

European Academies



Science Advisory Council

## Realising European potential in synthetic biology: scientific opportunities and good governance



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building science into EU policy

# EASAC

EASAC – the European Academies Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

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EASAC's activities include substantive studies of the scientific aspects of policy issues, reviews and advice about specific policy documents, workshops aimed at identifying current scientific thinking about major policy issues or at briefing policy-makers, and short, timely statements on topical subjects.

The EASAC Council has 25 individual members – highly experienced scientists nominated one each by the national science academies of every EU Member State that has one, by the Academia Europaea and by ALLEA. It is supported by a professional secretariat based at the Leopoldina, the German Academy of Sciences, in Halle (Saale). The Council agrees the initiation of projects, appoints members of working groups, reviews drafts and approves reports for publication.

To find out more about EASAC, visit the website – [www.easac.eu](http://www.easac.eu) – or contact the EASAC Secretariat at [secretariat@easac.eu](mailto:secretariat@easac.eu)

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# **Realising European potential in synthetic biology: scientific opportunities and good governance**

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# Foreword

Synthetic biology covers the design and construction of novel biological components, systems and processes – that are not already known to exist in nature – together with the re-design of existing biological systems. Synthetic biology is interdisciplinary, drawing on precepts and practices from a wide range of methodologies and disciplines, including the techniques of genetic engineering.

Although it can be sometimes difficult to demarcate synthetic biology from other established research areas, many within the scientific community believe that, by applying the principles of engineering and chemical design to biological systems, synthetic biology will lead to new applications of considerable societal value. Among the potential products and services are new systems for energy, materials and chemicals production; medical diagnostics, therapeutics and vaccines; and innovative approaches to the clean up of hazardous waste. Synthetic biology is important for Europe. There is significant potential for the European Union (EU) to invest in synthetic biology research and to capitalise on the emergent innovations.

This EASAC report was prepared by consultation with a Working Group of experts, acting in an independent capacity, nominated from across the EU. It also takes account of previous work by individual member academies. Our report discusses the distinguishing features of synthetic biology, describes a wide range of research approaches contributing to the current state of knowledge and explores potential applications in tackling societal priorities and supporting economic growth. We recognise, however, that in some respects this is becoming a controversial area and, in addressing the main concerns expressed about synthetic biology, we also assess the options for engaging in public dialogue and strengthening research governance and the regulatory environment in order to support sustainable development of the field. We emphasise the importance of making best use of all EU academic strengths—in the humanities and social sciences as well as the natural sciences and engineering.

In the time elapsed since the EASAC Working Group completed its task, a major research advance has been published<sup>1</sup>. This represents the first successful transplantation of a synthesised genome into a recipient cell: the synthesis of a slightly modified genome of the bacterium *Mycoplasma mycoides*, its placement into

the related species *Mycoplasma capricolum* and the demonstration of the replication of cells exhibiting the characteristics of *M. mycoides*. This important technical landmark represents a significant proof-of-concept in synthetic biology although it did not create a truly synthetic life form because the synthetic genome was inserted into an existing cell. The research provoked media accounts that reiterated previously expressed concerns about the creation of new forms of life, for example novel viruses as bioweapons. However, it is vital to ensure that the expression of these concerns does not inappropriately constrain the responsible conduct of science. One pervasive problem during the short history of synthetic biology has been the hyperbole expressed by some media and other commentators, but also by some within the scientific community. Our report observes that many concerns that are raised are not unique to synthetic biology, and that the scientific and regulatory frameworks that govern safe and accountable research and development are already in place, or can readily be adapted to cope with the scientific advances foreseen. Our recommendations identify tangible actions, building on what has already been achieved at both EU and Member State levels.

The EASAC report also discusses the early initiatives in public dialogue on synthetic biology—and recommends that these be augmented. In this regard, we welcome a recent survey of public attitudes by the UK research funding councils<sup>2</sup>. This survey showed that there is public support for synthetic biology research and its applications, subject to conditions on how and why it is conducted. EASAC endorses the emphasis on continued public dialogue to ensure that endeavours in synthetic biology reflect wide public interests and aspirations. That is why, for the first time, the EASAC recommendations for professional policy-makers in this report will be accompanied by a shorter communication for the lay public.

In his inaugural address, the new President of the German Academy of Sciences Leopoldina<sup>3</sup>, Jörg Hacker, in commenting on the potential of synthetic biology quoted Voltaire '*Any schoolboy can kill a flea, yet all the members of all the academies in the world cannot fabricate a flea*'. Nor can synthetic biology, so far in the 21st century. However, we are rapidly increasing our understanding of biology and the practicalities for engineering novel biological systems. And the academies have a continuing responsibility to interpret and communicate the

<sup>1</sup> Gibson, DG, Glass, JI, Lartigue, C, et al. (2010). *Creation of a bacterial cell controlled by a chemically synthesized genome*. Science, published online 20 May 2010, doi:10.1126/science.1190719.

<sup>2</sup> BBSRC, June 2010 'New report reveals public's views on synthetic biology', [www.bbsrc.ac.uk/media/releases/2010/100614-synthetic-biology-report.aspx](http://www.bbsrc.ac.uk/media/releases/2010/100614-synthetic-biology-report.aspx).

<sup>3</sup> Hacker, J (2010). Nova Acta Leopoldina NF **112**, no. 385.

implications of these advances. EASAC intends that this report will help to inform and stimulate further debate.

I thank the experts who contributed to the Working Group and my colleagues on the Council of EASAC who were responsible for organising the independent review of the draft report and its approval for publication. EASAC

welcomes further discussion on any of the issues that we have raised and on key matters that should be studied in future work.

Volker ter Meulen  
Chairman of the Working Group and  
President of EASAC

## Summary

Synthetic biology is the engineering of biology: the deliberate (re-)design and construction of novel systems to perform new functions, drawing on principles elucidated from biology, chemistry and engineering. It is an emerging field of increasing scientific and public policy interest.

This EASAC report is derived from activities by individual national academies of science together with analysis and advice from an EASAC expert Working Group:

- Identifying features that distinguish synthetic biology from, for example, genetic engineering and systems biology.
- Exploring what contribution synthetic biology might make across a wide range of applications (including health, energy, environment, agriculture, chemicals and security) to tackling EU societal needs and economic growth.
- Assessing what more may be needed to create an appropriate regulatory environment, what scientific and technological challenges need to be overcome and what societal concerns need to be addressed.
- Clarifying the implications for EU policy-making priorities.

