and continues at Imperial College London in 2008¹⁴. Synthetic biology has been particularly successful at encouraging young engineers to actively participate in the field through the International Genetically Engineered Machine (iGEM) competition¹⁵ that has run annually since 2006. In 2007 some 56 university or national teams took part, coming from twenty countries, including four from the UK. Journals specifically devoted to the field have begun to emerge, with the most recent being 'Systems and Synthetic Biology' published by Springer Netherlands, which put

¹⁰ <http://protocells.lanl.gov/>

¹¹ <http://www.istpace.org/index.html>

¹² http://www.istpace.org/research_overview/index.html

¹³ <http://syntheticbiology.org/Conferences.html>

¹⁴ <http://conferences.theiet.org/biosysbio/>

¹⁵ http://parts.mit.edu/igem07/index.php/Main_Page

out its first issue in March 2007¹⁶. BioMed Central publishes the open-access journal Systems Biology, which includes much scope for synthetic biology and has been publishing articles since January 2007¹⁷. Key reviews of the field were published in 2005 [Benner and Sismour 2005] and 2006 [Heinemann and Panke 2006].

Bhutkar [2005] briefly outlines the status of funding for synthetic biology in the US and Europe. Significant amounts of money are being injected into the field by the US government Defence Advanced Research Projects Agency (DARPA) and the Departments of Defense (DoD) and Energy (DoE). DARPA is interested in DNA computing and the DoD has allocated \$3m to Craig Venter's not-for-profit Institute for Biological Energy Alternatives. A new research centre at UC, Berkeley was opened in 2006 by a National Science Foundation (NSF) grant of \$16m, to be spent over five years¹⁸.

In addition, over the last couple of years, there has been a wave of commercial interest and investment in synthetic biology coming from wealthy individuals and venture capitalists. Such individuals, including Craig Venter and Bill Gates, have developed particular interests within synthetic biology. In 2006 Microsoft awarded \$570,000 to six projects with the aim of stimulating basic research in synthetic biology and DNA nanotechnology¹⁹. The Bill and Melinda Gates Foundation donated \$42.6m over five years (beginning 2004) to a collaboration between the Institute for OneWorld Health, UC Berkeley and Amyris Biotechnologies to develop a synthetic form of artemisinin, an anti-malarial drug²⁰. Amyris was also awarded \$70m by a consortium of venture capitalists to use the same technology platform to develop bio-fuels²¹. Amyris Biotechnologies was founded by well known synthetic biologist Jay Keasling at UCB and its CEO is presently John G. Melo, previously president of U.S. Fuels operations for BP²².

Codon Devices²³, founded by synthetic biologists Drew Endy, George Church, Jay Keasling and Ron Weiss, has 35 US patent applications and 10 issued US patents, 28 foreign applications and 12 issued and describes itself as a Constructive Biology Company. They claim their BioFab technology is the most advanced genetic construction platform in the world. In 2005 Codon's first funding round collected \$13m in capital²⁴ and in 2006 the second round brought in \$20m²⁵.

EraGen Biosciences²⁶, founded by Steven Benner uses his expanded genetic alphabet and holds multiple patents related to synthetic biology including a number with broad claims covering non-standard oligonucleotides²⁷. In 2006 EraGen closed a funding round with \$12m bringing their total capital raised to ~\$21m²⁸.

Craig Venter and Hamilton Smith's company Synthetic Genomics²⁹ is developing minimal genome living organisms as a basis for multiple applications in global energy

¹⁶ <http://www.springer.com/west/home/biomed?SGWID=4-124-70-173669004-0>

¹⁷ <http://www.biomedcentral.com/bmcsystbiol/>

¹⁸ http://www.Berkeley.edu/news/media/releases/2006/08/03_SynBerc.shtml

¹⁹ http://research.microsoft.com/ur/us/fundingopps/RFPs/Synthetic_Biology_Awards_2006.aspx

²⁰ http://www.gatesfoundation.org/GlobalHealth/Pri_Diseases/Malaria/Announcements/Announce-041213.htm

²¹ http://www.amyrisbiotech.com/projects_biofuels.html

²² <http://www.amyrisbiotech.com/management.html>

²³ <http://www.codondevices.com/>

²⁴ <http://masshightech.bizjournals.com/masshightech/stories/2005/05/30/daily39.html>

²⁵ http://www.boston.com/business/technology/biotechnology/articles/2006/12/18/dna_builder_closes_20m_in_financing/

²⁶ <http://www.eragen.com/>

²⁷ <http://www.eragen.com/contentPage.cfm?ID=375>

²⁸ <http://eragen.senscia.com/UploadedImg/Press%20Releases/PR0601EraGen.pdf>

²⁹ <http://www.syntheticgenomics.com/>

and environmental challenges. In particular, they aim to develop an efficient fuel. Synthetic Genomics has received at least \$30m from venture capital firms³⁰.

Another biotechnology company Ambrx³¹ is incorporating unnatural amino acids into its protein-based products and secured \$55m in financing in 2006³². It has been issued US Patent No. 7,045,337 entitled 'In vivo incorporation of unnatural amino acids'³³. In March 2007 synthetic biofuels company LS9³⁴, whose founders include George Church, announced it had raised \$5m in its first round of venture seeking and a subsequent \$15m in financing³⁵. Furthermore, April 2007 saw the firm Agrivida announce receipt of a Small Business Innovation Research Grant from the NSF to help fund their screening of biomass degrading enzymes in corn. In August the same year Agrivida announced a collaboration with Codon Devices to develop engineered proteins for biofuel development based in corn³⁶.

Other firms working on synthetic biology either as developers or suppliers include: Mascoma, Sangamo Biosciences, Genomatica, Genencor, Firebird Biomolecular Sciences, EngeneOS, Diversa, DuPont and Egea Biosciences [ETC Group 2007]. Several of these companies are working on the engineering of enzymes.

Across the Atlantic, firms in the UK include Glycoform³⁷ which has developed a synthetic glycoprotein designed to treat anaemia. They received £960,000 in a 2004 funding round with contributions from the ISIS College Fund managed by Quester Capital Management Limited and other share holders³⁸. A further \$1.1m was raised in 2006 from existing investors following completion of several milestones³⁹.

The EU's New and Emerging Science and Technology (NEST) programme provided early stage funding during 2003/04 and 04/05. Synthetic Biology featured as a case-study at the NEST 2005 conference and a fact sheet under the 6th Framework Programme 05/06 called for research proposals for:

...design and construction of new biologically based (or inspired) parts or systems, which involve a high level of internal complexity and which show logical or complex dynamical behaviour. The engineered parts or systems should show a tangible and useful standardised function or functionality with substantially different characteristics from natural systems.

