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**SYNTHETIC BIOLOGY**

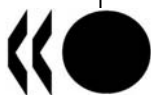
**REPORT FROM THE SYMPOSIUM ON "OPPORTUNITIES AND CHALLENGES IN THE  
EMERGING FIELD OF SYNTHETIC BIOLOGY"**

**8-10 February 2010**

For further information, please contact: Ms. Marie-Ange Baucher, tel: +33 1 45 24 94 22; email:  
marie-ange.baucher@oecd.org

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**NOTE BY THE SECRETARIAT**

This paper is a draft of the Synthesis Report of the Symposium on “Opportunities and Challenges in the Emerging field of Synthetic Biology” which was jointly organised by the OECD with the US National Academy of Sciences (NAS) and the Royal Society, the 9-10 July 2009 in Washington DC, United States. This summary has been prepared both by the OECD and the Royal Society. This is a work in progress. This draft is, at the moment, still being reviewed by organisers of the symposium. The final version will be released by the end of February 2010.

For more information about process and future projects on synthetic biology to be held within the WPB in 2010, please see paper DSTI/STP/BIO(2009)12REV1.

Delegates to the Working Party on Biotechnology are invited to:

- **Note** the Synthesis Report of the Symposium held in Washington DC on 9-10 July 2009.

## ANNEX

**SYMPOSIUM ON OPPORTUNITIES AND CHALLENGES IN THE EMERGING FIELD OF  
SYNTHETIC BIOLOGY**

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## **Introduction**

Synthetic biology is a dynamic and highly promising blend of science and engineering which aims to construct novel biological entities and to redesign existing ones. It is a new field, but one that has already stimulated substantial discussion over the power of its technical possibilities, its role in addressing key global challenges, and its use in increasing our understanding of biology. Further discussion has focused on burgeoning social, ethical and regulatory questions, and a conversation over the field's economic potential has opened up. Thought toward synthetic biology's position in national and international science and governance strategies has begun.

The myriad issues raised by synthetic biology are likely to be differently conceived and paid differing levels of attention across the international landscape, impacting on the development of the field, and on the realisation of benefits. The opportunities and challenges of synthetic biology therefore need to be understood and addressed on a global scale. This report, and the symposium on which it draws, intends to help this process.

## **Key points**

- Synthetic biology was presented as a set of tools and techniques that mixes engineering and biology and supports the development of new functions or applications. New applications in areas such as medicine, energy, environment and materials may be developed. Synthetic biology also aims to increase understanding of biological systems; in particular, it may offer an approach to managing complexity in biological systems.
- Focusing investments in foundation technologies, science, education and policy is crucial to assure a safe and efficient development of synthetic biology. Investments in automated technologies such as DNA synthesizers and combinatorial technologies are important in order to enhance research and optimize the time of researchers. Investments for rewarding and publishing advancements made in synthetic biology would also greatly stimulate the field.
- The gap between applications and tools and techniques must be bridged. Basic investments in both the development of tools and techniques are needed.
- It remains unclear how experience and knowledge gained from other emerging technologies are being drawn upon and used.
- Issues raised during the symposium which would benefit from further investigation and, in some cases, policy interventions at multiple levels, include:
  - Standardization of, for example, biological parts;
  - Intellectual property model shaping;
  - International collaboration and cooperation in the regulatory and governance environment for synthetic biology, as well as scientific and technical development and capacity building.

- Opportunities need to be created for public debate and discussion of synthetic biology. Part of the challenge will be developing a common and widely understood language to discuss ethical and social, as well as technical aspects of synthetic biology.
- Communication between the many stakeholders involved in novel technologies and science depends on different and complex factors and is also context dependant. It was recommended that the public should be involved in a healthy and open dialogue. More than a simple communication strategy, a real dialogue and engagement needs to be established with the public.

## **The Symposium**

Under the auspices of the United States National Academies, the Organisation for Economic Cooperation and Development, and the Royal Society, an international symposium entitled “Opportunities and Challenges in the Emerging Field of Synthetic Biology” was held in Washington DC on 9-10 July 2009.

This symposium brought together the different communities –scientific, engineering, policy, public, legal - involved in synthetic biology and explored the opportunities and challenges posed by this emerging field. The symposium was organised around expert presentations and discussions treating issues such as: the state of the field and its commercial and scientific potential; scientific, educational and commercial infrastructure needs; emerging financial and business models for its commercial development; the challenges synthetic biology may raise to legal and regulatory arrangements (e.g. biosafety, biosecurity, intellectual property rights); and the ethical dimensions of this new field.

This Symposium aims to foster the safe and efficient development of synthetic biology by identifying issues and areas for future study, and by informing policy-makers about synthetic biology.

Presentation slides, audio recordings and an unedited transcript of discussions at the symposium are available at [http://sites.nationalacademies.org/pga/stl/PGA\\_050738](http://sites.nationalacademies.org/pga/stl/PGA_050738). The agenda of the symposium is attached as an Appendix to this report.

The present report, prepared by the OECD and the Royal Society, aims to summarise discussions at the symposium and extract the emergent messages. It does not necessarily represent the views of the Royal Society, the OECD or the National Academies, or a consensus opinion of participants. The OECD and the Royal Society are grateful to those who gave their time to review this report.

## **Synthetic biology overview**

Over the last five or more years, synthetic biology has stimulated discussion and debate over the opportunities and challenges that it presents. The language of opportunities and challenges, adopted for the symposium, shifts attention away from only risk-benefit thinking, which lends itself to economic and other quantitative analyses, to focus on a wider conversation about the value of this emerging science. Risk-benefit analyses will remain important, but talking of opportunities and challenges helps us address the evolving nature of synthetic biology, the evolving public and policy conversation around it, and reminds us that risks and benefits shift and reconfigure over time: an opportunity one day may raise a challenge the next.

Synthetic biology arrives at time when the roles and positions for science in society are open to increased public discussion and debate. Difficult questions for science are posed, including: who gets to imagine the future of science; how do we decide which scientific and technological interventions we want to make to society; and who is responsible for the consequences of innovation, both positive and negative?

As we think through questions like these, Shelia Jasanoff argued that our imaginations are often limited. But the power of technologies like synthetic biology requires us to explore ways in which we might be ‘more in charge of the process by which imaginative futures enter our lives’.

### ***The scope of synthetic biology***

Drew Endy suggested that descriptions of synthetic biology tend to be limited. They typically emphasise one or more of the following elements: that synthetic biology is a natural science that contributes to expanding our knowledge of biology; that it is a synthetic science, analogous to synthetic chemistry, which seeks to construct novel molecules and systems for useful purposes; and that it is a technology available to engineers, again to put to useful purposes. It was argued that although accurate, descriptions in these terms are partial and tend to underplay key concepts in synthetic biology including ‘humanity’, ‘tools’ and ‘liberation’.

Following the call to expand our imagination, it was pointed out that synthetic biology raises opportunities for humanity at the same time as offering a revision of what humanity might mean. Synthetic biology intersects and can contribute to addressing key challenges facing the planet and its population, such as food security, sustainable energy and health. This potential raises questions for humanity including how we should (and how we will) change ourselves and our environments. Synthetic biology may be especially powerful in this respect because it liberates the design of biological systems from the process of natural evolution. The ability to first sequence and then synthesis DNA (and even to invent new base code) adds a new layer of power to nature: the ability to design and redesign biological systems in a manner that both encodes and enables humanity.

There have been significant inroads to meeting global challenges. The best known example remains the synthesis of artemisinic acid in *E. coli* and yeast. Artemisinic acid is a precursor to artemisinin, the most effective known anti-malarial drug. However, it was suggested that this achievement may better represent the high water mark of metabolic engineering. Relying on the tools of biotechnology and genetic engineering which have changed little in 30 or more years, success took several years and \$25m. However, resistance to artemisinin is already occurring even before the yeast-derived alternative has reached the market. For a more efficient and flexible biotechnology, new tools are needed.

Synthetic biology offers a ‘tool revolution’: to the established techniques of recombinant DNA technology, polymerase chain reaction, DNA sequencing, and more recently DNA synthesis, synthetic biology adds tools of abstraction (reducing information content to only that required to work with parts, devices, etc.) and standardisation (consistent definition and production of biological functions and biological parts). With new tools and concepts, synthetic biology holds promise to refine and extend metabolic and genetic engineering, and for developing ‘off the shelf’ components to bring an end to lengthy and bespoke biotechnology projects.

### ***Thinking and language for synthetic biology***

Paul Rabinow proposed further technical and non-technical features that may distinguish synthetic biology from previous developments in the life sciences, including: its emphasis on instrumental goods; a shift of attention away from the molecule and the gene as primary objects of interest; its attempt to render biology as an engineering discipline; and its endeavour to establish new collaborative ‘venues’ for scientific research. ‘Venue’ here means the organising concepts and forms of knowledge used, and not just the physical space within which these might be brought together and assembled.

Rabinow argued that synthetic biology requires refreshed venues with which to think through its significance, as well as the relative contributions of ethics and science. Frameworks developed for

recombinant DNA in the 1970's and then the genome sequencing effort in the 1990s fall short of the task, in part because the science and technology has evolved, but moreover because the social and political environment for this work has changed. Synthetic biology comes at a time of increased global exchange and connectivity, a changed security landscape, and the increased power and use of the internet, which facilitates the exchange of knowledge and materials. This, it was argued, pushes us to reconstruct our investigation of the technical, ethical and social aspects of synthetic biology and not rely on previous conclusions.