In addition to the multiple potential industrial applications, synthetic biology will lead to a better understanding of natural biological systems because synthetic systems can be simplified to allow for experiments that would be too difficult to interpret if done in their full natural context. Among the major scientific advances in methodology, both *in vivo* and *in vitro*, where EASAC identifies continuing opportunities for European research are the following:

- Minimal genomes—identifying the smallest number of parts needed for life as a basis for engineering minimal cell factories for new functions.
- Orthogonal biosynthesis—engineering cells to expand the genetic code to develop new information storage and processing capacity.
- Regulatory circuits—inserting well-characterised, modular, artificial networks to provide new functions in cells and organisms.
- Metabolic engineering—attaining new levels of complexity in modification of biosynthetic pathways for sustainable chemistry.
- Protocells—using programmable chemical design to produce (semi-)synthetic cells.

- Bionanoscience—developing molecular-scale motors and other components for cell-based machines or cell-free devices to perform complex new tasks.

In each case, synthetic biology offers the potential to engineer new levels of safety into the application, for example by ensuring that the new systems are dependent on exogenous regulation, are separated from endogenous systems and are only operable in the target cells.

It is not yet clear if specific policy for synthetic biology is needed to advance the field or whether this would risk creating additional obstacles by making unnecessary distinctions from other fields. There is, as yet, no consensus on whether synthetic biology will be a truly transformational technology or, merely, an incremental advance. Nonetheless, there are governance implications for biosafety (the protection of legitimate users) and biosecurity (protecting against intentional misuse). Broadly, we conclude that existing legislation is adequate as long as synthetic biology remains an extension of recombinant DNA technology and the scientific community commits to developing voluntary codes of conduct.

## Recommendations

The objectives of the EASAC recommendations are to support those Member States that are already active in the field of synthetic biology, to identify options for building capacity in the currently less active countries, and to clarify the policy priorities for a coherent EU strategy to cover regulation as well as research and innovation:

- Research capacity—there is a significant agenda for the European Commission and Member States in synthetic biology that includes: (1) strengthening the underpinning scientific disciplines; (2) development of integrative Centres of Excellence to foster interdisciplinary perspectives; (3) funding new initiatives to network smaller laboratories across the EU; and (4) supporting translational research and standardisation of technology platforms and tools. Moreover, progress in synthetic biology depends not just on input from laboratory-based sciences but also the social sciences and humanities. Therefore, funding agencies must provide support across a broad range of topics.
- Training—future progress is critically dependent on training the next generation of scientists, particularly in bridging the biology and engineering disciplines and incorporating skills from chemistry, physics and informatics, at all levels from undergraduate through to Master's, PhD and post-doctoral programmes.

- EU competitiveness—despite a leadership position in some areas in synthetic biology, the EU will face increasing international competition. The European Commission and European Parliament need to be aware of the opportunities emerging from research and development (R&D) that will influence many industrial sectors, with implications for smaller companies as well as the industry leaders. The current strategic investment of EU Structural Funds for innovation must continue and should include synthetic biology.
- Research governance—the scientific community has a responsibility to help EU regulators understand the changing boundaries of synthetic biology. There are biosafety implications and until a synthetic organism is demonstrated to be harmless, it should be handled with the high safety requirements adapted from those already in place for other research. With regard to biosecurity the initiatives, by the Industry Association for Synthetic Biology to construct a global code of conduct for DNA synthesis companies and by the academies in developing individual researcher and institutional codes of conduct, are welcome. We advise that there are implications for the European Commission and Member States in supporting education and training programmes and providing the necessary infrastructure. To those who are considering new options for governance, EASAC emphasises the principle that regulation should neither stifle research nor impede transparency in communication. We also advise that patent offices must be careful when requested to grant broad patents that might unreasonably deter competition and slow down the translation of research advances into products.
- Product regulation—the EU control of approval of novel products emanating from synthetic biology applications (for example, medicinal products, environmental products, other chemicals, materials and biofuels) should generally be subject to the same regulatory framework as exists for products from other sources.
- Societal engagement—it is very important to make provision of accessible and accurate information about synthetic biology and this should be done pro-actively, not simply as a reaction to emotive media reports. EASAC advises that it is now timely to progress further initiatives across the EU Institutions to provide balanced description in lay language on the scientific advances and the prospect for new applications. The academies stand ready to play their part in encouraging and informing public debate based on accurate and relevant information. There is concomitant need to support scenario modelling to generate a range of forecasts on the contribution that synthetic biology may make, its cost-effectiveness and the impact of different regulatory approaches. It is also important to support continuing discussion on ethical issues within the broad societal context and we suggest that the All European Academies (ALLEA) may wish to consider initiating such discussion in their Standing Committee on Science and Ethics.

EASAC recognises that synthetic biology represents a challenging subject for policy-makers because the field is still in its formative stage, it is progressing very rapidly and it overlaps with other emerging technologies. However, we conclude that synthetic biology may make a major contribution to future EU innovation and competitiveness as well as to the understanding of natural biological systems. The timetable for societal impact is difficult to foresee but it is vital to prepare for the longer-term advances as well as for the products more likely to emerge in the short term.

# 1 Introduction: scope and objectives of this EASAC report

Synthetic biology is the engineering of biology: the synthesis of biologically based or biologically inspired systems, which display functions that are not yet known in nature. Synthetic biology also offers the promise of a better understanding of natural biological systems because synthetic systems can be simplified to allow for experiments that would be too difficult to interpret if done in their full natural context. In addition to biology and engineering, synthetic biology draws on several other disciplines, including chemistry, physics and information technology (IT).

It is an emerging field of increasing scientific and public policy interest, and the EU synthetic biology community is growing. Several member academies of EASAC have recently organised meetings or published documents in this area, and EASAC judges that it is now timely to bring together these academy analyses and perspectives (see Appendix 1 for details of previous academy activity, some in collaboration with other bodies).