NEST Pathfinder Initiative Fact Sheet 2006⁴⁰

The factsheet on synthetic biology [NEST, 2006], produced by an expert working group, outlines a number of the potential applications that are promised by the new methodology under the heading, 'The Vision of Synthetic Biology'. These are listed under the following headings:

³⁰ <http://venturebeat.com/2005/12/30/synthetic-genomics-to-create-new-forms-of-life/>

³¹ www.ambrx.com

³² http://www.ambrx.com/wt/page/pr_1152200371 and http://www.ambrx.com/wt/page/pr_1153528812

³³ http://www.ambrx.com/wt/page/pr_1148420952

³⁴ <http://www.ls9.com/>

³⁵ <http://www.ls9.com/pr100907.htm>

³⁶ <http://www.agrivida.com/news.html>

³⁷ <http://www.glycoform.co.uk/>

³⁸ <http://www.glycoform.co.uk/documents/glycoform-april-news.pdf>

³⁹ <http://www.glycoform.co.uk/documents/Press%20release%201st%20in%20vivo%20and%20funding%2020070108%2002%20ms.pdf>

⁴⁰ Available here: <ftp://ftp.cordis.europa.eu/pub/nect/docs/5-nect-synthetic-080507.pdf>

- Biomedicine
 - Complex molecular devices for tissue repair/regeneration
 - Smart drugs
 - Biological delivery systems
 - Vectors for therapy
 - Personalised medicine
 - Cells with new properties that improve human health
- Synthesis of biopharmaceuticals
 - Complex natural products
- Sustainable chemical industry
 - Environmentally friendly production of chemicals
- Environment and energy
 - Bioremediation
 - Production of energy
 - GMO safety
- Production of smart materials and biomaterials
- Security/ counter-terrorism.

The report led to framework six funding for 18 synthetic biology research and policy projects [Parliamentary Office of Science and Technology 2008]. Further projects within the EU include: 'TESSY: Towards a European Strategy for Synthetic Biology'; 'SYNBIOSAFE: Safety and Ethical Aspects of Synthetic Biology', 'EMERGENCE: setting up the bases for synthetic biology in Europe' 'SYN BIOLOGY: an analysis of synthetic biology research in Europe and North America' 'SynBioComm: towards a European synthetic biology community'. The first intends to bring together research groups through workshops to develop a research roadmap for European research on synthetic biology. The second examines the ethics, perception, safety and security of synthetic biology, with the third being concerned with education and infrastructure.

In the UK a joint call for proposals in Networks in Synthetic Biology was made in October 2007 by the BBSRC, EPSRC, ESRC, and AHRC, for a total of £900,000, part of which was intended for ethical and social debate. The funding and development of 'systems biology'⁴¹ has also been considered by the Academy of Medical Sciences and the Royal Academy of Engineering⁴² [Academy of Medical Sciences and Royal Academy of Engineering 2007]. Their report recommends the establishment of three to five new academic centres at leading universities in the UK costing ~ £325m over ten years and suggests that government financial support would be needed for such a project. It also argues that the interdisciplinary nature of the field poses problems for the contemporary structures of university departments and the arrangement of research grant committees, stating that:

This needs to be reflected in approaches to leadership, career development, peer review and publication criteria. Universities must break down barriers between disciplines and consider new methods of organisation that promote the development of novel scientific approaches. A substantial change in culture is required, in which biology and medicine become more quantitative.

⁴¹ Some consider the term synonymous with synthetic biology, whilst others argue there are significant differences. Irrespective of such confusion, the concerns of the academies remain applicable since, if they are different, they still retain the common feature of interdisciplinarity and novelty.

⁴² Available at: http://www.raeng.org.uk/policy/engagement/pdf/Systems_Biology_Report.pdf

The Research Assessment Exercise, as currently structured, continues to be a barrier to interdisciplinary research.

[Academy of Medicine and Royal Academy of Engineering 2007]

The differences between Europe and the US regarding synthetic biology's development are not solely financial. The SYNBIولوجY report [SYNBIولوجY 2006] indicates that key stakeholders feel that whilst there is opportunity for joint funding schemes to be established between the US and Europe, there may be other barriers to efficient collaboration. Some of these obstacles are cultural, with respondents to the SYNBIولوجY questionnaire believing that the US is more open to competition whereas the EU is focused more upon collaboration. Furthermore, they believe that many American projects are driven by military or defence initiatives, which may inhibit collaboration with researchers outside of the US.

4. Synthethics, or Synbioethics: The rise of concerns about Synthetic Biology

The scientific community hasn't shied away from acknowledging the potential dangers of synthetic life forms, with ethics playing a role in international conferences and with almost every review of synthetic biology indicating a need for ethical debate, internal regulation and safe practice. Indeed a declaration made by members at the Second International Meeting on Synthetic Biology (Synthetic Biology 2.0) supports the adoption of policies to ensure safe practice in the scientific community⁴³. There is some feeling that similar ethics and standards guidelines could be produced as have been elsewhere:

A code of ethics and standards should emerge for biological engineering as it has done for other engineering disciplines.

Church 2005, P423

A particular theme that crops up in the discussion on the ethics of this emergent science is the comparison to the situation faced by genetic engineering in the 1970s and '80s:

Synthetic Biology needs to establish itself as a community effort that is safe and nurtures responsible practices and attitudes. For this, a code of ethics and standards need to be developed for biological engineering. Learning from gene therapy, we should imagine worst-case scenarios and protect against them.

Chopra and Kamma 2006, p408

The Laurence Berkeley National Laboratory and MIT have both developed programmes on synthetic biology that include some exploration of ethical issues. In 2005 the Alfred P. Sloan Foundation awarded MIT \$570,000 to explore the potential ethical issues arising from synthetic biology⁴⁴. At the European level, in 2007 NEST published a brief statement of intent to create a European framework of ethics, regulation and public consultation on synthetic biology called SYNBIOSAFE⁴⁵. The project is funded for €236,000. By answering the questions posed by an ethics of synthetics the project hopes to offer advice on risk assessment, safety, ethics,

⁴³ Available here: <http://syntheticbiology.org/SB2Declaration.html>

⁴⁴ MIT press release here: <http://web.mit.edu/newsoffice/2005/syntheticbio.html>

⁴⁵ <http://www.synbiosafe.eu/>

'watermarks' into the sequence that would not typically be found in Nature, which were discovered to be advertising for the Venter Institute⁵¹.

An example of how synthetic organisms may be deliberately released into the environment is for the bioremediation of soil (e.g. for removal of environmental pollutants), something Venter's various research teams are interested in. Whilst genetically engineered microorganisms have been developed for such purposes they have only once been tested in the field and there are none in the regulatory pipeline [Tucker and Zilinskas 2006].

b) Social and Ethical Issues Raised

The main concerns in this area are centred on the development of synthetic organisms that are either intentionally or accidentally released into the environment. The ETC Group raises this as a major issue that parallels the debates about GM crops. Their report was spurred by the widely publicised patent application for a minimal bacterial genome, a list of genes, submitted by the Venter Institute, detailing the least number of genes that the bacterium *M. genitalium* requires for survival and reproduction. Further concerns were expressed following the announcement of Venter's bacterial genome swap. Generally the media reports quickly dismiss certain concerns, celebrate the research, and present a rather balanced approach⁵², e.g.:

Would a synthetic bug cause havoc if it escaped from the lab? No, because it's too weak to survive in the wild. Could synthetic biology be used to build bioweapons? Yes. ... By the way, isn't it mindblowing that "life" can range from a gaggle of 400 genes mooching about in a Petri dish, to a free-thinking assortment of 30,000 genes, with sparkling eyes and heartstopping dimples?
Anjana Ahuja, 'Life is Just a Bowl of Petri' The Times July 2nd 2007

Scientists have converted an organism into an entirely different species by performing the world's first genome transplant, a breakthrough that paves the way for the creation of synthetic forms of life. ... The work is at the cutting edge of synthetic biology ... But critics fear the field is progressing too fast for society to grasp. Some are concerned that artificial organisms could escape and damage the environment, or that maverick scientists or terrorist groups could create powerful new bioweapons.