The Synthetic Biology Engineering Research Centre (SynBERC) in the US is critically examining the part synthetic biology plays in human wellbeing. It does this less in terms of any technical optimisation, but more in terms of asking what counts as a good life and what the biosciences may contribute. This metric (termed 'flourishing') takes over from previous metrics applied to the life sciences, including autonomy, security and responsibility. Whilst these are important, it was argued that they are not sufficient given the power and reach of synthetic biology.

Pushing this further, some argued that the continued value of established categories such as 'biotechnology', 'genetic', 'society' and 'public' is not even certain, although most discussants were hesitant to abandon these. It was more widely agreed that the meaning of terms like these is not fixed across natural language boundaries. The international character of synthetic biology sometimes makes it difficult to find mutually shared and consistent language, terminology and grammar. This is not limited only to its technical aspects. On the international stage, concepts such as risk, public good and ethics vary significantly. Communication across different sectors of the public also presents a challenge.

Yet, even if language and terms are yet to settle, the importance of starting and sustaining a conversation about synthetic biology was starkly described: we are at a point where we could fashion our own version of the living world but we must take collective responsibility for this. We need a 'post DNA-synthesis' conversation, one that must accompany the development of the science, and which allows us to revisit past conclusions on the basis of new information.

Participants discussed the difficulty of inventing structures and methods that would enable the public to access and influence the development of synthetic biology, given that the science is global, uncertain, contested and not currently part of popular culture and discourse. It was suggested that public discussion needed to begin with a realistic appraisal of the promise of synthetic biology, and that current visions for the field trade too much on unfounded hype. In reply, it was pointed out that it can be difficult to secure research resources without claiming that your science will help solve important problems. This may have an additional pay off in building interest and excitement in the public space outside of research and funding communities. The role of the public in this new conversation about synthetic biology was a recurrent theme in discussion throughout the symposium, and public engagement and dialogue is further discussed below.

### **National and international public policy**

Emerging national strategies and policies will play a role in the development of synthetic biology, but how they will impact on research, and their effect on grass roots activity and international exchange, is not currently clear. What is certain is that different nation states will differently intervene in the development of synthetic biology. A richer comparative understanding of national cultures of innovation will help us to recognise international differences as well as opportunities for collaboration and harmonisation. Toward this, three national perspectives were highlighted at the symposium:

### ***United States***

The US National Science Foundation (NSF) is a major federal supporter of basic research. The NSF has identified synthetic biology as a transformative field, which has the potential to deliver great knowledge and benefits to society, revolutionise and disrupt accepted research and theory, and destabilise markets. The NSF recognises that investigating and understanding social, ethical and public aspects of synthetic biology is essential if we are to devise what Arden Bement described as ‘sophisticated and subtle solutions, the very best we can devise’ to the challenges that synthetic biology presents. The NSF funds research into these wider aspects of synthetic biology at the SynBERC center, as well as SynBERC’s research on basic and applied research on synthetic biology. The NSF has also collaborated with the UK Engineering and Physical Sciences Research Council (EPSRC) in an intensive workshop (or ‘sandpit’) to develop and allocate funds to innovative projects in synthetic biology.

### ***United Kingdom***

Central funding for specific research projects is just one of a range of interventions that governments may make in synthetic biology, and governments play a higher strategic role in innovation. In the UK, Government sets the overall strategy for funding and research. However, once the funding has been distributed to the seven UK research councils, Government plays no further part in detailed decision-making about the particulars of research spending. The UK Government distributes around US\$9bn a year in this manner, which is augmented by other third sector funding partners such as The Wellcome Trust.

Synthetic biology is beginning to feature in the funding distributed by these research councils. Overall, around £17m has been allocated to synthetic biology projects and related activities. In line with much of the discussion at the symposium, Adrian Smith said, ‘the science and thinking about the science must continue in parallel’. As well as the EPSRC/NSF sandpit, Smith cited the EPSRC funded Centre for Synthetic Biology and Innovation (CSynBI) which bring together the scientific research labs at Imperial College London and the social science focused BIOS Centre at the London School of Economics. From the outset CSynBI will integrate scientific and social scientific research, just as SynBERC before it.

In a separate initiative, four UK research councils came together to put just under £1m into seven Networks in Synthetic Biology. Spread across eight institutions, the Networks are aimed at facilitating multidisciplinary working and finding a ‘common language’ between bioscience and engineering research groups. Some Networks are addressing the development of basic tools, whilst others are exploring specific technical challenges and applications. Some institutions involved in the networks, in particular the University of Edinburgh, the University of Cambridge and Imperial College, are developing education and training opportunities at undergraduate and postgraduate level.

Activities in the UK benefit from, and are often part of, activities taking place at European level. The European Union (EU) funds synthetic biology research through its general Framework Programmes, as well as via specific initiatives. The latter include the New and Emerging Science and Technology programme, which provided early stage funding for 18 synthetic biology research and policy projects, and Towards a European Strategy for Synthetic Biology (TESSY), which developed a research roadmap for Europe.

But for Adrian Smith remained an open question whether or not the UK Government should or need to develop a centralised innovation strategy for synthetic biology over and above the types of activities noted here. Investment in synthetic biology needs to be considered against competing investment opportunities. Moreover, the balance of responsibility between Government and other actors for issues such as security, ethics and public dialogue needs to be found. Interaction with business and industry will be crucial, especially as they will deliver many impacts and applications. The UK government regularly



engages with business leaders on a range of science and technology issues, and increasingly so over the last few years.

The regulatory implications of the field are currently closer to Government's immediate concerns. It was noted that the official view in the UK is that the majority of synthetic biology research will be covered by current Genetically Modified Organism (GMO) regulations and that there is no need, at present, for any new regulations relating specifically to synthetic biology. However, in discussion, it was suggested that it is common to assume that current regulations are suitable for new technologies because we are not in a position to neatly define these fields and draw boundaries around what is included or excluded. It was argued that this pattern holds for synthetic biology. In contrast, it was also argued that in genetic engineering's early days, regulators and others were quite clear on the nature of the science and its boundaries. This facilitated the construction of regulations. It was suggested this clarity is not available for synthetic biology, so self-regulation is likely to prevail.

### ***China***

In China, synthetic biology has only recently gained ground. Haunming Yang described China as a late comer to the field, as it was for genomics. From a search of public databases of all Chinese funding agencies, the first synthetic biology project to involve Chinese researchers was funded by the European Commission in 2006. The project – PROBACTYS: Programmable Bacterial Catalysts – involved scientists from the Beijing Genomics Institute in partnership with researchers from across the EU. Three further synthetic biology projects with centralised funding are currently underway and most research is undertaken at Government laboratories in Shanghai, Tianjin, Chengdu and Taipei, with a focus on metabolic pathway analysis.

Although early Chinese research in genomics and synthetic biology has benefitted from international collaboration stimulated by partners outside China, China is increasingly in a position to lead partnerships. For example, the Beijing Genomics Institute is the third biggest sequencing centre in the world and is an integrated part of international sequencing efforts. If synthetic biology is conceived as a natural extension of genomics – from the reading to the writing of genome sequences – then China is well placed to take an active part.

### ***Prospects for international collaboration***

Delegates discussed the challenges of international collaboration on several levels, from individual scientists and research groups, up to nation states and wider geographic areas. It was noted that the UK, along with other countries in Europe and the US, is positioning science and technology as an important part of national recovery in the current economic downturn. By making this part of a *national* strategy for recovery, there is a chance that international collaboration may suffer. It was pointed out that the link between science and innovation and economic growth is well founded. But it was suggested that the danger in emphasising science's economic potential is that it may lead to investment in areas of science with an eye on short term economic gain. To realise the benefits of synthetic biology, sustained, long-term investment is likely to be required. It was further suggested that international collaboration thrives on bottom-up, researcher led activity not determined by centralised policies.

International communication and collaboration amongst scientists, including those from emerging economies, will be a key part of the successful development of synthetic biology, but there remain system factors that work against it. For example, synthetic biology collaborations might be effected by the protection of intellectual property and security threats. International cultural and regulatory disjoints might also present challenges. It was suggested for example that China and other developing countries may benefit from genetically modified crops but have been pressurised by some European countries to reject

them. It was further suggested that China may lack an international forum to assert its views. However, there are notable examples of collaboration success; it was pointed out that collaboration played an important role in completing the human genome project and that, although painfully slow and difficult, international cooperation to mitigate climate change has made progress. Yang proposed the founding of an international synthetic biology consortium. This could promote communication and exchange, coordinate effort and resource, explore data sharing and consider international responses to biosafety and biosecurity challenges.

## **Innovation in Synthetic Biology**

### ***Enabling Innovation: Tools and Techniques***

Synthetic biology was presented as a set of tools and techniques that mixes engineering and biology and supports the development of new functions or applications. Caroline Ajo-Franklin specified that new functions include the ability to create new ecosystems by enabling intercellular communication, and novel regulatory networks in which the amount and why gene products are made can be controlled. The development of these tools and techniques underpin synthetic biology's promise to tackle challenges such as greener energy production (e.g. development of alternative energy sources such as biofuels), environment and health improvement (e.g. cellular therapeutics).