Synthetic biology as an identifiable scientific field can be said to have started ten years ago when defining experiments were reported that transposed two of the traditions of physics and chemistry to biology: first, constructing something in order to understand it and secondly, starting from the simplest principles (Anon 2010). In 2002, the chemical approach to the first synthetic virus (polio) was published (Cello et al. 2002). In 2003, the Lawrence Berkeley National Laboratory opened the world's first synthetic biology department at a major research institution. The USA dominated much of the early research in synthetic biology (Ball 2004). As shown in the academy outputs document (Appendix 1), however, there are active research groups in several EU Member States. The European Commission was also supportive during Framework Programme 6 in examining the issues for capacity building and the strategic research agenda. However, these Commission-funded projects were completed in 2008 and, if less

funding is made available in Framework Programme 7, there is danger of a loss of momentum at the EU level. It is part of the purpose of the present report to identify the most promising areas in synthetic biology for support—from both the academic and industry perspectives.

Among the policy questions that this report attempts to explore are the following:

- What contributions can synthetic biology realistically make to tackling European societal needs and to promoting economic growth?
- What scientific and technical challenges need to be overcome in order for that potential to be realised? Where is investment needed in basic and translational research and technology development? What are the associated needs for training?
- What could prevent synthetic biology from making this contribution? What more needs to be done now to identify societal concerns, support public interaction, and modify the regulatory environment for biosafety, biosecurity and product development?
- What is likely to be the global competitive status of Europe in synthetic biology?

Commercial success in this field depends on the translation from basic research to applications. The hyperbole expressed by some commentators and, indeed, some scientists risks inflating public expectations. Therefore, it is an important responsibility for the scientific community to communicate a balanced account of current progress, future opportunities and the implications for policy-making. However, notwithstanding uncertainty about industrial applications, it is also of the greatest importance to appreciate and communicate the great scientific importance of synthetic biology in helping to achieve better understanding of natural biological systems.



## 2 Definition and relationships with other scientific disciplines

The academies express their definition of synthetic biology in different ways but they agree on a core meaning: ‘the deliberate (re)design and construction of novel biological systems to perform new functions, that draws on principles elucidated from biology and engineering’. At present, most synthetic biology is focused on microbes and embodies some key distinguishing characteristics:

- Synthetic biology is a convergent field, still in its infancy, incorporating knowledge from microbiology, genetics, genomics, chemistry, physics and IT as well as biology and engineering.
- It encompasses the hierarchy of biological structures from individual molecules to cells, tissues and organisms. A variety of entities is generated—parts, devices, systems.
- The manipulation of sets of genes is now routine in the leading international research centres. These capabilities will become more widespread as ever more rapid genome construction will become possible by the continuing methodological innovation and automation that is accelerating productivity and scale and reducing the cost of oligonucleotide and gene synthesis. Genome transplantation is likely to continue to be a significant rate-limiting step.
- Synthetic biology is free of the constraint on some earlier DNA research methods that only used genetic material from existing organisms.
- The design is intended to be rational and systematic. The objective is to create functions that do not exist in nature, but also to increase our understanding of biology.
- Further advances in synthetic biology will be aided by progressive understanding of the cell response to engineering. The reaction of organisms to oppose engineering presents a challenge to progress in some areas.

There are differing views on whether synthetic biology is a discrete field and is radically different from what has gone before. Is it revolutionary or merely an incremental advance? Are the expectations of the field unrealistically high, given the challenges inherent in understanding the complexity of living systems (Kwok 2010)? Some researchers and commentators see it as a natural and reasonable extension of genomics—a transition from reading to writing genome sequences. Others expect synthetic biology to be a truly transformational technology. It can be difficult to distinguish some current examples of synthetic biology unambiguously from recombinant DNA technology in general; the novel element in synthetic biology may often be one of scale. This present uncertainty in assessment of scope and impact of synthetic biology will be reflected in subsequent discussion in this report and represents a challenge for identifying where new policy may be needed.

Although the boundaries may be blurred, the aspirations of synthetic biology in complex systems can be distinguished from genetic engineering, in that it more explicitly seeks to model and predict the outcomes of the experiments. Conceptually, synthetic biology aims to use components with known functions (standardised constructs) to design predictable systems. Synthetic biology with its focus on engineering new functions can also be distinguished from systems biology, where the emphasis is on the description and analysis of the dynamic interactions between components of a biological system (Academy of Medical Sciences and Royal Academy of Engineering 2007). However, there will be many occasions when the integration of synthetic and systems biology is necessary to advance research and its applications (Anon 2010): the ability to model and quantitatively predict biological effects in systems biology is complemented by the aim in synthetic biology to construct biological systems in order to understand them.



### 3 Envisaged societal applications

Recent market research<sup>4</sup> estimates that the current global market for synthetic biology is approximately US \$230 million, much of which is attributed to synthetic DNA and other reagents and tools. The same market research predicts that the world market could expand to US \$2.4 billion by 2013, with the chemical and energy sectors dominating.

Numerous specific applications have been postulated for medicine, agriculture, environment, energy, materials and national security—both new products and services and more efficient production platforms. The timetable for delivery is not clear and much remains to be done to translate the advances in fundamental science into applications. It is notable that much of the discussion about possible impact has been framed in terms of the societal benefits rather than benefits to the producer. In this sense, the proponents of synthetic biology have learned a lesson from the poor uptake of an earlier emerging technology in genetically modified (GM) agriculture, where public scepticism was based, in part, on a lack of immediate evidence for consumer benefit. Some of the more likely applications are listed in Table 1.

As synthetic biology covers a broad technology domain, it is not easy to forecast which societal applications will surface first although many commentators agree in expecting biofuel products within the near future. Synthetic biology can contribute to the objectives

for developing second-generation biofuels to avoid competition with food production resources, for example in generating ethanol from agricultural waste and plant residues. A recent review (Sheridan 2009) lists some of the leading, smaller, innovative companies who are using advanced biological engineering to produce biofuels (ethanol, diesel, algal oils); most of these examples are from the USA although the UK and Denmark are also represented<sup>6</sup>. It is debatable whether these early activities can be considered to fall within mainstream definitions of synthetic biology. However, there have also been recent major advances in microbial engineering that enable the consolidation of many key reactions within a single strain of *Escherichia coli* to convert inexpensive biomass into both fatty-acid-based fuels (biodiesel) and other renewable chemicals. This recent work (Steen et al. 2010) demonstrates the reduction to practice for scalable, controllable and, perhaps, economic routes to commercial production. In addition to these advances in complex microbial engineering, other synthetic biology approaches to biofuel R&D may become viable over a longer time-frame, for example to produce hydrogen from water and solar energy using engineered microorganisms or biomimetic catalysts.