Ian Sample, 'First genome transplant turns one species into another' June 29th 2007

The ETC however were very critical and wrote to Venter and the patent authority asking that it be withdrawn or rejected on the basis that it was contrary to the public morality and safety. They claim that the patent application represents a "high-stakes commercial race to synthesize and privatize synthetic life forms" [ETC Group 2007c]. They raise many other fears such as potential misuse of the organism, including creating a biological weapon and also ask, "How could their accidental release into the environment be prevented or the effects of their intentional release be evaluated?" [ETC Group 2007c]. They draw comparisons to other controversies including the Dolly clone and are sceptical about the promise of synthetic biology:

Synthia may not be as cuddly as a cloned lamb, but we believe this is a much bigger deal. ... It's purely speculation and hype that says [synthetic living organisms] will be used to ameliorate climate change by producing cheap

⁵¹ <http://blog.wired.com/wiredscience/2008/01/venter-institut.html>

⁵² It is interesting to note that in the review of UK newspaper reports of synthetic biology undertaken for this paper, there were few signs of sensationalist reporting, with most journalists writing in a balanced manner that, if anything, underplayed the debate on the social and ethical issues raised by this technology.

ethanol or hydrogen ... The same minimal microbe could be harnessed to build a virulent pathogen that could pose grave threats to people and the planet.

Jim Thomas, ETC Group 'Patenting Pandora's Bug' June 7th 2007 [ETC Group 2007c].

A major issue raised by the critics of this technology is that by their very nature biological machines are evolutionary machines; they are subject to natural selection and potentially gene flow [Benner and Sismour 2005]. This means that mutations in the genome of the synthetic organisms could produce unexpected interactions with the environment and other living, natural organisms. Considering the myriad unusual functions enabled by BioBricks that could be integrated in synthetic genomes, a concern is that functions upon which nature has never operated may provide advantages over natural organisms leading to unexpected proliferation of a synthetic biology product, thereby radically altering the ecosystem. Microorganisms intended for clean up of one particular chemical may interact with others, potentially passing synthetic genes to natural species thereby "contaminating" the gene pool [Tucker and Zilinskas 2006]. It's also claimed that even without such evolutionary intervention the released species may interact with naturally existing substances and cause unexpected side-effects [Bhuktar 2005]. These fears are reminiscent of the concerns voiced by anti-nano groups and individuals such as Prince Charles, who famously envisaged a world reduced to "grey goo" by out of control nano machines⁵³.

In this context questions have been asked about the adequacy of existing regulatory regimes for the control of GMOs, which are based on assessing relatively simple genetic changes to bacteria [Schmidt, 2008]. In particular, established risk assessment methods may not be adequate to deal with the much more complex changes brought about by synthetic biology, which involves the engineering of entire biochemical pathways. This challenge may require important changes to the methods and procedures used to assess the environmental risks posed by the novel organisms created by synthetic biology.

c) Scientific and Policy Response

These concerns are quite similar to those raised about the 'old' genetic engineering. A number of commentators have suggested that none of the more pressing fears about recombinant DNA has yet emerged as real threats due to early, strict regulation that was eased over the course of the field's maturation [Tucker and Zilinskas 2006; Garfinkel et al. 2007]. Furthermore, in addition to working within the established regulatory regime, a number of technical measures have been adopted to tackle this issue. Specifically, the threat of escape and proliferation has been offset by engineering bacteria dependent on particular nutrients that don't readily occur in the natural environment, thereby significantly reducing their competitive capacity. Similar proposals are being made with regards to using synthetic components of the DNA structure (e.g. synthetic amino acids) such that the organism cannot replicate in an environment devoid of them. Other strategies involve utilising some of the naturally-inspired⁵⁴ BioBricks that monitor the size of the population as it divides. These could be connected to a 'self-destruct' mechanism that is triggered should a population spurt occur or should the population density become too great [Benner, S.A. and Sismour, M. 2005]. It has also been suggested that engineering biological systems to reduce their viability outside the lab should become common practice [Church 2005]. Tucker and Zilinskas [2006] advocate the precautionary principle,

⁵³ <http://news.bbc.co.uk/1/hi/uk/3883749.stm>

⁵⁴ Quorum sensing

'treat synthetic microorganisms as dangerous until proven harmless.' Using the NIH guidelines for genetically engineered microorganisms they suggest that any synthetic DNA containing BioBricks would have to be studied under high levels of physical containment (level three or four).

A report, produced by Drew Endy of MIT, several of the J. Craig Venter Institute team and G.L Epstein from the Center for Strategic and International Studies proposes numerous 'options for governance' of synthetic genomics [Garfinkel et. al. 2007]. The authors attribute the current biosafety framework to the "foresight of the scientists who invented recombinant DNA" and argue that any proposed framework for synthetic genomics should be based upon this existent scheme, since it has "enabled the demonstrably safe development and application of recombinant DNA technology over the past three decades".

They identify six policy options to improve the safety of benign/beneficial synthetic genomics:

1. Education about the risks of, and guidance on best practice for, synthetic genomic experiments at the undergraduate and postgraduate levels
2. Production of a safety manual specifically tailored for synthetic biology labs
3. Development of a clearing house mechanism to dispense advice on best practice and emergency procedures
4. Broadening of the Institutional Biosafety Committees' (IBC) remit
5. 4 & - Creation of a National Advisory Group for extra-risky/novel experiments
6. Broader IBC review and enhanced enforcement of compliance with biosafety guidelines

The first two options form part of a 'modest' portfolio of options, these two combined with 4 and 5 may indirectly produce a more effective portfolio, but at greater expense. Implementation of all six options would, according to the report, represent an 'aggressive' policy towards biosafety.

6. Bioterrorism

a) Scientific/Technical Development

The development of biological weapons has a long history, with military programmes using advances in basic biology, including recombinant DNA techniques, to try to create new forms of offensive weapons [Dando, 1999]. In this context, it is notable that a CIA Report from 2003 [CIA 2003] painted a dark picture of the bioweapons future suggesting that some "engineered biological agents could be worse than any disease known to man" and that the genomic revolution had made such rapid progress that the traditional methods of monitoring weapons of mass destruction could prove inadequate. To ensure that the intelligence services remained knowledgeable on the potential applications of bioengineering the report suggests a closer working relationship with the biological science community. In the UK similar concerns have arisen about synthetic biology with the Ministry of Defence highlighting the field as one that may impact future military capabilities and in 2006 the Defence Science Advisory Council agreed to examine the military opportunities and threats arising from the field (Parliamentary Office of Science and Technology 2008).

The major issues about synthetic biology's ability to be misused centre around the production of known, modified or new microorganisms designed to be hostile to humans either directly or indirectly. The development, production and stockpiling of bioweapons is restricted under the 1972 Biological and Toxin Weapons Convention⁵⁵. Tucker and Zilinskas [2006] point out that synthetic biology not only allows for production of new forms of life, but also the synthesis of those that exist already. By reproducing known pathogens in the lab, such as influenza, one might be able to obfuscate the controls imposed on the movement of such organic substances.