#### *A gap between tools and applications*

Synthetic biology promises to advance smart therapeutics. However, Christina Smolke described hurdles that still impede the use of synthetic biology for enabling innovation in health or other domains. Principally, there is a gap between technology and tools development and applications. Bridging this gap is an important step for assuring the growth of the field, but it still represents a significant challenge which is not often appreciated. It was argued that the difficulty of translating tools into applications rests on the following:

- First, the development of a tool, its refinement and optimization (e.g. going from the conceptual design of a function to a genetic sequence that fully implements the function) represents a significant technical challenge and therefore a significant investment of time and money.
- Second, it was highlighted that invention and implementation of engineering design principles into biology is critical to effective tool development and thus for the field to move forward more applications. However, the culture of biological research traditionally rewards novelty and does not equally celebrate engineering contributions. To enhance the whole contributions of synthetic biology, this tendency should evolve. Enhancing the engineering part of synthetic biology is becoming increasingly important.
- Thirdly, from a technology development point of view, it is important to develop computer-aided design tools which support the design and programming of devices and their implementation into systems. These types of tools are not developed and accessible enough at the moment.
- Fourthly, in order to address scalability, large libraries of refined parts would need to be set up. These libraries could also include many different classes of molecules such as: metabolites for those working on biosynthesis; disease biomarkers for those working on biomedical research; and exogenous chemicals for those working on agricultural biotechnology.
- Lastly, applications are generally narrowly directed to the end product and not towards developing a technology base to broadly support many different products. For instance, a

company often bases its strategy on the end product that it will be distributing. Investing in or integrating new tools and technologies is often not a priority when they do not directly lead to a specific product.

These arguments highlighted the importance of initially investing in tools development to move the field toward more applications. Thinking about strategies and mindsets that support the implementation of foundational technologies and tools was presented as a key point. Funding is also important to support tools and technologies development in synthetic biology at scales and time frames appropriate for the challenges that synthetic biology seeks to address.

Issues linked to intellectual property (IP) models and regulatory frameworks were also raised. The current IP model for biotechnology, in general, is heavy and might not correspond to the way synthetic biology is developing today. The need to see if synthetic biology fits within current regulatory frameworks was also seen as a key element to assuring the future of synthetic biology. For example, with today's ease of producing DNA sequences, Staehler highlighted the importance for companies, such as genetic tool provider companies, being involved in developing guidance for risk management. Groups such as the International Association for Synthetic Biology in Europe and the Synthetic Biology Industry Agency in the United States have taken a step forward in joining together companies and developing instruments – for example a code of conduct – for facilitating risk management in tools development.

### ***Eco-Innovation***

Industrial and environmental biotechnology was described as the third wave of biotechnology innovation (following healthcare and agriculture). James Greenwood highlighted that this increasing attention on innovation in industrial biotechnology is partly due to the major challenges that this century is starting to raise: How do we reduce our dependence on petroleum? How do we decrease pollution? How can we improve manufacturing processes so we generate less hazardous waste and use less energy? How can these processes serve the developing world as well as they do the developed world? These and many other questions were raised, and synthetic biology was presented as being able to help shape their answer.

### ***Synthetic biology, biotechnology and the chemical industry***

Sven Panke argued that biotechnology is increasingly used in the chemical industry for the following reasons:

- First, biotechnology improves the chemical industry's sustainability, and offers the qualities of recyclability, stability, and biodegradability of bio-based products as well as increased safety and sustainability of the production process itself. A good example of the latter is vitamin B12 production where about 12 steps of reactions have been replaced by a one-step fermentation thanks to bioprocesses. Another example is the use of biotechnology in amoxicillin production where 50 kilograms waste per kilogram of product in the 1970s had been reduced to 2-5 kilograms waste today.
- A second driver is the ease and efficiency of using biotechnology processes instead of chemistry to obtain certain end-products. For example, a product marketed under the name of Sorona and developed by Dupont, is a polymer composed of propanediol, a monomer easily made by biotechnology but synthesized with difficulty by chemistry processes. By looking at the life cycle analysis for this particular product, the energy required to produce a kilogram of propanediol goes down by 35 percent when using biotechnology. But when looking at the overall energy balance of making the polymer, the energy balance is pretty much the same as when not using

biotechnology. The primary interest in using biotechnology therefore is that the end product is simply much more easily produced by biotechnology.

What can synthetic biology bring into the chemical industry? Biotechnology in the chemical industry is today mainly about metabolic engineering. However, “traditional” metabolic engineering is raising some important challenges because of the complexity of metabolic pathways. The example of the production of a pharmaceutical composed of five precursors was given to illustrate this complexity. The easiest way of producing such a molecule would be identifying the enzymes that help convert glucose to these five precursors in a certain number of steps, putting them all together in a reactor and finally obtaining the end product. However, control over reaction pathways is difficult to achieve and, for example, there is a possible accumulation of particular intermediates which creates unbalance and may be toxic for the cell, making the system collapse. Because of the complexity of biological systems, chemical processes are sometimes considered to be more reliable than biotechnology which accounts for some of the delay in delivering biotechnology promises in this industry.

Complexity in biological systems frustrates their engineering, and is colourfully described by engineer Endy: ‘Engineers hate complexity. I hate emergent properties. I like simplicity. I don’t want the plane I take tomorrow to have some emergent properties while it is flying’. Metabolic engineering hardly tackles the issue of complexity, but synthetic biology may be able to address it. For example, minimal chassis strains might allow evading the issue of interconnectivity and complexity of biological systems. It was argued that synthetic biology would allow reducing complex networks to small ones and rationalizing the design of the desired pathway. The pathway would thus be fitted into a chassis strain (not the conventional microorganisms as *E.coli*) that will be able to run this particular pathway orthogonally avoiding extensive interactions with the remaining metabolism.

The production of the drug Artemisin by Amyris is the first example of the successful combination of synthetic biology techniques with traditional chemistry processes. Artemisin is now produced in a cheaper and faster way.

In order for biotechnology to accomplish all its potential in the chemical industry, synthetic biology was presented as essential. It would allow more predictable and faster chemical development. It would also allow the development of much more complex production pathways and novel products. Again however, some issues still impede a larger development of synthetic biology in the chemical sector. For example, the development of chassis strains is still at its infancy and there is also a lack of high quality parts registries. Access to material is not always straightforward, in part because of compartmentalized intellectual property structures.

Kinkead Reiling also highlighted that the scalability of synthetic biology tools is yet to be tested. Currently, synthetic biology works on a very small scale but industry needs to produce large amount of products, especially for biofuels. How can synthetic biology processes be scaled-up? How can low cost, profitable end-product be achieved from an innovative front-end microbe? These and many other questions need to be answered to assure the uptake of synthetic biology tools and techniques by industry.

#### *Synthetic biology for bioremediation*

In the 1970s and 1980s, the use of genetic engineering for environmental purposes emerged. Bacteria with superior catalytic activities were produced and a bacterium able to digest petroleum or petroleum components was developed. This modified bacterium was the first living organism to receive a patent by the Supreme Court of the United States.

Genetic engineering, and to a greater extent synthetic biology, can now be used in many different ways to tackle the challenges of the environment, for example:

- For mobilization purposes: such as bacteria being modified to increase their ability to absorb metal.
- For detection through biosensors.
- For transformation: such as setting up catalytic reactions allowing the conversion of industry waste in CO<sub>2</sub> or water.
- For bioremediation or degradation.

This last point raises difficult issues. Great expectations were placed on genetic engineering for bioremediation purposes in the mid-1980s. However, Victor de Lorenzo highlighted that many issues arise when putting modified bacteria in a contaminated environment. For example, bacteria developed in laboratories are not robust enough to survive in the environment, and their capacity for bioremediation developed in a laboratory was not readily transferred to the natural environment.

As in the case of the chemical industry, the complexity of biological systems has hampered their use in bioremediation, and engineering bacteria that are predictable when released in the environment has proved difficult. Here again synthetic biology was shown as being able to help tackle complexity, particularly conceptually by emphasizing the importance of engineering principles (such as standardization of parts or plasmids) blended with biology principles (such as the Darwinian evolution).

#### *Synthetic biology and the food industry*

The current scope of synthetic biology in the food industry is limited to incremental modifications in current processes or applications. Vitor Martins Dos Santos showed that key contributions are likely to be made in the areas of health and nutrition, although there are further applications of synthetic biology. Five particular areas of the food industry likely to profit from synthetic biology tools and techniques were described:

- Metabolites, health products (e.g. vitamins) and processing aids in the manufacturing process of food and food derivatives, such as nutraceuticals, probiotics and glycol-nutrients used to raise the value of certain foods or nutrient-enriched plants.
- Preservatives, an area already largely based on genetic engineering
- Flavors and fragrances
- Biosensors, for example to replace human “nose” in the food industry with an artificial nose
- Food waste processing.