Other examples of the applications listed in Table 1 will be discussed in subsequent sections: in particular, there is a considerable amount of European research focusing on applications for the health sector.

**Table 1** Examples of potential innovation<sup>5</sup>

Societal impact	Proposed specific application
Medicine	Protein therapeutics, low-molecular weight drugs (e.g. antibiotics), vaccines, gene therapy; controlled release drug delivery systems and DNA-like polymers for location-specific drug release; tissue engineering; rapid, sensitive <i>in vitro</i> diagnostic tests and multi-chip detection arrays.
Energy	New microbes for generating hydrogen and other energy; second-generation biofuels; artificial photosynthesis.
Environment	Detection of pollutants; bioremediation.
Chemical industry	Improved production platforms for fine and bulk chemicals; microbes engineered to produce proteins as alternative route to natural fibre manufacturing and 1,3-propanediol, precursor of artificial fibres.
National security	Biological weapon sensors.
Agriculture	Food additives.
Biologically inspired nanomachines and biosensors	Molecular-scale switches and other devices.

<sup>4</sup> 'Synthetic biology: emerging global markets', BCC Research, USA (June 2009), cited by Nelson (2009).

<sup>5</sup> Examples are drawn from the Academy outputs, POST (2008) and [www.tessy-europe.eu](http://www.tessy-europe.eu). A recent review by Khalil and Collins (2010) also provides detailed information on a broad range of applications. In addition to the medical applications listed in Table 1, Khalil and Collins note the importance of synthetic biology approaches in devising new lead screening platforms and for engineering organisms as novel anti-infective (phages) and anti-cancer agents (bacteria).

<sup>6</sup> EU multinational companies such as Shell are also investing in algal oils. The European Algae Biomass Association ([www.eaba-association.eu](http://www.eaba-association.eu)) provides information on R&D activities, standards and product specification and the legislative framework.



## 4 Public expectations of synthetic biology research and applications

The first product class to emerge is likely to have a major influence on public expectations. From a policy perspective, what is perhaps more important than the short-term predictions of specific product outputs is the need to build the R&D infrastructure and culture for the longer-term to underpin the emergence of multiple applications, including those that are presently unanticipated.

A recent survey of public perceptions commissioned by the Royal Academy of Engineering in the UK<sup>7</sup> showed that awareness of synthetic biology is low but that, when information is provided, members of the general public expressed great interest in the prospect of designing microorganisms to help manufacture biofuels and medicines. Concern was expressed, however, about

deliberately releasing artificial organisms into the environment to tackle pollution. Public respondents wanted government to regulate synthetic biology but were concerned that regulation should not stifle development of the area. Public views on patenting were mixed but there was understanding that investors are entitled to a return on their time and money, within the broader context of balancing returns on investment and social responsibility.

It is important for this work on public attitudes to be extended across the EU; there has already been some examination of societal attitudes in work funded by the European Commission (Appendix 2) and there is an Austrian study in progress<sup>8</sup>.

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<sup>7</sup> 'Synthetic Biology: public dialogue on synthetic biology', The Royal Academy of Engineering, June 2009, at [www.raeng.org.uk/news/publications/list/reports/Syn\\_bio\\_dialogue\\_report.pdf](http://www.raeng.org.uk/news/publications/list/reports/Syn_bio_dialogue_report.pdf). This public dialogue was held to complement the Academy's inquiry, published in May 2009, 'Synthetic biology: scope applications and implications', at [www.raeng.org.uk/synbio](http://www.raeng.org.uk/synbio).

<sup>8</sup> "COSY – Communicating Synthetic Biology", at [www.idialog.eu/index.php?page=cosy](http://www.idialog.eu/index.php?page=cosy). Further information on this study and other societal aspects of synthetic biology was published in a special issue of the journal *Systems and Synthetic Biology* (Schmidt 2009).



## 5 Methodological approaches in synthetic biology

'The synthesis of increasingly complex unnatural networks embedded in living matter is an emerging theme in synthetic biology' (Chin 2006). Such achievements have become possible because of the major improvements in the precision, speed and cost reduction in gene sequencing and DNA synthesis, coupled with the techniques of gene transplantation, genome assembly, model building and computational design.

Synthetic networks have enabled the generation of systems endowed with genetic components and expanded genetic code (see section 5.2). Broadly, there are two approaches to doing this: involving either the assembly of well-characterised, freely combinable, naturally occurring modules<sup>9</sup> into novel networks or the creation of unnatural, standardised modules. Although the experimental approaches may vary widely, the common challenge is to exert the necessary molecular control in time and space to achieve the desired outcome. As Chin (2006) observes, endowing living organisms with new functions can be difficult for several reasons—they are complex, open systems that operate far from thermodynamic equilibrium, there is lack of information on the cell-wide specificity of molecular interactions, and components *in vivo* are much harder to define and control than *in vitro*. Despite these challenges, significant success has been achieved in demonstrating the novel techniques. Advances are also being made towards the objective of creating artificial cells *de novo*. Where possible, examples of research taking place in Europe are described in the following sections, but areas where Europe is lagging behind the USA are also highlighted. The examples have been chosen to illustrate key points rather than to be a comprehensive account of the field and to cover approaches *in vivo* (sections 5.1–5.4) and *in vitro* (sections 5.5–5.6). The *in vitro* systems are, as yet, limited in relying on self-assembly but offer additional possibilities to sample the 'chemical space'.