Researchers funded by DARPA at Stony Brook University successfully synthesised polio virus from scratch [Josefson 2002]. The lead scientist, Dr. E. Wimmer, under criticism from the media and fellow scientists defended the research suggesting that it would not fuel bioterrorism since they created the virus from readily available components and that it underscored the need to continue vaccination against the disease [Josefson 2002]. Three years later another team of scientists published a paper in *Science* announcing they had sequenced and built the pandemic Spanish Flu virus of 1918 [Tumpey et al. 2005], which killed an estimated 20-50 million people worldwide. This research was undertaken to understand the virus in more depth, since much that was known about it was largely speculative. It was also hoped that the research would help scientists understand virulent flu viruses more generally. An editorial of the same issue of the journal *Science* defends its production and publication [Sharp 2005]. Craig Venter described this as the 'the first true Jurassic Park scenario'⁵⁶.

b) Social and Ethical Issues Raised

Though researchers in the field are quick to point out the potential ethical dilemmas and social implications, or at least acknowledge that they need to be investigated⁵⁷, the media has continued to see this as a major issue. In 2006 a Guardian reporter ordered part of the DNA sequence of the smallpox virus and had it sent to his home [Randerson 2006], which raised questions about the regulation of DNA sequence supply. An article in the *New Scientist* [Aldhous 2005] on the sequence suppliers found that, "Of the 12 companies that replied [to their communications], just five said they screen every sequence received. Four said they screen some sequences, and three admitted not screening sequences at all". The Guardian article [Randerson 2006] also found that of three UK sequencing companies, "one did not screen customers or sequences, one carried out checks on customers only and a third checked customers and had carried out a pilot study on screening DNA orders but is not currently doing so." The major question raised by these reports is that if a Guardian or *New Scientist* journalist can order and be supplied with genetic sequences from dangerous pathogens then who else may have, or may be able to do so?

Whilst the academic community continues debating regulation and ethics, biohacking or 'garage biology' is, according to some media reports [Rowan 2006], being established as a home hobby. As DNA sequencing becomes cheaper and quicker and second hand equipment becomes available on eBay the power to create synthetic sequences may be dispersed to many individuals and groups. Biohackers have also become known by the portmanteau 'biopunk' (biotech punk)⁵⁸, that has its

⁵⁵ Available here: <http://www.fas.org/nuke/control/bwc/text/bwc.htm>

⁵⁶ <http://webcast.berkeley.edu/events/details.php?webcastid=15766>

⁵⁷ As evidenced in most scientific reviews of the field and the few ethical reviews

⁵⁸ <http://en.wikipedia.org/wiki/Biopunk>

origins as a science fiction genre. The most recent, and significant addition to this movement has been the online publication of a 'Primer for Synthetic Biology', a manual, written in simple, non-technical language, for those wishing to engage themselves in some bio hacking [Mohr 2007]. Interestingly Mohr, a student at Boston University at the time of writing, includes in his 72 page draft a notice of intent to provide an outline of the key ethical issues facing synthetic biology titled 'ethics for everyone'. Though biohacking is beginning to develop a web presence, and is certainly becoming quite prominent in the blogosphere there is little evidence, as yet, that it has any active/practising following. Tucker and Zilinskas identify two potential terrorist categories: the 'lone operator' and 'the biohacker'. The lone operator is a rogue synthetic biologist and the biohacker is, as above, a college kid eager to demonstrate their technological prowess. If indeed second hand tools for genome assembly are becoming available to the public at affordable costs then this would seem to add weight to the concerns over possible terrorist use of synthetic biology research.

However, Tucker and Zilinskas [2006] argue that 'At present, the primary threat of misuse appears to come from state-level biological warfare programs'. They suggest that the construction of an entirely new pathogen using synthetic sequences is unlikely given the present state of the art and that the more likely threat is from the creation of already known pathogens, such as polio, as discussed above. The technological obstacles to producing either pathogen are seen as a limiting factor that renders synthetic biology no more concerning than previous debates about genetic engineering [Tucker and Zilinskas 2006]. Furthermore, even if such organisms could be produced, they are hard to 'weaponise' – something which would be essential for their role as offensive weapons or instruments of terror.

Whilst the prospects for the creation of biological weapons based on synthetic biology remain contentious and uncertain, a more fundamental problem has been raised about the level of awareness within the scientific community of the potential military uses of the technology. Most proposals for governance and oversight depend on scientists being aware of and reporting potential misuses. However, this in turn will critically depend on researchers being aware of the possible applications and risks of synthetic biology. A recent study carried out by Alexander Kelle found a low level of awareness of the key policy documents and debates about biosecurity amongst synthetic biology researchers in Europe [Kelle 2007]. This raises major questions about how easy it will be to implement any such measures in this area.

c) Scientific and Policy Response

The US policy agency, the National Science Advisory Board (NSABB) Working Group on Synthetic Genomics produced a report that addresses itself to the dual use nature of synthetic genomics – meaning that technology and knowledge from the field can be both used and misused for and against the public health and national security [NSABB 2006]. The working group sought to establish whether the existing regulatory framework for Select Agents was sufficient to cover the generation of synthetic organisms *de novo*. They highlighted a potential difficulty with the present regulatory framework with regards to identifying whether or not a synthetic organism is a Select Agent due to problems with screening sequences that may not exactly resemble those covered under SAR⁵⁹. Following consultation with various groups⁶⁰ the NSABB considered and rejected a number of proposals, including:

⁵⁹ Select Agent Regulation

- Restricting access to new sequence information about Select Agents;
- Monitoring the sale of chemicals and lab equipment used to synthesize DNA;
- Voluntary/involuntary surveillance/tracking of researchers/students using or trained to use synthetic genomics;
- Modifying the SAR so that all select agent genomes are covered; and
- Modifying the SAR or issuing new regulations defining Select Agents in terms of their sequence.

The four recommendations that the working group settled on were:

1. The HHS⁶¹ and USDA⁶² should collaboratively disseminate harmonized guidance to investigators and suppliers on the SAR in relation to synthetic biology
2. The USG⁶³ should: instruct federal agencies and outside experts to improve the screening process; require federal grantees and contractors to order from providers that screen; encourage international collaboration on establishment of standards and practices
3. Repeal statute 18 U.S.C. 175c which makes it illegal to produce, synthesise or engineer any part or whole variola virus. Examine the current language to ensure that it fully covers synthetic organisms.
4. The USG should invite examination of the SA classification system to ensure it meets the requirements of future scientific development and to consider alternative frameworks.

The Sunshine Project, an anti-bioweapons NGO, argued that there was a conflict of interest at the NSABB [Sunshine Project 2006]. In particular, the Project claimed that the NSABB has set up a working group to ostensibly make recommendations for the safe government of synthetic biology, but that it ‘will instead assault regulation of a wide range of biodefense and biotech risks’ [Sunshine Project 2006]. This, they argued, came from pressure exerted by powerful scientists on the NSABB and the working group. The Sunshine Project identified a competition for funding between two scientific camps: synthetic biologists and infectious disease researchers. Whilst the two compete for funding they have a shared common goal, “to take down what they perceive as a threat: biosecurity legislation designed to protect the public” [Sunshine Project 2006].

The Sunshine Project has been very sceptical about the report and suggests that the findings and recommendations are not logically coherent. They go even further and argue that the report is a pre-emptive attack on the regulation of synthetic biology and the SA rule to free up regulatory space for the development of synthetic applications.