A lot of money is invested in these fields, and again synthetic biology is seen as being able to facilitate, enhance and reduce the cost of production processes. The example of the food preservative Nisin was given. This molecule is traditionally obtained by a natural fermentation of *Lactobacillus plantarum*. Fermentation can have a relatively low efficiency, especially for these kinds of compounds from the lantibiotics family. Taking a synthetic biology approach will facilitate the design of compounds that may be produced more efficiently than by usual fermentation. The design of compounds from scratch beyond

those found in nature will also be possible. This will enable the food industry to enlarge its portfolio of products.

Biosensors are another example of efficiency gains that may be possible through synthetic biology. For example, employing a human nose to test aromas is expensive, and industry would profit from an automatised of this role. Researchers are working on the development of an artificial nose composed of thousands of different microsensors. Each microsensor would be based on particular bacteria or enzyme systems that would allow detecting the concentration of one specific compound.

Challenges in developing these advances in the food industry are similar to those described for the chemical industry and bioremediation. Technology platform development was again seen as a crucial point for structuring the field. Intellectual property is also an issue: in complex systems there are worries about the protection of all the parts needed to construct that system. Work is needed to overcome the many technical issues which still impede synthetic biology development into applications.

### ***Health and Medicine***

Richard Kitney highlighted that synthetic biology is expected to bring important advances in the field of biomedical research such as the development of biosensors, vaccines and the optimization of drug development processes. For example, synthetic biology is expected to help improve and reproduce natural therapies. Synthetic biology should make it possible to scale up and improve pharmaceutical production processes. Artemisin is an example of this. Synthetic biology may also have a part to play in developing novel, more efficient biosensors. For example, these biosensors could be useful to tackle complex diseases that are not really understood by allowing the collection of quantitative dynamic data in minimally invasive ways. Further, it may influence on the development of personalized medicine. Personalised medicine is about identifying groups which have a better chance of responding to particular therapies by using markers and other techniques to confidently segment patient groups.

#### *Synthetic biology in immunology*

Several applications of synthetic biology for detecting viruses, trigger antiviral activities or developing vaccines were presented.

Frank Notka showed the opportunities that gene synthesis can offer to synthetic biology. According to Notka, gene optimization (codon choice, sequence modification) and gene synthesis can greatly contribute to synthetic biology development. The example of vaccine development was given. The objective was to develop a HIV vaccine based on HIV genes, a highly difficult task which could benefit from synthetic biology research. HIV genes are not expressed to high level in human cells. In order to circumvent this problem, the codons used by the HIV were exchanged with codons used in human genes; gene expression was increased to a satisfactory level. Then the following steps were undertaken to define which virus strains to use, which targets to include in the vaccine and which delivery systems to use.

The main strain used was the C virus whose genetic sequence was kept almost integrally in order to include as many relevant epitopes as possible in the antigen. For safety reasons, part of the proteins were split, the active sites were removed and some additional modifications were introduced to enhance the efficiency of the production and secretion of the antigen. An algorithm was developed to optimize a given gene expression for a specific host. Negative elements such as repeated sequences, RNA secondary structure and splice sites were removed. Naked DNA and viral vectors were chosen as delivery systems: the New York *Vaccinia Ankara* viral system. The final step was the clinical trial: one half of the volunteers received the vaccinia virus only, the other half the synthetic DNA expressions construct. The overall response was very good and responders had a great capacity for inducing memory immune cells.

Roman Jerala presented two others possible applications of synthetic biology in the immunology domain. The first device was able to recognise a viral infection, in this case HIV infection, and trigger antiviral activity once the infection has been detected. The device is designed to detect a specific viral function (attachment of the virus to cells or a HIV specific protease activity) rather than to detect specific viral proteins which frequently mutate in the case of HIV and thus could compromise the functioning of the device. Once the infection has been detected, the device triggers different mechanisms that will, for example, prevent further spread of infection or will prime other neighbouring cells against the virus.

The second application concerns the design of vaccines able to uncover the stealth of bacteria and make bacterial components visible to the immune system. The example of *Helicobacter pylori* was taken. The flagellin (a specific protein contained in the flagella of bacteria) of *Helicobacter pylori* is not recognized by the immune system, however, the flagellin of *E.coli* is. A vaccine has been designed based on a chimeric flagellin composed of a segment from *E.coli* and a segment from *Helicobacter pylori*. This chimeric protein is able to activate the immune system and make it produce antigens that will recognize a future infection by *Helicobacter pylori*. Jerala underlined that the combination of immunology knowledge with synthetic biology tools show great promise for developing novel therapeutics, vaccines or detection tests.

#### *Developing smart therapeutics*

Christina Smolke described the use of synthetic biology tools in the field of cellular therapeutics. This example showed how synthetic biology can help engineer the immune system to treat different diseases.

Normally, T cells (one type of immune system cell) work by binding through receptors to a pathologic cell. Once bound, T cells release cytolytic proteins to kill the disease cell and release different types of other proteins that will send the signal to amplify the immune response as other disease cells are detected. In the case presented, the goal was to:

- Engineer receptors that would allow T cells to recognize disease cells that they would not normally recognize, for example cancerous cells.
- To built a synthetic system control that can induce the amplification mechanism which does not exist in ex-vivo engineered cells.

The whole system is based on a biosensing device built through RNA construction (input/output tools). This device will be able to recognize a drug once administrated to a patient. Once recognized, the device implements the circuit that tells T cells to bind to target cells (e.g cancerous cells), activate and proliferate. This circuit system principle can be used for many different purposes, for example it could be able to recognize a certain biomarker of a disease and release a specific drug once the marker is recognized.

#### **Developing the field: needs of academia and industry**

In order for synthetic biology to move forward, a better environment – including research infrastructures, education and intellectual property – needs to be developed.

#### ***Research infrastructures***

For synthetic biology to become a technology which enables innovation, the importance of developing strategies and mindsets that support the implementation of foundational technologies, adequate

research infrastructures, and technology platforms was stressed throughout the symposium. Francois Képès suggested the following steps in order to develop these supportive infrastructures:

- **Funding blue-sky projects and assuring an efficient cooperation between academia and industry:** Synthetic biology was presented as being between exploration and exploitation. Currently, the step of exploration needs particularly to be enhanced and the funding of foundational studies and blue-sky projects appears to be especially important. In the particular case of synthetic biology, where research encompasses applied and fundamental aspects, small and medium size companies are going to be increasingly involved in this baseline research. Synthetic biology is seen as a model where the collaboration between academia and industry will be particularly enhanced with a true scientific cooperation. This cooperation could suggest that academia should have the capacity to retain and capture intellectual property in the spirit of not “doing the job of the industry”, but rather maintaining balanced relations between academia and industry.
- **Establishing technology transfer units:** There remains some uncertainty over the best way to establish technology transfer units and where to locate them. In the talk, it was suggested that these units should be located within academic laboratories.
- **Developing full stream translational research:** There is a need to encourage multidisciplinary training of students by, for example having PhD supervisors from biology, mathematics and physics, as well as facilitating student mobility across borders.
- **Developing technology platforms:** Developing capabilities such as DNA synthesisers and DNA robotic assembly available to both industry and academia was raised as an important step to assure efficient synthetic biology research. These capabilities can be augmented by biological resource centers (e.g. DNA banks, cell banks, and biological models). However, it was pointed out that work is still required to adapt in-place repositories to the needs of synthetic biology research (e.g. good practice, standards). These platforms can also act as a good meeting point for academia and industry. Képès highlighted that developing such technology platforms needs initial financial support. Such platforms could become self-sustaining by charging fees to customers for services,. The suggestion was made to locate these platforms near or within centres of excellence.
- **Developing standards for biological parts:** Standardization is important for measurement with omics techniques. For DNA parts, it was noted that better standards, characterization and annotation would be welcome. An iGEM standard already exists and others are possible. But it might be too early to set up a universal standard.



### Developing the field: case study

#### Synthetic biology in the health industry

Adriano Henney highlighted that major pharmaceuticals companies are not yet involved in synthetic biology to any great extent although they already consider its sister field “systems biology” as crucial to tackling complex diseases. Synthetic and systems biology are particularly tightly linked in the context of human biology and medicine.

Synthetic biologists are confident that their work is of interest and importance to industry. However, Henney suggested that industry needs more proof of utility before making significant use of synthetic biology in health innovation. Some propositions were put forward to shape a more persuasive position for synthetic and systems biology. For example, it was highlighted that from December 2000 to February 2008 the top 15 companies in the industry lost approximately US\$850 billion in terms of stakeholder’s value, it was also highlighted that current processes and approaches to generating pharmaceuticals were not going to be sustainable for the future. The pharmaceutical industry needs to find new ways to innovate and systems and synthetic biology can be part of those.

Why is the pharmaceutical industry facing this crisis? Post-genome biology is focused on entities: isolated proteins and engineered cell lines which are outside of any physiological context. Then it tries to translate the data obtained to humans by using associative models which may or may not have any relationship to human physiology. To further compound the issue, the individual may already be taking other drugs which may affect the action of the target entity, and this is not taken into account by such models. Henney highlighted that to understand why a biological network has shifted into pathology, an understanding of a dynamic and complex series of network interactions is required. Studying entities separately does not allow such an understanding. A systems biology approach is needed which means being able to rationalize and model a specific biological system to extract high quality hypotheses that will allow progress in treating the patient.