### 5.1 Minimal genomes

This is a major research area, initiated in the USA, to define the minimal number of parts (genes) needed for life, based on a full description of those parts and their interaction, to serve as a basis for engineering minimal cell factories for new functions. Such work builds on advances in several areas of genomics and related disciplines—the use of comparative genomics approaches to identify shared core genome sequences across species;

systematic gene disruption studies to explore function; the characterisation of naturally evolved minimal gene sets (for example in parasites or endosymbionts for survival in specialised environments); and the systems biology-based computational approach. Combining the insight gained from these research methodologies helps to identify an obligatory set of bacterial genes for survival in defined laboratory settings, with more genes required to survive in natural environments<sup>10</sup>. However, the size of this minimum gene set is still controversial. An estimate of 500–800 genes was made based on detailed analysis (Pal et al. 2006; Feher et al. 2007) but subsequent work based on gene essentiality studies (which may underestimate the number of genes needed for independent life) indicates a range of 300–400 genes.

Based on the accumulating understanding of these minimal gene sets, the experimental approaches that can then be taken to construct the minimal genome can be described either as bottom-up, that is *de novo* synthesis, or top-down. The latter process involves stepwise reduction of different bacterial and eukaryotic genomes (e.g. *E. coli*, *Bacillus subtilis*, *Saccharomyces cerevisiae*, *Cornebacterium glutamicum*, *Aspergillus oryzae*) to a reduced gene set that allows them to function. It is noteworthy that the systematic deletion of mobile genetic elements (e.g. insertion elements, transposons and prophages) can increase genome stability (Posfai et al. 2006); this may be important for technical applications and for the construction of safe strains.

In a scientific breakthrough, bottom-up work was pioneered by researchers at the Craig Venter Institute (Gibson et al. 2008) synthesising the *Mycoplasma genitalium* genome<sup>11</sup>. This organism, with a small genome and minimal metabolic complexity, may become a platform for understanding how the simplest cell works. Assessing the resilience of such minimal cells, in particular how they behave under stressful conditions or in an industrial setting, represents an important topic for future research. The bottom-up approach has potential advantages in flexibility of design and rapidity of construction, but relies on improvements in speed of DNA synthesis and genome transplantation. The top-down alternative is perhaps more controllable but the genetic tools are not yet available for many species. The greatest opportunity may reside in merging the approaches, where a modular core genome serves as a chassis for replacement by synthesised elements. For example, the

<sup>9</sup> A module is defined as a collection of molecules whose function can be perceived as discrete.

<sup>10</sup> Other research funded by the Sixth and Seventh Framework Programmes (3D-REPETOIRE and PROSPECTS respectively) provides detailed information on the cellular machinery required for *Mycoplasma pneumoniae* to survive independently (Kuhner et al. 2009).

<sup>11</sup> In the period since the Working Group finalised their drafting of the EASAC report, this scientific team has made further very significant accomplishments in synthetic biology (see footnote 1 in the Foreword to this report).

characterisation of *Mycoplasma pneumoniae* (footnote 10) as a potential chassis for importing novel biological functions through synthetic biology may bring new therapeutic applications within range.

There is a rapidly growing database of synthetic building blocks (DNA sequences of defined structure and function). Significant impetus in this area has been provided by the Massachusetts Institute of Technology (MIT) initiative to develop a standard registry of biological parts (BioBricks<sup>12</sup>) and to host an international student competition (International Genetically Engineered Machine Competition, iGEM), where participants design new systems based on BioBricks.

The research area of minimal genomes may lead to many new utilities. One application currently being pursued is the design of novel microbes to produce hydrogen or other biofuels<sup>13</sup>. Other, still limited, experimental data discussed in the Berlin meeting (Appendix 1) show that some reduced genomes are more productive in certain respects (for example amino-acid synthesis), potentially supporting various other applications in industrial production.

## 5.2 Orthogonal biosystems: expanding the genetic code

As an alternative approach, new properties of cells might be engineered to expand information storage by adding coding capacity—for example, by building a parallel protein translation capability within the cell. The strategy associated with orthogonality aims to modify subsystems without causing significant disturbance elsewhere. Several routes have been proposed for engineering the genetic code to incorporate artificial amino acids. One approach, pioneered in the USA and UK over the past decade, is to create ribosomes (nucleic-acid-dependent amino-acid polymerases) with expanded chemical scope to act as novel cellular translation systems able to synthesise unnatural proteins. Control over macromolecular interactions exerted by this parallel modular synthesis requires orthogonal ribosome/messenger RNA (mRNA) pairs (the latter generated by the unique aminoacylation of transfer RNA (tRNA) with unnatural monomers). The artificial proteins can be synthesised with high efficiency (Wang et al. 2007), bringing various applications *in vivo* within range. For example, it will be possible to incorporate specific functionality in order to study the topology of protein interactions in systems that have been hard to characterise hitherto (within biological membranes) and to encode specific post-translational modifications, creating homogenous protein therapeutics (such as

polyethylene glycol-derivatised proteins to improve pharmacokinetics)<sup>14</sup>.

An alternative and complementary approach is based on propagating *in vivo* additional types of nucleic acids (xeno-nucleic acids, XNA), whose chemical backbone differs from deoxyribose and ribose (Herdewijn and Marliere 2009; Marliere 2009). XNA building blocks would not be found in nature but can be supplied exogenously to cells that would also have to be equipped with the additional, appropriate, enzyme machinery for replicating and expressing XNA. This would result in the establishment of a genetic enclave unable to exchange genetic information with the natural nucleic acids. First steps in this endeavour are being explored in the Framework Programme 7 Orthosome project.

As discussed in the German Statement on synthetic biology compiled by the academies together with the major research funder, DFG (DFG, German Academy of Sciences Leopoldina and Acatech 2009), orthogonal biosystems offer a generalisable way of increasing biological safety because an artificial genetic code can only be translated in organisms with the respective orthogonal translation system.

## 5.3 Regulatory circuits

Novel cellular function is a matter not just of molecular chemistry but also of circuitry. Synthetic gene circuits that emulate the expression dynamics of living systems, and are perceived as analogous to electronic circuits, are beginning to provide new insight into complex control networks. Although there is no clear boundary between classical biotechnology and synthetic biology with respect to the development of artificial circuits, recent work has led to the regulation of post-transcriptional mechanisms as well as transcriptional control.