Where the Sunshine Project, along with many other civil society organisations, advocate external regulation, the majority of the scientific community seek to establish self-regulatory practices. In preparation for debate on self governance at the Synthetic Biology 2.0 conference, Maurer, Lucas and Terrell [2006] produced a report on safety and security. Their document argues that self regulation is important,

⁶⁰ Practising synthetic biologists, representatives from the intelligence community, organisations that have conducted or are conducting policy studies on the implications of synthetic genomics or synthetic biology, and federal agencies responsible for implementing and enforcing the SAR.

⁶¹ Department of Health and Human Services

⁶² Department of Agriculture

⁶³ United States Government

but that it shouldn't 'necessarily displace traditional interventions based on regulation, legislation, and treaties' [Maurer et. al. 2006]. They argued that the difference between the ethical problems associated with more traditional biotechnological developments and synthetic biology are minor and suggested the risk posed by synthetic biology is relatively small. The four main areas of concern in the paper are: i) sequence screening; ii) community norms; iii) continuing debate; iv) technological solutions.

- i) The practice of screening genetic sequences by oligo companies is mixed. The paper suggests enforcing screening practices at the commercial side and a community pledge not to place orders with any company that fails to adequately screen from Jan 1st 2007. Furthermore, companies should interconnect to ensure that dangerous sequences are not split over multiple orders. Software for such screening should also be improved.
- ii) Synthetic biologists have a responsibility to ensure their work isn't making terrorism easier. An ethics advisory committee should be developed. Advice should be freely available and confidential, perhaps via an Ethics Hotline.
- iii) The ethics of synthetic biology are not fully clear and may change over time and as such debate must continue. An ethics 'clearing house' website where members could report potential accidents and biosecurity threats should be established. Creation of professional entities such as formal standards, codes of ethics, advisory bodies, and a professional society seem reasonable.
- iv) Synthetic biologists may be perfectly poised to develop solutions to ethical problems at the design level. Barcodes that identify the creator of a synthetic organism could be implemented and should be explored. Inherently safe organisms can be developed that do not survive and propagate in nature.

In reaction to these proposals for self regulation a 'global coalition of thirty-eight international organisations including scientists, environmentalists, trade unionists, biowarfare experts and social justice advocates'⁶⁴ wrote an open letter asking the Synthetic Biology 2.0 delegation to 'withdraw your declaration of self-governance and join with us in seeking a wider inclusive dialogue' [ETC Group 2006]. A *Nature* editorial following the conference [Nature 2006] argued that self-governance does not preclude other forms of regulation and voiced some suspicion about the motivations of the signatories with respect to campaign practices.

As has been described elsewhere several synthetic biologists co-authored a report on 'Options for Governance' of the field [Garfinkel et al. 2007]. The focus of that report was on biosafety and biosecurity. Their recommendations as regards enhancing protection against synthetic biology becoming a tool of biological warfare focus on recommendations to be implemented at four levels: (1) gene firms; (2) oligo manufacturers; (3) DNA synthesisers; and (4) users and organisations. Recommendations include such things as:

- 1&2 (Gene firms/Oligo manufacturers): firms must screen orders and biosafety officers must verify applications.
- 3 (DNA Synthesisers): Equipment must be registered and licensed and a license must be required to purchase reagents and services
- 4 (Users and Organisations): broaden IBC review and creation National Advisory Board

⁶⁴ http://www.etcgroup.org/en/materials/publications.html?pub_id=8

The debate over policy options clearly demonstrates that many synthetic biologists are highly concerned about ethical issues, both in regards to not wanting to cause harm and not wishing to lose the promise of synthetic biology to unwarranted media, public controversy or regulation. Others fear the concentration of power over policy, arguing that those practising the science cannot also be those regulating it. In particular, they suspect that science will be supported by governments irrespective of its potential risks and that public concerns are being sidelined.

All measures to control the potential misuse of synthetic biology, including self-governance and statutory regulation, critically depend on policymakers and researchers being vigilant. Evidence of a lack of awareness of the potential threats to biosecurity posed by synthetic biology within the scientific community must therefore be addressed as a matter of priority in order to meet this challenge.

7. Patenting and the Creation of Monopolies

a) Scientific/Technical Development

A major aspiration of synthetic biology is the alteration of microorganisms by genomic intervention for production of living machines that can turn biomass into fuels such as ethanol or hydrogen. Venter's team hopes to produce a synthetic form of *Clostridium* by amalgamating the genomes of two separate species, *Clostridium cellulolyticum* and *Clostridium acetobutylicum*, that together could do just that [Ball 2007]. This application is garnering a lot of funding from multiple sources with the Joint BioEnergy Institute, a team of national US laboratories, expecting \$125m over the next five years from the US Department of Energy⁶⁵. As huge amounts of money are being invested in synthetic biology groups it is clear that there are high expectations of a significant commercial return.

b) Social and Ethical Issues Raised

One of the main issues raised is that synthetic biology falls into US intellectual property 'at the confluence of biotechnology and computing' [Rai and Boyle 2007]. Rai and Boyle highlight that patenting appeals have proven a rather problematic case for the Federal Circuit Court of Appeals, which has consistently ignored the 'obviousness' clause of patent legitimacy, relying instead on *per se* rules developed for 20th century chemical inventions. Coupled to this are the problems that software caused by neither fitting into the intellectual property regime of patents or copyrights; an issue that was hardly resolved by forcing it under both. Rai and Boyle suggest that difficulty with the way in which the law handles software and biotechnology individually could come together to form 'a perfect storm'.

There are two major concerns about the intellectual property puzzle of synthetic biology, namely patents that are too broad and those that are too narrow. The difficulty is that broad patents may restrict collaboration and stifle development in the field, and narrow patents may over-complicate the process, meaning that hundreds of patents have to be negotiated to produce a system from standardized parts.

The spur for debate on the IP problems surrounding synthetic biology has come from Venter's patenting of Synthia. He hasn't only sought a patent for the minimal living cell in the US, but also at the international level through the World Intellectual

⁶⁵ <http://jbei.lbl.gov/team.html>

Property Organisation⁶⁶. More recently Venter has filed patent applications for making synthetic genomes (UPSTO no. 20070264688) and putting them into cells (20070269862). The ETC Group claims that Venter's 'enterprises are positioning themselves to be the Microsoft of synthetic biology' [ETC Group 2007b], or what they called Microbesoft [Anjana Ahuja 2007]. ETC argues that the landmark ruling of *Diamond vs. Chakrabarty*⁶⁷ opened the door to patent all biological products and processes, and that synthetic biology easily fits into its scope. Other than the detraction to potential research on synthetic biology the ETC Group doesn't expand on why such a monopoly on synthetic life forms should be avoided.

c) Scientific and Policy Response

MIT's BioBricks project has been setup as a way round the restrictions placed on innovators by broad patent claims and hopes to replicate the open-source software movement. Since 2004 the registry has increased from around 100 available parts to approximately 2,000 in 2008. The BioBricks Foundation (BBF)⁶⁸ is a non-profit organisation established to ensure that the parts produced for the registry remain freely available to the public. As part of that goal the BBF has trademarked 'BioBrick' and 'BioBricks'. This project has been referred to as a 'Synthetic Biology Commons' [Rai and Boyle 2007]. Rai and Boyle suggest that copyright backing for the commons might not be easily attainable and patents may prove far too expensive for a not-for-profit organisation. A possible solution may lie in their analysis of recent movements in statements of non-assertion, whereby those that hold patents on parts may make a statement to the effect that they promise not to assert their right over academic researchers. Another possibility they identify is the 'Clickwrap' license, as used in the International HapMap project that disables those purchasing the license from patenting products utilising the SNP data and from distributing it to anyone who has not also signed the license.