A possible solution to current problems in health innovation in the pharmaceutical industry could be to combine synthetic biology’s innovative tools with a holistic understanding of human physiology and novel therapies. These key developments in synthetic and systems biology will largely be driven by academia, but Henney highlighted that it is important that academia and industry start to work closely together. As a push, academia would have to be ready to demonstrate the applicability of its knowledge in an industrial and commercially relevant context. Indeed, industry is increasingly facing economic and regulatory hurdles which reduce its willingness to invest in blue-sky research. To bring to industry the benefits of synthetic and systems biology, it is crucial to put the different communities and stakeholders together to drive change. Better coordination is needed to generate a significant impact and mechanisms need to be found to get industry on board.

#### *Education in synthetic biology: The iGEM example*

“Can simple biological systems be built from standard interchangeable parts and operable in living cells?” This question, raised by Randy Rettberg in a biological system design class for undergraduate students at Massachusetts Institute of Technology (MIT), led to an innovative way to train students and interest them in biology and engineering.

The International Genetically Engineered Machine (iGEM) competition draws on this new course at MIT. iGEM is an international design competition primarily for undergraduate students, although some high school teams are involved. The goal of this competition is to realize a synthetic biology design project using specific standard biological parts called biobricks. A kit of about 2000 parts is given to each team at the beginning of the contest. The philosophy for iGEM is “get and give”. Parts developed by a team are made available to other teams. The iGEM registry now has about 3500 parts. There is a standard method for assembly. Almost all the parts are compatible so that they can be attached to each other.

The iGEM programme includes a large number of students, instructors and schools (1180 participants in 2008). The number of teams registered for the competition raised from 84 in 2008 to 211 in 2009. Final

projects are presented during an annual jamboree. Amongst the projects are ideas and inventions at the leading edge of synthetic biology (many iGEM projects have been published in academic journals) and some of these projects are very ambitious. An example project is the development of a “bactoblood”, where students have introduced hemoglobin system in bacteria. It was highlighted that centers for synthetic biology have grown up at sites where iGEM teams were set up.

iGEM is a competition which strongly recognizes the social issues that synthetic biology can raise. For the iGEM community “science can only work successfully and develop useful inventions if it is based on a high level of acceptance in the society”. iGEM competitors are highly involved, as part of their projects, in interacting with the public, doing surveys and interacting with the press. The issue of safety is also central. Each iGEM team will now have to write a report on how the safety of their project relates to the world around them.

Education plays a central role for assuring advances in synthetic biology. iGEM is a very innovative example which shows how the field tends to develop. However, a couple of questions were raised on how to maintain and enrich education for such emerging fields. Pam Silver raised the following: how can one have a system at all levels in engineering and science that allows students to be skilled? How do we have a training environment that maintains the level of excitement with which students come into the field? How can students be more involved in the process to drive innovation into commercialisation?

### *Intellectual Property challenges*

iGEM works on an open system where parts are freely accessible and exchangeable. What would happen to this contest if parts became patentable, or patented? The answer to this is not clear, and many questions over intellectual property in synthetic biology await resolution. Richard Johnson highlighted that the complexity of the patent landscape is real and especially significant in the synthetic biology field because it is dealing with a cumulative convergent set of technologies. The chances of patent thickets that hold back the ability to do research and to commercialize applications are real.

A lot of research is and has been done to clarify the way patenting should be organized in the field of synthetic biology, but this is still a difficult issue. Many in the field advocate openness and minimal patenting, but others indicate that, in some cases, having a strong intellectual property regime that you can control is the best way to protect openness.

The major issues presented by Johnson were:

- **Patents:** the world of patents is highly complex, especially for a discipline like synthetic biology which plays on multiple technologies. Moreover, there are a range of unresolved patent issues that are going to have a major impact in shaping the future of synthetic biology (e.g. patentability, how prior art is applied, non-obviousness).
- **Material transfer agreements:** there are major concerns over ownership and access for material and information coming out of synthetic biology. There are unresolved questions, as we have already seen before, about how university tech transfer offices are developed and how they operate.
- **Interaction and bundles of rights:** there are potentially some very interesting issues around design rights, especially in Europe. In the UK, 10 to 15 years ago, there was a series of cases on how one can assure interoperability among parts. At this time there was a must fit, must match exemption to intellectual property rules for designs. Does this apply for synthetic biology?

- **Databases operation:** information and materials (e.g. parts) coming out of synthetic biology research are already being placed in registries or other types of database. There is concern about how these databases might operate. OECD publications on human genetic research databases, as well as the guidelines on biological resource centers, already address some of these issues.
- **Copyright:** copyright protects originality and expression. In synthetic biology, an increasing decoupling of design from manufacturers and processes might increase the likelihood of copyright issues.
- **Trademark:** Biobricks have value. Its logo and its trademark are important quality control tools.

An important point, often raised when talking about synthetic biology and intellectual property, is the question of openness. Competitive visions of openness were described:

- Open source is a term which is often misinterpreted. Open source relies on a very robust intellectual property system. Copy left and other types of licenses require a very efficient and effective intellectual property system to work.
- Open innovation is an important notion for industry and universities. Johnson highlighted that “you don’t have to do it all and to be vertically integrated”. One can, for example, look at strategic opportunities that you don’t need as a core part of your business by taking them outside of your company.

In the synthetic biology community the term “semi-commons” is increasingly used to enhance the fact that biological parts are interacting commons and are at the same time for private uses. These resources are dynamic, scalable and can adjust to different mechanisms.

Johnson pointed out a number of other issues with IP in synthetic biology. In the synthetic biology community, a clash of cultures is also likely to become an issue. The way a pharmaceutical company, a chemical industry, a university or a semiconductor company is seeing intellectual property rights is different. Aligning the interests of all these players is difficult. The synthetic biology community is also building around trust because its output volume is relatively low. But with the community becoming bigger, there will be a transition from trust to contract, and then the role of intellectual property will be particularly interesting.

Synthetic biology is going to be a user driven innovation. Johnson highlighted that it is important to think of new policies that are user focused and not, as it is commonly the case, oriented on the traditional producer side. Open development is another important point. It needs to be community driven and align its needs with priorities in the shared resources and open access.

As synthetic biology is an emerging field, some comparison with other fields was shown to be useful when thinking about intellectual property. So far, analyses and analogies have tended to focus on biotechnology and information technology. The analysis of semiconductors - and to some extent nanotechnology where patent tickets have developed in a way that they might for synthetic biology devices - could also make a viable analogy for anticipating the needs for intellectual property in synthetic biology. The work that the OECD has done on different types of collaborative mechanisms is also a good source of references.

## **Investment Model for Synthetic biology**

Investors from government funding agencies, philanthropic foundations and private investors gave an overview of who is investing in synthetic biology and how and what are the challenges which could slow down investment.

### ***Factors influencing investment***

Investment in synthetic biology relies on different factors, and Mark Waxman noted the following: the perception of synthetic biology by the public; the regulatory regimes that will be developed for synthetic biology; the need or not for products liability insurance; industry involvement; and patent tickets and intellectual property models.

The industry and the venture community are looking for wealth creation and sustainability. According to Greg Kisor, public good alone is not sufficient to attract venture funds, so innovation could end up relying on philanthropy and government funding. Property rights drive the ability to derive wealth creation, and this is key to attracting venture investments. Companies which work with venture investment models in intellectual property currently have limited involvement in synthetic biology. Kisor specified that synthetic biology is a small part of an investment in two of his company's funds. It was proposed that to help funding the next generation of research, governments may look at grants in the future and consider if there is Intellectual Property coming out of these grants. If so, governments should take the IP Rights and make them more generally available.

A further investment influence on the development of synthetic biology is the balance of investment between tools and applications. The question of whether more funding is currently allocated to build next generation of applications than to enhance tool development directly is difficult to answer precisely. As a first impression, discussants felt that funding seems to be more oriented toward applications than tools.

### ***Philanthropic funding***

Several grants from philanthropic organisations are directed toward synthetic biology. Paula Olsiewski stressed the significant involvement of the Alfred P. Sloan Foundation in synthetic biology, especially in governance issues. With the goals of improving understanding of ethical, social and policy issues by scientists and engineers and of improving understanding of the science and engineering by the policy makers, journalists and the public, the Sloan Foundation has invested at least US\$2 million in addressing the societal issues raised by synthetic biology.

In 2005 for example, the Sloan Foundation funded a grant which was a joint venture between the Venter Institute and MIT and the CSIS (Center of Strategic and International Studies). A report came out of this group entitled "Synthetic Genomics: Options for Governance". The Foundation also actively participates in the Synthetic Biology #.0 meetings all over the world, particularly on the societal issues sessions. Recent engagements of the foundation include the present symposium, projects with the Hastings Center, the Woodrow Wilson International Center for Scholars, and the J. Craig Venter Institute.

### ***The European Commission funding plan***

The European Commission is investing in synthetic biology; this investment is part of a wider structure of investment. Two sets of projects were launched and some continue through publications or public relations like Synbiosafe or TESSY. Ioannis Economidis pointed out that the idea was to cover not only the basic research linked to synthetic biology but also to cover more applied topics such as medicine, new generation of pharmaceuticals, new chemicals, environment and energy.