Artificial gene networks can be designed from modular, well-characterised and compatible genetic components, such as molecular switches and biological memory, implanted into natural systems. For example, the work of Fussenegger and colleagues in Switzerland, part-funded by Framework Programmes, produced a synthetic mammalian oscillator based on an auto-regulated, sense-antisense transcription control circuit, that enables autonomous, self-sustained and tuneable oscillatory gene expression (Tigges et al. 2009). Earlier work by this group described a range of new tools for circuitry; including gas-inducible transcription control in a heterologous system (Weber et al. 2004) and a synthetic time-delay circuit in mammalian cells (Weber et al. 2007b). Even more ambitiously, a synthetic ecosystem (interconnection

<sup>12</sup> <http://parts.mit.edu>.

<sup>13</sup> International patent applications were filed by the Craig Venter Institute in 2007.

<sup>14</sup> [www.ambrx.com](http://www.ambrx.com).

of bacterial, yeast and mammalian cell signalling) that begins to mimic fundamental coexistence patterns in nature such as symbiosis and parasitism, involved the engineering of sender cells to transmit volatile molecules to recipient cells to induce their expression of target genes (Weber et al. 2007a). It is also envisaged that prosthetic gene-network devices can be integrated into cells and functionally connected to their metabolism in order to sense and correct metabolic disturbances, by triggering a self-sufficient therapeutic response. Proof-of-principle was demonstrated recently in a model system whereby homeostasis of urate (elevated in tumour lysis syndrome and gout) was maintained in the mouse bloodstream (Kemmer et al. 2010).

Other European research is combining the techniques of synthetic biology and systems biology to design new *in vivo* functions. For example, a synthetic network in yeast, comprising five genes regulating one another in multiple ways, provides a test-bed for benchmarking reverse engineering and modelling (Cantone et al. 2009).

These examples can be seen as constituting the first steps towards interconnecting basic modules in complex systems. There are still obstacles to translating the findings: the artificial circuits are integrated within a biological system that is not itself well understood and the new components are subjected to the host organism's complexity. Unintended interactions between the synthetic circuit and cell physiology can influence circuit function and their interplay can only be predicted to a limited extent and must, therefore, be assessed empirically. Nonetheless, these research advances are enabling the understanding of structure-function correlation in cellular signal process circuitries and may engender various novel applications, for example in gene therapy, tissue engineering and biopharmaceutical manufacturing. As a basic safety principle, it is prudent to ensure that the functioning of artificial gene circuits depends on exogenously applied inducers.

A recent review of other developments (Kiel et al. 2010) compared the current situation for engineering genetic circuits with the longer-term opportunities and challenges for engineering signal transduction pathways in prokaryotic and eukaryotic cells. Whether signal transduction pathway engineering can become a discipline analogous to DNA engineering depends to a significant extent on the generation of reliable standardised parts. Although crosstalk between synthetic and native elements does not appear to be so significant a problem as originally feared, a continuing lack of understanding about negative feedback regulation could be problematic if such regulation dampens signalling outcomes in engineered systems (Kiel et al. 2010).

More broadly, the manipulation of circuits in cells and other methodologies in synthetic biology will be facilitated by developments in other technology platforms, for example micro-fluidics (Gulati et al. 2009). Micro-fluidics offers the prospect of working with smaller reagent volumes, shorter reaction times and in parallel operations enabling, for example, integration as the 'lab-on-a-chip'.

## 5.4 Metabolic engineering

One significant development in synthetic biology is the engineering of modified biosynthetic pathways to produce useful materials that they do not produce in their wild-type form, building on a relatively long tradition of using genomic technologies to produce increased quantities of natural products<sup>15</sup>. The most frequently quoted synthetic biology example is the production in yeast and *E. coli* of artemisinic acid, a precursor of the isoprenoid artemisinin, an anti-malarial drug traditionally obtained, in inadequate amounts, from the plant *Artemisia annua*. It was predicted that artemisinin derived from yeast, potentially reducing production costs by 90%, could be marketed within two years<sup>16</sup>. Other recent examples of metabolic engineering include the following:

- Production of the anti-cancer drug taxol in *S. cerevisiae*.
- Production of a precursor of spider silk in *Salmonella typhimurium*, capitalising on the ability of the pathogen to secrete the protein (which is toxic to cells).
- Second-generation biofuels, for example engineering yeast to catabolise C<sub>5</sub> sugars (xylose) as well as C<sub>6</sub> sugars (glucose).
- Genetically modifying a plant virus with additional lipase activity to create a biocatalyst with programmed self-assembly and reproduction (Carette et al. 2007), thereby providing proof-of-principle for a cascade catalytic system operating like a metabolic pathway.
- Synthesis of hydrocortisone from glucose in yeast.

The question remains as to the extent that the current examples illustrate novel attributes of synthetic biology or can be regarded instead as an extension of previous research in genetic engineering. What is clear is that examples are appearing that increasingly represent more complex biological systems embodying the application of engineering principles in rational design and capitalising on the standardisation of predictable modular biological components, based on detailed understanding of the

<sup>15</sup> For example, the improvement of strains of actinomycete bacteria to alter the regulation of the biosynthesis of antibiotics and their precursors (Lum et al. 2004).

<sup>16</sup> Press release at [www.amyrisbiotech.com/pdf/Amyris\\_Press\\_Release\\_03\\_03\\_08.pdf](http://www.amyrisbiotech.com/pdf/Amyris_Press_Release_03_03_08.pdf). Estimates that are more recent forecast 2012.

biosynthetic pathways. Thus, this field is entering a new dimension in terms of generating products from complex gene clusters rather than a single gene. It can be expected that such products will become less expensive than when produced by conventional routes and that, in many cases, there will be environmental advantages in sustainable chemistry<sup>17</sup>. One particularly interesting example is offered by the engineering of non-ribosomal peptides of polyketides in bacteria on naturally modular assembly-line multi-enzymes. Many of the natural products of these multi-enzyme systems are clinically validated drugs, and rational redesign of these pathways appears to offer a relatively near-term societal and commercial benefit from synthetic biology in the shape of improved antibiotics and other bioactive natural products (Zhang et al. 2008).

## 5.5 Protocells

By contrast with the approach based on reducing biological systems, researchers are also attempting to create synthetic cells *de novo* by programmable chemical design, i.e. from inorganic as well as organic molecules. The ambitious objective is for such cells to have properties of self-repair, self-assembly, self-reproduction and evolvability (Rasmussen et al. 2004). Whereas the biological community dominates the various work on systems *in vivo*, the research on protocells is strongly supported by the chemistry, physics and bioinformatics communities.