Henkel and Maurer [2007] point out that the development of registries of standardised parts is likely to stimulate the emergence of competing libraries that may seek to license the entire library rather than individual components: "Suppose that Company Y owns 70% of the most popular parts and Company Z owns the remaining 30%. Then, Company Y can get 100% of the business by offering a complete suite of whatever parts that the users need, that is, turning the contest into a competition between libraries instead of individual parts." This potential problem of monopoly stems from what economists call a network effect, wherein the competition between parts is mediated by reducing costs as some parts are used more frequently than others [Henkel and Maurer 2007]. Costs reduce as experience increases. Thus a part may become 'locked in' by being used more initially: those in the network benefit by using the same parts over and over; whilst other competing parts become used less frequently and may ultimately fall out of use. This is known as a 'tipping dynamic'. Henkel and Maurer go on to argue that the challenge to the open-source synthetic biology movement is to foster the design of institutions that encourage appropriate decision making as regards patents. They cite research that they say indicates companies can earn more by sharing information rather than hoarding it. They provide a further alternative to Rai and Boyle's [2007] versions of the patenting puzzle by suggesting that the registry be open only to those whom agree to make the parts they develop similarly available, perhaps after a specified number of years of

⁶⁶ number WO2007047148

⁶⁷ <http://digital-law-online.info/cases/206PQ193.htm>

⁶⁸ http://openwetware.org/wiki/The_BioBricks_Foundation

royalty returns. In a presentation given at SB 3.0⁶⁹ Henkel and Maurer indicated that parts of the MIT registry were already patented and that the registry may benefit from making it clear which these are so that researchers can avoid using them. They conclude that synthetic biology will require a mixture of IP and open-source.

Whereas Rai and Boyle [2007] fear the intellectual property ‘perfect storm’, a *Nature* editorial [Nature 2007] considered this conjunction to be more a ‘tempest in a test-tube’. The editors claim that Venter’s patent looks unlikely to be awarded on the basis that (a) it doesn’t give sufficient information to enable an expert in the field to make or use it; and (b) many of the non-essential genes described are already in the public domain. However, if Venter’s patent application for the minimal genome is successful then he could monopolise the market for biofuel production. Henkel and Maurer [2007], as paraphrased above, indicate that via the ‘tipping dynamic’ early leaders in a field may become steadily entrenched over time and come to dominate. Indeed Venter’s plans do sound grand, he told the Sunday Times, “Obviously, if we made an organism that produced fuel, that could be the first billion or trillion-dollar organism” [Sunday Times 2007] and according to the Guardian he plans to do it within a decade [Ian Sample 2007]. The question, asks the Sunday Times is, “who will benefit most - Venter or mankind?”

8. Trade and Global Justice

a) Scientific and Technical Developments

Perhaps the biggest success and at least the most applied research in synthetic biology to date has been in the production of terpenoids⁷⁰. These natural products are often isolated from plants and are used ‘as commercial flavour and fragrance compounds and antimalarial and anticancer drugs’ [Martin et al 2003]. It is for the purpose of producing antimalarial drugs that the Gate’s Foundation has funded a collaboration between UC Berkeley scientists, Amyris Biotechnology and the Institute for OneWorld Health. The particular compound, artemisinin, commonly known as wormwood [Herrera 2005], has found limited use because of the cost of extracting it from plant sources. At present, farmers in East Asia and some parts of Africa are growing wormwood for medicinal production. Thanks to synthetic biology the gene responsible, amorpha-4,11-diene synthase, and the mevalonate isoprenoid pathway from *S. cerevisiae* have been engineered into an *E. coli* for mass production [Martin et al 2003]. Due to increasing resistance to other drugs the synthetic artemisinin holds significant promise for malaria victims worldwide.

b) Social and Ethical Issues Raised

The ETC Group [2007] claims that the development of artemisinin has ‘become the *raison d’être* of synthetic biology and given the field a philanthropic sheen’. They draw a comparison to the poster child of the agricultural biotech industry ‘Golden Rice’ which was designed to feed the poor and tackle vitamin deficiencies. The ETC group suggests that the scale of the success has been drastically inflated to ensure continued funding of Keasling’s lab and that ongoing research on synthetic biology for such social and economic problems diverts resources from other more effective approaches. It is recommended by the WHO that artemisinin should be mixed with other malaria drugs, Artemisinin Combination Therapies (ACTs), to ensure that

⁶⁹ Available here: <http://www.syntheticbiology3.ethz.ch/proceedings/Henkel%20Maurer%20-%20On%20the%20economics%20of%20SB%20SB3.0%202007-06.pdf>

⁷⁰ A class of isoprenoid – a highly diverse family of natural products

resistance does not build up. However, ETC argues that Novartis has a virtual monopoly on ACTs and quote the Royal Tropical Institute of the Netherlands 'This monopoly-like situation has created an imperfect market defined by scarcity of raw materials, speculation and extremely high retail prices'. Critics contend that synthetic artemisinin would ensure that no local production of natural *Artemisia* could be stimulated or sustained, thereby maintaining the discrepancy of wealth and health.

The Gates foundation has been applauded for its charitable and practical aim, but it is not clear that producing a drug of this sort in developed countries is the best way of either eradicating malaria in the long term or supporting sustainable development in the poorest countries. As with many other advanced technologies, such as GM crops, when applied to issues of economic development, public health and global justice, a number of important questions are raised about the extent to which these innovations help tackle these problems or make them worse.

9. Creating Artificial Life

a) Scientific and Technical Developments

One of the core ideas in synthetic biology is the notion of creating 'artificial life'. This has simultaneously provoked fears about scientists 'playing God' and raises deeper philosophical and religious concerns about the nature of life itself and the process of creation. The principle area of synthetic biology to raise these issues is the production of life-like cells, which has been outlined above. Venter's team calls these minimal genome microorganisms, synthetic biologists more broadly may refer to them as chassis, those in the UK synthetic chemistry field have named them chells. Whichever term is utilised in this discussion, the significant feature of their controversy is that they may be alive through human invention. Indeed, a recent media furore [see for examples: Blakemore, 2008; Jha, 2008] was related to this project of life creation following the announcement of the synthesis of the first bacterial genome at the J. Craig Venter Institute.

A number of research teams have the creation of life-like cells as a major objective. For example, a consortium of 13 partner institutions has been formed under the banner 'PACE'⁷¹ (Programmable Artificial Cell Evolution) and has, as its mission statement, the goal of bringing the binary and living worlds closer together⁷².

b) Social and Ethical Issues Raised

The NEST high-level expert report [NEST 2005] indicates that the discussion of artificial life is likely to be prompted by public concerns over scientists 'playing God'. The same report welcomes the discussion on synthetic life, but cautions 'that it will be productive only if we can develop a more sophisticated appreciation of what is meant by 'life' than is current in popular discourse'. As witnessed by a number of media reports, there is a feeling that the science of synthetic biology may have outstripped our ethical reference points:

On the moral front, Mooney [of the ETC Group] says of Venter: "God has competition." To argue that the making of life should remain the province of a divine creator is no argument at all.