The current funding programme of the European Commission is called the Seventh Framework Program and it covers funding for seven years at a level of €53 billion. This funding program is divided into different dimensions. The first one is linked to basic research; this dimension includes some projects on synthetic biology. Another dimension is dealing with human resources, including student training. The major funding comes from the Cross Cooperation Programmes which encourage young scholars to exchange their experiences. Synthetic biology might also be funded under different dimensions such as health, environment and nanomaterials development.

It was highlighted that within the context of the Knowledge-Based Bioeconomy Programme of the European Commission, synthetic biology is considered an advanced tool, and a merging of biotechnology knowledge essential to promote bioeconomy. An investment of €1 million has been dedicated to using synthetic biology for approaching and solving environmental issues and aspects of bioremediation. This programme puts together scholars to create a critical mass to work on these particular issues. A greater investment of €3 million is under discussion to broaden the issue and try to understand what synthetic biology can bring to biotechnology more broadly.

Other investments from the European Commission aim to establish a network and facilitate people to work together. Three types of networking were presented: the European Network of Semantic Work; a network composed of designated specialists in their field nominated by each advisory country who are asked for advice and share information on activities in their member states.

#### **Company's funding: the example of the genetic tool provider Febit**

Febit is a genomic tool provider company. Its goal is to help understanding the issues raised by biological functions and processes. It does that by providing platform technologies which allow, for example, resolving gene sequencing and expression profiling challenges.

Febit is financed by two types of investors. The first one is Diet Hopp, founder of the software giant SAP. Cord Staehler noticed that a number of people who became famous in the software industry are now also investing in synthetic biology. The second investor and strategic partner is In-Q-Tel, especially the CIA (Central Intelligence Agency). The interest of this second partnership is first to assure Febit to have access to the most advanced technologies; and second to assure an easy access to risk management – risks which could come out of the activity of the company.

#### ***Outstanding issues: thinking of a roadmap for investment***

The discussion highlighted the need for a comprehensive study on investments in synthetic biology. There are a range of questions that would help better clarify how the field is organised, including: Is funding directed more toward applications than tools? Who is investing in tools and who is investing in applications? Is it different between countries? Is there a fundamental difference between these two types of investment, given synthetic biology is still an emerging science and the link between applications and tools is still very tight?

Developing a roadmap for funding agencies and government to help them plan how and when to invest in synthetic biology was suggested as a useful outcome of the meeting and next step. More than only focusing on synthetic biology, this roadmap could be a strategy to make sure that sustainable investments are made for improving processes in engineering biology more broadly.

It was highlighted that investments would need to be made that ensured that the synthetic biology community has all the tools and resources it needs to make this field move forward. According to discussion, this is currently not the case.

## **Governance Issues Related to Synthetic Biology**

### ***Biosafety***

Robust regulations for the safe use of biotechnology and recombinant DNA technology are in place, and it was contended that no known accidents have occurred. However, synthetic biology is frequently conceived as an extension to these established technologies, and perhaps even a step change, and so it is frequently asked if current biosafety procedures and regulations remain sufficient. In response regulators and synthetic biologists typically argue that current regulatory regimes are adequate for the work that they do. In contrast, it is more commonly acknowledged that adaptation may be required with regard to biosecurity. However, it was argued that biosafety and biosecurity should not be treated as separate issues. They face many of the same problems, including the same root issue: how to assess and respond to risk. The following difficulties that overlap safety and security for synthetic biology were identified:

- **It is more difficult to identify agents of concern:** taxonomy can act as a guide to pathogenicity, but for synthetic biology it is less useful. Novel organisms would present a particular challenge for we have no experience to draw on. Identifying sequences with pathogenic properties is also difficult. Our conventional tools may no longer fit.
- **Science and politics have changed since the laying down of initial rDNA regulations:** things have moved on since Asilomar. Science and technology is increasingly distributed and easy to access, and the proliferation and distribution of knowledge makes oversight increasingly difficult. In the lab, the inter-mingling of disciplines progresses synthetic biology, but awareness and training in biosafety issues differs across disciplines. Outside the lab, heightened security threats focus increased attention on biotechnologies as possible sources of harmful agents.
- **The context for biosafety may have changed:** notions of ‘harm’ – what it is that we want to prevent and how we are to do it – are fluid. For example, debate continues over the meaning of the ‘natural environment’ that is under threat from biotechnological interventions.
- **The purpose of regulation may not be clear and needs to be examined:** for example, regulation may serve a technical need or public anxiety.

These challenges suggest that synthetic biology offers an opportunity to revisit established concepts in biosafety and biosecurity.

### ***Learning from work on viruses***

Prior experience with potentially hazardous materials such as RNA viruses can provide useful lessons for synthetic biology, assisting safety and security efforts. RNA viruses use RNA, rather than DNA, as their genetic material but reverse transcribe their RNA genome into DNA which is inserted into the host genome in order to be transcribed into RNA. RNA viruses include in their class those responsible for influenza, mumps, measles, ebola and HIV. The first infectious cDNA clone of a RNA virus (polio) was reported in 1981 and work on infectious viruses has delivered great understanding of their life cycle and pathogenesis, delivering progress in anti-viral drug and vaccine development.

Work on RNA viruses is not without risk including the accidental spread of artificial viruses to nature and the acquisition of virulent strains for bioterrorism. The likelihood of the latter varies to an extent on the complexity of the target pathogen. In 2002 the first chemical synthesis, using only sequence information, of polio virus was achieved. The synthesis of polio is comparatively easy. If a virus can be synthesised using only sequence information, there is an increased risk of construction for nefarious intent. The estimated cost of infectious virus production is just \$7500 using the types of labs typical in a university.

Perhaps more than the threat of bioterrorism, the relative ease of production of viruses raises the chance of accident. There are documented cases of virus leaks from laboratories, including small pox in the UK (1978), SARS in Singapore (2003) and China (2004), and several cases of accidental polio release including the identification in 2003 of a laboratory strain circulating in the general population. This emphasises the importance of regulations and guidelines, their enforcement and the vigilant containment of pathogens.

#### *Reviewing the US National Institute of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules*

Proposed updates to NIH guidelines for research involving recombinant DNA to account for recent advances, including synthetic biology, are currently under consideration in the US. The review was prompted in part by a report from the National Science Advisory Board for Biosecurity (NSABB) that suggested the current guidelines are deficient in certain respects. In particular, the report *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents*, noted biosafety concerns arising from the diverse institutional settings and disciplinary backgrounds of the practitioners of synthetic biology. Some of those undertaking research in synthetic biology are educated in disciplines that do not routinely conduct formal training in biosafety and NSABB found some are unclear as to the circumstances under which they should consult their Institutional Biosafety Committees (IBC). Furthermore, some research is now undertaken within institutions such as high schools without access to an IBC. Taken together with technical advances that fall outside the scope of the guidelines (such as synthesized RNA viruses and synthetic DNA that is synthesized *de novo*) a decision was taken through a trans-federal policy coordination process to modify the NIH Guidelines.

The NIH Recombinant DNA Advisory Committee (RAC), which advises the NIH Director on rDNA research, was charged with considering the application of the NIH Guidelines to synthetic biology. The RAC looked at the degree to which this technology is covered, and whether the scope of the guidelines needs to be modified to capture synthetic biology research. The RAC made a series of proposed modifications including: a revised definition of rDNA molecules; an exemption for synthetic nucleic acids that cannot replicate, provided they are not used in human gene transfer; and an update of the 'spirit clause'. This clause recognises that mitigating risk depends in a large measure on the motivation and good judgment of individuals and that all conceivable experiments involving recombinant and synthetic DNA cannot be foreseen. In revision, it is proposed to emphasise that new genetic manipulation techniques may enable work to be accomplished faster, more efficiently or at larger scale, and to reiterate that as the field develops, the Guidelines may need to be updated.

It was noted that the NIH Guidelines are not legally binding although adherence to them is a condition of grant for research funded by the NIH, and other funding bodies have adopted the guidelines as best practice. Because the guidelines apply at the institutional level, it is the responsibility of IBCs to ensure compliance. To facilitate their work, the NIH promotes observance of its guidelines and updates IBCs on developments through site visits and information on its website. The NIH is aware of IBCs that are reviewing their work in the light of synthetic biology. The approach taken by the NIH is therefore to work with practitioners and oversight committees toward shared goals rather than act as a sanctioning and regulatory body.

The NIH guidelines apply only to research, but synthetic biology is further covered by existing regulations, in particular when used for commercial purposes. It is not, or would not be, regulated as synthetic biology *per se* but according to its use, for example industrial biotechnology, consumer products or agriculture by the relevant federal agency.

The NIH was noted for its foresight in updating its guidelines to accommodate advances in synthetic biology, and delegates discussed the situation in other countries. In Japan, researchers are required by law to notify the Ministry of Education of any research involving rDNA. In Europe, biosafety is captured within legally binding directives, and regulatory bodies in member states undertake compliance checks. A European Commission working group is currently exploring if existing directives need updating to accommodate synthetic biology.

One issue was left hanging however: would we recognise the point at which evolving synthetic biology research posed a fundamental challenge to the current regulatory structure, a challenge that could not be met by modifying existing structures?