Significant progress has been achieved in the Framework Programme 6 project, PACE (Programmable Artificial Cell Evolution, [www.istpace.org](http://www.istpace.org)). The protocell model can be viewed as an enclosed laboratory to study chemical reactions in confined geometries and depends on integration of lipid metabolism (the basis for cell containment), genetic information (the basis for replicability) and redox metabolism (for energy production). There is the prospect that methodological advances will allow the same high information density in chemical processing as is found in living cells. One experimental challenge is to create selective membrane permeability and, in part, this research can build on the considerable European experience on artificial vesicles and the understanding of membrane function. For example, semi-synthetic membrane systems have been constructed with channels that can be controlled using light or pH change (Kocer et al. 2007).

Other European-funded work on semi-synthetic minimal cells, the 'Minimal Life Project' (Chiarabelli et al. 2009), exemplifies the potential for novel applications, for example in drug delivery systems, where the drug is produced within the minimal cell compartment. Such work is also helping to identify those essential characteristics of minimal cells that enable them to reproduce, interact with the environment and evolve.

In parallel with the technical work on development of artificial cells, the EU is supporting efforts to foster informed public discussion about the social, safety and ethical issues that may be raised by these specific developments (European Centre for Living Technology, [www.ecitech.org](http://www.ecitech.org)). In time, many assume that research on artificial life will illuminate the perennial questions such as 'what is life?' (Rasmussen et al. 2004)<sup>18</sup>. In the meantime, however, there are some very practical questions to be answered. What are the obstacles to integrating genes, proteins and energetics within a container? How can theory and simulation better inform experiments? What are the most likely early applications of this research? Work on protocells is helping to understand how natural self-replicating systems emerge but can also be expected to lead to the engineering of self-replicating machines.

## 5.6 Bionanoscience

Biological cells are equipped with a variety of molecular machines that perform complex tasks such as cell division and intracellular transport. It is envisaged that analogues of these biological motors could be employed in artificial environments (Van den Heuvel and Dekker 2007) in cells or cell-free devices. Proof-of-principle for a variety of systems has been demonstrated in a series of publications from researchers in the Netherlands, described in the Netherlands Academy's report, using motor proteins (particularly kinesin- or myosin-based) for manipulating and powering nanoscale components, a key step in the development of nanomachines. For example, molecular-scale motors can be light-driven (Eelkema et al. 2006) or constructed as controlled biohybrid motors where enzymes working in tandem create kinetic energy (Pantarotto et al. 2008)<sup>19</sup>. The bionanosciences are likely to deliver many other applications, for example in biosensing and catalysis.

<sup>17</sup> One illustration of the magnitude of these opportunities for sustainable chemistry is provided by the diverse natural landscape represented by secondary metabolites in symbiotic bacteria (Piel 2009). Current extraction of drugs and other chemicals from such sources in their natural habitat is unsustainable.

<sup>18</sup> EASAC member academies continue to stimulate discussion on these fundamental issues. For example, 'What is life?' is the title of the Leopoldina biennial assembly to be held on 23–25 September 2011 ([www.leopoldina-halle.de](http://www.leopoldina-halle.de)).

<sup>19</sup> Biohybrid motor systems are an active area of research elsewhere in the EU, for example funded by the Framework Programme 6 Network of Excellence MAGMANET. In a recent publication (Lee et al. 2009), it was noted that research on molecular machines has been impeded because most such molecules have been organic whereas the physical properties that are most desirable in molecular machines – such as magnetism or the ability to conduct electrons – are usually found in inorganic compounds. This obstacle is being overcome by research on biohybrids.

The research portrayed in these examples falls within the remit of what is usually termed nanotechnology. It is probably premature as well as unnecessary to attempt any demarcation that would assign individual approaches unambiguously as synthetic biology rather than nanotechnology although, in time, the precise definition of synthetic biology (chapter 2) may come to exclude research within the broader field of bionanosciences. The currently blurred boundary does not apply just to molecular motors. For example, some recent suggestions for possible customised applications in biology-inspired nanotechnology to fight infectious diseases (Morris 2009) might also be seen as qualifying as synthetic biology.

A detailed discussion of the current scientific status of nanotechnology is beyond the scope of this EASAC report

but key developments are discussed at the following websites:

- [www.etp-nanomedicine.eu](http://www.etp-nanomedicine.eu), the European Technology Platform on nanomedicine. A Vision Paper was published in 2005 and the Strategic Research Agenda in 2006. A recent meeting in the European Parliament reviewed nanomedicine developments analysed by the NanoMed Round table, funded by the Seventh Framework Programme<sup>20</sup>.
- [www.nano.gov](http://www.nano.gov), the US national nanotechnology initiative. The US National Institutes of Health (NIH) focus on nanomedicine is available at <http://nihroadmap.nih.gov/nanomedicine>.

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<sup>20</sup> June 2010, 'Nanomedicine in Europe: present and for the future'.



## 6 Safety, social and governance issues

### 6.1 Identifying what is new

Does synthetic biology bring qualitatively new governance challenges or merely an extension of known issues?

Many emerging technologies elicit social concerns but experience teaches that the social and ethical issues arising from the application of new technologies are rarely new or unique to that technology. However, whenever significant social and ethical issues arise, they must be addressed, irrespective of whether they are genuinely new.