Anjana Ahuja, 'Life is Just a Bowl of Petri' The Times July 2nd 2007

⁷¹ <http://www.istpace.org/press/index.html>

⁷² http://www.istpace.org/svx_media/pace-ist-results.pdf

Fears have been raised about the dangers of tinkering with life and releasing malignant bugs. "We don't yet know what are the social, ethical and even bio-weapons implications of this research," said Hope Shand of the ETC technology pressure group. The most ominous note was struck by a scientist at MIT: "The genetic code is 3.6 billion years old. It's time for a rewrite." Feature, 'The Scientist Who Wants to put a Microbe in Your Tank' Sunday Times July 1st 2007

Scientists are a step closer to creating artificial life after transforming one type of bacteria into another. ... But the announcement has also triggered unease, with some critics warning that the scientists were 'playing god'. Reporter, 'Scientists 'Closer to Creating Artificial Life'' Daily Mail June 29th 2007

Synthetic biology has been touted as the discipline geared towards 'engineering life' [Chopra and Kamma 2006]. It is the notion of artificiality, the unknown quality, of synthetic biology's products that seems to underlie many of the aforementioned ethical concerns. Furthermore, the living, breeding nature of the synthetic biology output makes the threat of environmental contamination or the development of biological weapons so powerful. In this way, the ascription of the term life gives them agency; as though these microbes might seek to destroy us. It shouldn't be surprising then that this framing of the potential of biological engineering taps into the concept of risk and that some of the responses, particularly the regulative strategies outlined earlier that are aimed at identifying 'risky' engineers, are focussed on minimising potential harms whilst enabling scientific progress. However, such concerns are largely utilitarian, 'what might happen if this microorganism escaped?'

Whilst these arguments are brought to the fore what have been pushed to the edges of the scientific discourse are potentially more fundamental issues about tampering in natural systems and creating 'life itself'. It has been suggested by Edward Machery⁷³, a philosopher of science at the University of Pittsburgh, that a stable definition of 'life' is impossible and useless. Machery argues that synthetic biologists (amongst other researchers) are confused over what life is, where it begins and particularly, how complex it must be. This, he suggests, is no surprise and is consistent with a whole programme of 'life definitionism' that fails to confine its object. A similar set of issues have been raised in a recent *Nature* Editorial [Nature 2007], which notes that "Many a technology has at some time or another been deemed an affront to God, but perhaps none invites the accusation as directly as synthetic biology." It then goes on to argue that 'It would be a service to more than synthetic biology if we might now be permitted to dismiss the idea that life is a precise scientific concept.'

The final step in Venter's three step process of creating a synthetic organism involves inserting the synthesised genome into a bacterial cell and waiting to see if it springs to life. The publication of this information in January 2008 resulted in quite extensive media coverage with many articles leading with the life aspect: 'Scientist Creates Artificial Life – Almost'⁷⁴; 'Synthetic Life: Watch this Space'⁷⁵. The Economist concluded its article on the publication with the lines:

...if Dr Venter can take the final step of kicking the new, wholly synthetic genome into reproductive life, he will not only have made a great technological

⁷³ <http://www.pitt.edu/~machery/> - his paper was available for download but is no longer – he is currently (spring 2008) revising it.

⁷⁴ <http://www.time.com/time/health/article/0,8599,1706552-4,00.html>

⁷⁵ <http://www.newscientist.com/blog/shortsharpscience/2008/01/synthetic-life-watch-this-space.html>

leap forward, he will also have erased one of the last mythic distinctions in science—that between living and non-living matter.

Anon, 'Nearly There' The Economist January 24th 2008

Whilst others were less impressed:

But what does doing this really signify? What does it teach us about life that we didn't know before? There was indeed a time when scientists believed there was something fundamentally different about living matter and nonliving matter. It's called the Middle Ages.

Carl Zimmer, 'Artificial Life? Old News' Wired.com January 25th 2008

If Machery is right, that the idea of life is highly complex, but *can* possibly be defined by science, it would require multiple definitions across multiple fields. What implications might this have for an ethics that sought to trouble synthetic biology at the level of life definition? Put another way, if life is not a stable concept how might one argue that it is fundamentally immoral to create it? In contrast, if Zimmer is right that our definition of life, or at least the scientific definition, hasn't changed since the Enlightenment, then perhaps the claim to be creating life is less about heresy and more about hype. He argues that whilst being expertly technical and scientifically significant, the research doesn't reveal the mysteries of existence; in fact he argues that it doesn't even reveal the mysteries of genetics⁷⁶ and that creating a new living organism will lead to a whole new set of mysteries. In this sense we are a long way from playing God.

c) Scientific and Policy Response

This ontology of emerging objects, whether synthetic products are living or not, is being discussed by SynBERC, the NSF funded synthetic biology Engineering Research Centre⁷⁷. SynBERC's 'Human Practices' project, lead by Paul Rabinow (UCB) and Ken Oye (MIT), is also interested in general bioethical issues, security, health, environmental effects, and IP. The 'life' side of the project seeks to do such things as:

- Reflect on the form and essence of the parts, devices, chassis, and systems being created by synthetic biology;
- Analyze the differences between the objects created in older recombinant technologies and those projected in synthetic biology;
- Empirical research tracking how these parts, devices, chassis, systems, and test beds are designed and the ways that evolution and contemporary synthetic approaches differ from and enforce each other;
- Observe and design new institutional arrangements and interventions appropriate to the new objects being brought into the world;
- Eventual standardization of this new mode of productively assembling scientific, technological, economic, cultural, ethical, and security components.

Similarly, researchers from the PACE consortium have acknowledged ethical exploration to be part of its remit, though the development of this work is limited to date⁷⁸.

⁷⁶ Some 110 of the genes identified as being essential for life are as yet a complete mystery as regards their function.

Zimmer's column: http://www.wired.com/science/discoveries/commentary/dissection/2008/01/dissection_0125

⁷⁷ <http://www.synberc.org/humanpractices.html>

⁷⁸ http://www.istpace.org/research_by_partners/artificial_life_group_at_du/social_and_ethical_implicat.html

A number of the scientists involved in the chell programme have argued the case for a modified version of Turing's test for life imitation [Crowin et. al. 2006]. Turing developed a test as a response to the perceived uselessness of the question 'can this machine think?' Turing argued that the more pertinent and pragmatic proposal should be to assess to what degree the machine is capable of imitating living beings. He believed, incorrectly, that machine imitations would be sufficiently sophisticated by the year 2000 to be indistinguishable from human communications [Crowin et. al. 2006]. Others have found a longer history to the concept of an imitation test, with some tracing it to Descartes' observations on machines and men in his *Discourse on Method*⁷⁹.

The proposal made by the chell scientists is that the imitation test (or game) could be modified to allow for a more universal means of assessing whether something is living or not. They argue that such a method is required so 'researchers from a variety of communities ... [may] objectively recognize success' in creating life-like cells. Their version of life is one that requires individual self-replication, self sustaining systems, and a mechanism that allows for spatio-temporally resolved organisation of information within these systems, though they themselves find this somewhat restrictive [Crowin et. al. 2006]. The equivalent of the Turing test would be one in which the chell was able to interact with natural cells in an appropriate manner so as to be unrecognisable from those same cells. They foresee an ever increasing level of complexity in both their understanding of the cell in its natural environment and their capacity to imitate those processes such that the test for life becomes ever more stringent.