### ***Biosecurity***

“Synthetic biology presents risks, but so does biology and in fact so does everything we do on a day to day basis” said Michael Imperiale. It is difficult to quantify the risk linked to synthetic biology but it is important to create governance systems which are sustainable, forward looking, dynamic and which allow innovation in synthetic biology to come through.

### *The factors of risk*

Imperiale presented four risks for synthetic biology: the technologies themselves, the practitioners of these technologies, the biology and the public.

- **Technologies:** Imperiale divided synthetic biology into two types of technologies: genome synthesis and engineering. These two sets of technologies present risks. As noted genome synthesis allows the synthesis of virus genomes, and, eventually the derivation of a virus from this genome. It may also become possible to build de novo an organism which can escape current system controls. Engineering techniques include molecular shuffling or self-replicating systems which might also pose security threats. The following actions would help integrate all the components to evaluate risk and assure an efficient regulatory framework for synthetic biology:
  - Developing uniform and standardised screening tools to determine what is dangerous and what is not, especially in the case of synthetic genomics.
  - Developing a rationalized list of agents to determine the most dangerous/risky and prioritise screening. This is however difficult and managing risk in this case is complex because pathogenic agent mechanisms are not fully understood and it is currently difficult to define agents that may be hazardous.
  - Building a database of sequences or experiments which are risky would help to stratify and keep track of risk.
- **Practitioners:** practitioners include traditional scientists, other groups such as iGEM competitors and, perhaps in the future, terrorists. Although we must be mindful of risks associated with terrorism, the risks posed by the scientific enterprise itself were presented as needing immediate



attention. Students from the synthetic biology community are already having specific dialogues amongst themselves about biosecurity issues. This is for example the case for the iGEM group but also for the DIY (Do It Yourself) bio community which has set up a safety and security working group.

- **Biology:** biology can be more or less predictable or unpredictable. The behaviours of designed circuits, selection, and virulence for example are things that can be difficult to anticipate.
- **The public:** if hazards result from synthetic biology activities, there is a chance they will impact on the public. They have an important voice in the acceptance of an emerging technology. Engaging the public in a dialogue and discussing potential risks and benefits is important.

Debates are already taking place concerning the safety, security and ethical aspects of emerging technologies. The presentation pointed out that it is important to get back to these debates and learn from the past.

It was highlighted that industry should start a dialogue with the public and should be engaged in establishing a framework to regulate synthetic biology, especially for providing relevant data. An important first step is to make sure that the current regulation can respond to the regulatory issues synthetic biology is raising and will raise as well as building a regulatory framework which allows innovation.

It was suggested that there are more discussions about the adequacy of the regulatory framework in the US than in Europe because the original network of regulations is somewhat stricter in Europe. Many initiatives and discussions are already ongoing which deal with synthetic biology and security. The initiative taken by Berkeley was quoted as an example. Steve Maurer has developed a portal where if questions about whether an experiment can pose a risk can be submitted and a group of experts will anonymously discuss it and provide advice. There is also an important dialogue already in place between scientists and the security community at national and international levels.

#### *The French approach*

The generic tools to improve biosecurity are regulation, recommendation and awareness. A lot of recommendations have been published for governments and authorities to improve biosecurity. The French Academy of Science has not published a specific report on synthetic biology but it did do a report on biological constraints, biological security and scientific responsibility which can be linked to synthetic biology. A number of instruments have been analyzed in France which could have an interest for synthetic biology regulation (e.g. federal regulation to monitor and control DNA synthesis; guidelines; harmonization and controls; education and training programs; and a committee to check and control synthetic biology research). Nicolas Bécard presented four recommendations that came out of this analysis:

- **Adaptation to limit malicious applications.** Instruments are already in place to limit malicious application. There is an international regulation with United Nation resolutions. The chemical Weapons Convention and the Biological Weapons Convention normally limit the risk for development of new agents. There are also European regulations for export control. The list of biological and chemical items is determined by the Australia group list. European regulation for biological risk and warfare is more oriented toward biosafety but deals with some issues raised by biosecurity. Specific regulations, which are in place in different countries, allow control over the order of DNA parts (this includes DNA synthesis, DNA sequences, microorganisms and toxins). However, according to Bécard, further analysis is required to indicate if these regulations are sufficient to cover all the risks that synthetic biology could raise. This work is ongoing in France.

- **Controlling DNA synthesis.** It seems difficult to directly control DNA synthesis from a biosecurity point of view. To have efficient control, a good database as well as international oversight is needed. This is not in place yet. Another approach aims to educate the gene synthesis industry on how to identify suspicious DNA orders and inform them that there are national points of contact they can report to. This is the approach taken in France; the same kind of approach is taken in the United States.
- **Awareness and education in the scientific community.** In France, the French Academy of Science has reported that by developing a good awareness and education program for the scientific community, biosecurity could be significantly improved. In France, conferences and seminars on this topic to train and inform scientists are in place. University degrees containing modules dealing with biosecurity and biosafety issues are also in place and others are being developed.
- **Monitoring and controlling commitment for awareness by the researcher.** Such committees would need to be international and have a framework of unity. This recommendation is under reflection in France.

These recommendations are not specifically directed at synthetic biology, but are for all emerging technologies said Bécard. There will be guidelines in France specifically dealing with biosecurity for synthetic biology.

### **Public engagement and participation**

A drive to engage with the public and promote a dialogue on the issues raised by synthetic biology has come from both within the synthetic biology community and from outside (for example from policy-makers, civil society groups, research funders and academies). It is not clear why some forms of science and technology provokes calls for public dialogue, whilst others do not. Although it was suggested that one factor is the extent to which that science or technology is framed as new or emerging. Synthetic biology typically falls into this category.

Accepting that public engagement and dialogue is important for synthetic biology, general questions remain. These include: what do we mean by ‘the public’- especially in a globalised environment; how is the public to be engaged and do we have successful models; will engagement succeed with so few products to talk of; and what is the role of the media? Delegates discussed studies on emerging public views of synthetic biology, the potential participants in engagement, and the functions and roles of the media.

### ***Emerging public views on synthetic biology***

A study undertaken by the Woodrow Wilson Center Synthetic Biology Project explored public awareness and views on synthetic biology in the US. The research consisted of a representative national telephone poll and two focus groups (one with female and one with male participants). The results were compared with focus group undertaken in the UK as part of the Royal Academy of Engineering inquiry into synthetic biology, and with earlier work undertaken on nanotechnologies.

In the poll, 67% had not heard about synthetic biology (nanotechnology is better known, with 49% having not heard the term before). In the focus groups, participants discussed which applications of synthetic biology they viewed as most promising. Both males and females considered biofuels the most promising potential application, a finding reflected in the UK research. Drugs for treating diseases, and new ways to treat cancer and clean up the environment were also well supported.

When asked who is best placed to regulate or manage risks associated with synthetic biology, participants showed little trust in industry holding all responsibility for testing the products they make. The Federal Government was considered most appropriate to manage risks, but females also tended to favour the scientific community and others involved in advancements to regulate synthetic biology. Some male participants favoured an immediate ban on further synthetic biology work. Generally however, participants did not favour a moratorium and recommendations for the road ahead, such as increasing trust through openness and transparency, were similar across the Atlantic.

The research also pointed to potential challenges in the public communication of synthetic biology. For example, David Rejeski noted that the reaction of participants when first introduced to the term synthetic biology was ‘stunning’ and that ‘it pushed buttons that nanotech never pushed for them’. It may be that the term will be a liability in a way that ‘nanotechnology’ is not. Added to this, a convergence of factors might mean that there is high potential for risk amplification. These factors include: raised public anxiety over biological issues and threats following the H1N1 pandemic; a general decline in the number of dedicated science journalists; a decline in trust in government agencies; and the possible rise of new opponents. The last of these is based on reported research by Kahan *et al* who showed that a group known as ‘environmental risk naysayers’, who are typically unconcerned by potentially hazardous issues such as nuclear power, climate change and BSE, but do show concern for synthetic biology.

Why ‘environmental risk naysayers’ show concern for synthetic biology requires further exploration, and is just one suggested avenue for further research on the public and communication aspects of the field. Other near-term needs include applied research on public attitudes and perceptions, including international comparisons that may then be used as the base for a communications and engagement strategy. Differing reactions to synthetic biology across nations and regions may affect the future geography of synthetic biology. For example, the generally negative public reaction to GMOs in Europe is well documented and it is possible to estimate the economic loss to the US economy of the failure of GMOs on the European market; \$300-400m a year was suggested. However, research commissioned for the Royal Academy of Engineering inquiry into synthetic biology noted a more positive reaction to synthetic biology, including the term itself, than from US counterparts. It was suggested UK participants preferred to learn more about the science and technology before making a judgement.

The increasingly global nature of modern life science is an important consideration for discussion and debate on the meaning and significance of synthetic biology. It will not be possible, and not desirable, for public debate and dialogue to be restricted to a few nations and a few experts. Facilitated by information communication technologies, both the science and debate about the science will be widely distributed.

### ***Participants in engagement***

Robert Cook-Deegan argued that emerging research points to a difficult public the public landscape for synthetic biology: it has an unfavourable name; no apparent communication strategy; no clear leadership; and no media channels through which to pass on information. Yet it was suggested that the issues raised by synthetic biology are shared by many new technologies such as neuroscience, stem cells and agricultural biotechnology. It was argued that, therefore, the required task is not to educate all the public so that anyone and everyone can slot into policy discussions, but to determine which broad set of stakeholders is likely to be affected by *this* technology and bring them into a dialogue. This also needs to be done with an awareness of the broad nature of the synthetic biology research base. This is in terms of the range of different research agendas that are taken to constitute ‘synthetic biology’, but also that synthetic biology is being developed outside of the traditional arenas of science and technology R&D, as well as within it. The iGEM competition and the rise of the ‘garage biotechnologist’ illustrate this. A wide range of people therefore need to be engaged in policy discussions.

### *Media roles*

Some perceive more reasons for optimism in the public communication of synthetic biology. Adam Bly argued that synthetic biology arrives at a time when US Government support for science is at an all time high, and science is currently considered essential to the vitality of the nation. Synthetic biology can be part of this positive conversation about science. Furthermore, the synthetic biology community is more attuned to exploring non-traditional media forms for communicating their work. This means that synthetic biologists could augment, even circumvent, traditional media sources and more closely control their messages.

Bly argued that synthetic biologists may be 'failed' by traditional media because it lacks the required scientific literacy to deal with a field that is this complex and challenging and which is developing at a rapid pace. Bly summed up his position by suggesting that 'I wouldn't even contemplate the need for mainstream media ...; bypass it and focus on new tools for scientific communication.' He argued that the synthetic biology community has an opportunity to revise and reform science communication and science literacy based on four factors: a shared sense of social responsibility within the synthetic biology community which will appeal to the wider public; synthetic biology has the potential to be a participatory science; forms of open and transparent communication currently preferred by many within the community are readily transferable and are already accessible to the public; and, because it is in a stage characterised by unpredictability, synthetic biology can pave the way for a new form of debate about science, where unpredictability and uncertainty is openly discussed. Bly suggested unpredictability is likely to be an increasing feature of future science.

The synthetic biology community is already undertaking some public engagement both passively (through researchers' use of open access web based tools) and actively. When added to initiatives undertaken and planned by other organisations (e.g. the Woodrow Wilson Centre, the Royal Academy of Engineering, the UK Research Councils), the question arises whether communication and engagement needs a more detailed and coordinated strategy. A stronger question was also asked: whether it would make any difference if there were no public engagement effort at all.

Some participants felt that there was little need to centralise public engagement. However, this was set in tension against the examples of GMOs and human gene therapy (HGT). It was suggested that a better public engagement strategy in the early development of GMOs may have led to a more productive technology which better matched perceived needs. In the case of HGT, it was suggested that powerful religious groups in the US lobbied the federal administration and influenced subsequent decision-making. This constituted a narrow evidence base on which to base policy. Wider dialogue about emerging science and technology may lead to different outcomes.

It was also noted that in the UK and elsewhere there is a general move away from communication strategies that resemble marketing campaigns toward dialogue initiatives that foster a conversation amongst scientists, policy-makers and the public in a manner that is intended to feed into decision-making at the research and policy levels. This is the intention of forthcoming dialogue work to be undertaken by the UK research councils. In the US, engagement initiatives connected to policy processes have already taken place. For example, as part of the redraft of NIH Guidelines for Research Involving Recombinant DNA, proposed changes were considered at a stakeholders conference. However, the number of public participants was described as disappointing, although turn-out from civil society groups was better and led to rich discussion.

**ANNEX: AGENDA OF THE SYMPOSIUM: OPPORTUNITIES AND CHALLENGES IN  
THE EMERGING FIELD OF SYNTHETIC BIOLOGY**

**UNDER THE AUSPICES OF**

**THE U.S. NATIONAL ACADEMIES**

**THE ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT**

**THE ROYAL SOCIETY**

**9-10 JULY 2009**

**THE NATIONAL ACADEMIES' KECK CENTER, 500 5<sup>TH</sup> STREET, NW**

**WASHINGTON, DC, SYMPOSIUM AGENDA**

**Thursday, 9 July**

**Welcome:** Ralph J. Cicerone, President, National Academy of Sciences

**Keynote Address:** Arden Bement, Jr., Director, National Science Foundation

**Session 1: Synthetic Biology Overview**

**Moderator:** Sheila Jasanoff, Pforzheimer Professor of Science and Technology Studies, Harvard University

**Speakers:**

- Drew Endy, Assistant Professor, Department of Bioengineering, Stanford University
- Paul Rabinow, Director of Human Practice, Synthetic Biology Engineering Research Center

**Session 2: Public Policy – Government Perspectives and Approaches**

**Moderator:** James Wilsdon, Director, Science Policy Centre, The Royal Society

**Speakers:**

- Adrian Smith FRS, Director General for Science and Research, Department for Business Innovation and Skills
- Huanming Yang, Director, Beijing Genomics Institute

### **Session 3: Roundtable Discussions on Innovation in Synthetic Biology**

#### **Tools and Techniques – Enabling Innovation**

**Moderator:** Caroline Ajo-Franklin, Staff Scientist, Biological Nanostructures Facility, University of California, Berkeley

**Speakers:**

- Christina Smolke, Assistant Professor, Department of Bioengineering, Stanford University
- Cord Straehler, Chief Executive Officer and President, Febit Biomed GmbH

#### **Eco-Innovation**

**Moderator:** James Greenwood, President and CEO, Biotechnology Industry Organization

**Speakers:**

- Sven Panke, Associate Professor for Bioprocess Engineering, Department for Biosystems Science and Engineering, ETHZ-Basel
- Victor De Lorenzo, Research Professor, Spanish National Research Council, National Center of Biotechnology
- Kinkead Reiling, Co-Founder and Senior VP, Corporate Development, Amyris
- Vitor Martins Dos Santos, Systems and Synthetic Biology Group, Helmholtz Center for Infection Research

#### **Health and Medicine**

**Moderator:** Richard I. Kitney, Director of the Graduate School of Engineering and Physical Sciences; Chairman of the Institute of Systems and Synthetic Biology; Professor of BioMedical Systems Engineering, Department of Bioengineering, Imperial College

**Speakers:**

- Adriano Henney, Director, Obsidian Biomedical Consulting Ltd.
- Frank Notka, Manager, Research and Development, Geneart
- Roman Jerala, Head, Department of Biotechnology, National Institute of Chemistry - Slovenia

**Friday, 10 July**

**Welcome:** Charles M. Vest, President, National Academy of Engineering

**Session 4: Developing the Field – Needs of Academia and Industry**

**Moderator:** Pam Silver, Professor, Department of Systems Biology, Harvard University

**Speakers:**

- Francois Kepes, Research Director, French National Center for Scientific Research and Founding Director, The Epigenomics Project, Genopole
- Randy Rettberg, Director of the Registry of Standard Biological Parts; Director, The International Genetically Engineered Machine (iGEM) Competition; Principal Research Engineer in Biological Engineering, Massachusetts Institute of Technology
- Richard A. Johnson, Senior Counsel and Senior Partner (Ret.), Arnold & Porter LLP and CEO, Global Helix LLC

**Session 5: Roundtable on Investment Models for Synthetic Biology**

**Moderator:** Ed Lazowska, Bill and Melinda Gates Chair in Computer Science, Department of Computer Science and Engineering, University of Washington

**Speakers:**

- Mark Waxman, Partner and Chair of the Health Care Industry Team, Foley & Co
- Greg Kisor, Vice President, Investor Relations, Intellectual Ventures
- Paula J. Olsiewski, Program Director, Alfred P. Sloan Foundation
- Ioannis Economidis, Principal Scientific Officer, European Commission

**Session 6: Governance Issues Related to Synthetic Biology**

**Health / Safety / Environment**

**Moderator:** Helge Torgersen, Senior Researcher, Institute of Technology Assessment, Austrian Academy of Sciences

**Speakers:**

- Takuji Wakita, Director, Department of Virology II, National Institute of Infectious Disease
- Jacqueline Corrigan-Curay, Acting Director, The Office of Biotechnology Activities, Office of Science Policy, National Institutes of Health; Executive Secretary, Recombinant DNA Advisory Committee

### **Security**

**Moderator:** Iain Gillespie, Head, Science and Technology Policy Division, Directorate for Science, Technology and Industry, Organization for Economic Cooperation and Development

**Speakers:**

- Nicolas Bécard, Chargé de mission, Secrétariat de la Défense Nationale
- Michael Imperiale, Arthur F. Thurnau Professor of Microbiology and Immunology, University of Michigan

### **Session 7: Public Engagement and Participation**

**Moderator:** Mike Rodemeyer, Lecturer, Science, Technology, and Society, University of Virginia

**Speakers:**

- David Rejeski, Director, Foresight and Governance Project, Woodrow Wilson International Center for Scholars
- Robert Cook-Deegan, Director, IGSP Center for Genome Ethics, Law and Policy, Duke University
- Adam Bly, Founder, CEO and Editor-in-Chief, Seed Media Group

### **Session 8: The Path Forward**

Roundtable of All Session Moderators

Adjourn