However, taking into account Machery's observations we may find that even the obfuscation of the more intangible questions, via use of a Turing-like test, there remains a fundamental barrier to translating the concept of life into a scientifically robust concept. Furthermore, it is unclear if these moves to undermine folk or lay concepts of life will ameliorate deeper fears about the blurring of the boundary between the artificial and the natural world.

10. Conclusion and Recommendations

This report has argued that synthetic biology should be understood in terms of both well established traditions within molecular biology and as an emerging field in its own right. The idea of biological engineering has a long history and can be seen as a central motif in 20th century biology. However, this promise has only started to be realised as the speed and scale of existing technologies has increased. In this sense, there is nothing completely new about synthetic biology that hasn't already been discussed in relation to the earlier development of molecular biology, recombinant DNA and genetic engineering. Debates about biosafety, bioweapons and the ethics of engineering life all took place in the 1970s and 80s.

However, it is also important to recognise that something new and important is happening. In part this represents a growing confidence in the scientific community to undertake the project of engineering life, but it also marks the maturity of a series of powerful technologies, which are converging with other developments in computing,

⁷⁹ <http://plato.stanford.edu/entries/turing-test/>

materials science and nanotechnology. Furthermore, synthetic biology can point to some important success, both in terms of creating new technology platforms, and in developing practical applications in the manufacturing of drugs and the synthesis of pathogenic viruses.

Despite its novelty, it is clear that the emergence of synthetic biology is following a now well established path in terms of the debates about the social and ethical issues. Many of the early fears surrounding the growth of recombinant DNA have never come to pass, but this is, in large part, due to the creation of robust governance regimes at local, national and international levels that have controlled the applications of the science and technology. These have included rigorous containment measures and multilateral controls on some aspects of their military use, as well as public debates over sensitive ethical issues. This is not to say that all concerns have been successfully resolved, but it points to a continuing dynamic in relation to synthetic biology, where societal issues will have a major influence on the funding of science, the types of technologies developed, their application in the real world, how they are ethically framed and the extent of regulation. The history of genetic engineering tells us that these debates can sometimes be long and difficult, but that they have been essential to negotiating uncertainty around the risks and benefits of the technology, regulating its socially acceptable use, and addressing concerns over who should control it. In this way, we can think of the science, technology, regulatory frameworks and social implications as co-evolving through a process of mutual shaping.

Another important lesson from the development of biotechnology over the last 30 years is that whilst the technology holds great social and economic potential and rapid scientific progress is possible, it is far more problematic to translate this knowledge into real world applications outside the laboratory [Nightingale and Martin, 2004, Martin and Morrison, 2006]. High expectations of both the promise and threat of synthetic biology should therefore be tempered by a realistic sense of how difficult it is to create successful new biotechnologies.

10.1 Responding to the Challenge

How then should different stakeholders respond to the challenging issues raised by synthetic biology? Firstly, it is vital to recognise the importance of maintaining public legitimacy and support. This is an important principle in its own right, but is also imperative if funding and other forms of institutional support are to be maintained. This was clearly shown by the decline in public funding for the genetic modification of crops following the GM food controversy in Europe in the 1990s. In order to avoid this scientific research must not get too far ahead of public attitudes and potential applications should demonstrate clear social benefits. Furthermore, the potential benefits of the technology must not be overhyped or this risks both creating excessive public anxiety and unrealistic hopes that cannot be fulfilled.

Secondly, the scientific community must take, and be seen to be taking, a lead in debating the implications of their research and engaging with broader society around the issues raised by synthetic biology. It is not sufficient to wait until particular issues arise through the practical application of the technology, as this will be too late. Public debates do not develop in a linear or rational fashion, but are unpredictable and driven by often deeply held cultural attitudes to nature, the environment and the place of science. Anticipatory intervention is therefore essential.

Thirdly, partnership with civil society groups, social scientists and ethicists should be pursued as a highly effective way of understanding critical issues, engaging with publics and winning support for emerging scientific fields. However, at the same time it must be recognised that this is a two-way process and that some ethically problematic scientific projects and potentially controversial technologies may have to be abandoned in order to maintain trust. From this perspective, experiments in upstream engagement and public consultation should be undertaken as they provide a valuable channel for helping negotiate the boundaries of what is socially acceptable science.

Finally, a robust governance framework must be in place before many of the applications of synthetic biology are realised. This will require a thorough review of existing controls and regulations, and the development of new measures in the areas highlighted in this report, particularly relating to biosafety, environmental release and biosecurity.

Research agencies, such as the BBSRC, therefore have an important role, not just in terms of funding the best science, but also in steering and shaping the field so that research is undertaken in a way that ensures ongoing public support and helps realise the potential social and economic benefits of these powerful technologies, whilst controlling their risks in a way that reassures both the public and the scientific community.

Given the pervasive nature of synthetic biology and its potential for widespread application in what ultimately may be a mundane fashion, its development and application will need to be governed at multiple levels and using a range of policies and practices. These may include the establishment of new professional norms in the scientific community (e.g. codes of conduct concerning dual use technology), local and national research oversight, statutory regulation (e.g. new laws and formal regulatory agencies) and international co-operation and treaties. Such a multi-level governance framework will have to provide a robust overarching framework, whilst respecting different national traditions and empowering local enforcement. It will also have to be fully supported by the scientific community and other professional groups involved, through a process of training and awareness-raising. Finding the right balance between formal statutory regulation and self-regulation of the scientific community remains a contentious issue and will occur only after the risks of synthetic biology are more widely understood and debated.

In thinking about how synthetic biology might be governed a number of important questions must be answered:

Biosafety

- Are there new potential threats posed by synthetic biology in terms of risks to health?
- Does synthetic biology require new forms of risk assessment and governance beyond those already used in relation to established practices of genetic engineering?

Environmental release

- Are there new potential threats posed by synthetic biology in terms of the risk of unplanned release and damage to the environment?
- Under what circumstances could synthetic biology based products be safely released into the environment?

- Do existing risk assessment procedures and controls on the release of GMOs adequately cover novel organisms created using synthetic biology?

Bioterrorism

- What problems are posed by synthetic biology in terms of the development of new technologies and capabilities for the development of biological weapons by individuals, states and non-state groups?
- Do established international regimes for the control of bioweapons need to be amended to incorporate the introduction of synthetic biology?
- What measures should be taken to increase awareness within the scientific community of the biosecurity issues surrounding synthetic biology?

Scientific and economic monopolies

- To what extent are broad patents being granted that might lead to monopolies over the exploitation and application of synthetic biology?
- How can policy be developed to balance the claims of inventors and broader public interests to promote scientific research and affordable access to new technology?

Exacerbating global inequalities in trade

- To what extent will synthetic biology create new, or exacerbate existing, inequalities in international trade and development?
- What measures can be taken to promote global equity in areas most affected by new technologies such as synthetic biology?

Creating artificial life

- To what extent does synthetic biology fundamentally challenge established notions of what constitutes life?
- How can constructive public debate on the cultural and philosophical implications of advances in synthetic biology be fostered?

Addressing the important questions raised by synthetic biology should be a policy priority for government, research funders, and the scientific community in order to ensure that it realises its potential in a way that is ethically acceptable and commands broad public support.

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