In the joint Royal Society (2008b) report with the Science Council of Japan it was remarked that new and emerging technologies present challenges for national and international governance, particularly when their development and impact is faster than the construction of international safeguards. This may require new models of international co-operation in governance. Appraisal of the governance framework issues for synthetic biology can draw on those previously described for other emerging technologies, for example, for nanotechnology (Royal Society and Royal Academy of Engineering 2004). Acceptance and use of a new technology will depend upon a range of social factors associated with whoever controls the technology and whoever benefits from its exploitation—individual consumers and political decision-makers, within the broader macro-economic environment. The impact of any new technology can be located on a continuum between the extremes of incremental progress and radical disjunction. One noteworthy point might be emphasised in the context of the Royal Society and Royal Academy of Engineering's report on nanotechnology. At that time (2004), their report noted especial public concern about the notion of self-replicating systems but judged that outcome to be some considerable time in the future. In consequence of the scientific advances made in synthetic biology since 2004, it may be that this future point has come much nearer. The options for an ethical framework for synthetic biology are discussed in a Focus issue of the *Journal of the Royal Society Interface*<sup>21</sup>. We emphasise a key issue here in terms of the responsibilities of academies: the scientific community must encourage open debate and warn of the consequences if excessive regulation inadvertently constrains scientific advance. Furthermore, it is vital for the academies, research funders and other scientific bodies to provide accessible and accurate information about synthetic biology developments so as, pro-actively, to inform the broader debate rather than simply reacting

to the latest alarmist assertions in the media. EASAC advises also that the academies must do more to support continuing discussion of the ethical issues within the broader societal and philosophical contexts and EASAC recommends that the All European Academies (ALLEA) should consider initiating such discussion within their Standing Committee on Science and Ethics<sup>22</sup>.

There is a lot that can be done by the scientific community to develop a framework that ensures safety of research and product use. There are two main objectives: (1) biosafety, which encompasses the protection of legitimate users and (2) biosecurity, protecting against the intentional misuse of biosciences, whether at the State level, by a terrorist organisation or by the misguided individual (increasingly possible in consequence of the progressive 'deskilling' of biotechnology<sup>23</sup>). As the Netherlands Academy report notes, there are some important practical questions to answer. Are effective and adequate protection measures in place if these microorganisms unintentionally find their way into the wider environment? How controllable are these microorganisms if their application lies outside the laboratory or factory? Is the world adequately protected against biohackers and bioterrorism, now that standard biological components are so easy to obtain?

Both biosafety and biosecurity were discussed extensively at the Berlin meeting (Appendix 1). The following material draws on that discussion and the publication of the German Statement, which concludes that the aims of synthetic biology do not yet mandate additional requirements to ensure biological safety in laboratories or on deliberate release, and do not incur risks with regard to possible misuse other than those arising from genetic engineering. And, as noted in previous sections, the methodologies involved in synthetic biology can be used as means to engineer additional safety, for example by creating dependence on exogenous nutrients or inducers, or on endogenous subsystems.

### 6.2 Biosafety

Risks might arise from the uncontrolled, accidental, release of self-replicating systems outside of the research environment but also from the deliberate release that may be required for the novel application, for example in environmental remediation. Related issues were

<sup>21</sup> 'Synthetic biology: history, challenges and prospects', organised by Haselhoff, J, Ajioka, J and Kitney, R, 2009. Available at [http://rsif.royalsocietypublishing.org/site/misc/syntheticbiology\\_focus.xhtml](http://rsif.royalsocietypublishing.org/site/misc/syntheticbiology_focus.xhtml).

<sup>22</sup> [www.allea.org/Pages/ALL/12/72s.bGFuZz1FTkc.html](http://www.allea.org/Pages/ALL/12/72s.bGFuZz1FTkc.html).

<sup>23</sup> Opinions vary on the size of the threat posed by "biohacking". Alper (2009) concluded that there is relatively little evidence but significant hyperbole about do-it-yourself biotechnology whereas Bennett and co-workers (2009) take the threat more seriously. Currently, the situation is uncertain but most of the discussion emanates from the USA.

central to the GM agriculture debate when public/non-governmental organisation (NGO) concerns prevented the widespread application of GM crops in Europe. Potentially, some of these concerns could be allayed if synthetic organisms were modified such that they could only survive on substrates not found in nature. However, the potential for horizontal gene transfer and for evolution to escape design constraints is difficult to quantify. Until a synthetic organism is demonstrated to be harmless, it should be handled with high safety requirements, adapted from those already in place for uncharacterised microbes and existing genetically modified organisms (GMOs) and subject to the well-established systems of regulation in place at the EU and national level.

As discussed in the German Statement, in cases of high complexity and uncertainty, application of the precautionary principle necessitates spatial and temporal containment of experiments together with close monitoring and problem-oriented flexibility. It is reasonable to assume that the current management systems can serve as a basis for regulating synthetic biology research proportionately to risk. The recent updating of the guidelines from the US National Institutes of Health (NIH) for research involving recombinant DNA, to bring synthetic biology within the present framework of procedures for safety, assessment and management<sup>24</sup> provides a very timely stimulus for updating EU legislation. In the NIH view, replication is the unique risk characteristic of synthetic biology so that an exemption can be made in the guidelines for non-clinical research using synthetic nucleic acids that cannot replicate.

It should also be appreciated, however, that the increasingly easy access to DNA sequences will lead to the adoption of the techniques of molecular biology by other disciplines, such as engineering, where there is little experience in dealing with biological agents. It is important to ensure consistent standards of scientific management as well as education for those who join the community.

Although risk assessment should not be fundamentally different for synthetic biology than for other recombinant DNA research, assessment may be challenging for some of the products of synthetic biology, given the diversity of scientific approaches currently used such as minimal genomes, DNA-based biocircuits and protocells. Unsuspected interactions might produce new properties for artificial systems. It is desirable to develop the framework in advance to assess risk and benefit together although this is a demanding task when both benefit and risk are unquantified and, as at present, intangible in some respects. A 'calculus of risk' has been proposed<sup>25</sup>

to enumerate the degree of risk for new developments. Inevitably, this would be a crude tool but might be useful to distinguish remote risks from more immediate ones.

As noted by the European Group on Ethics (EGE, Appendix 2), it is important for the European Commission to compile information on current risk assessment procedures in the EU as a basis for determining if there might be gaps in regulation that need to be addressed in preparation for the advent of novel products developed using the methods of synthetic biology. Safety of different product classes would fall within the relevant legislation previously established (see chapter 7), taking account of the concomitant need, where it exists, to develop international standards and procedures.

### 6.3 Biosecurity

The procedures for ensuring biosafety will not protect against those whose objective is to misuse biosciences. Policy-makers in the EU have been less active than in the USA in considering the issues for biosecurity. An early Central Intelligence Agency (CIA) report (2001) warned that synthetic biology could produce engineered agents worse than any disease known to man and proposed that a qualitatively different working relationship was now required between the intelligence and biological sciences communities. Some in the scientific community doubt that this is a real threat, if only because it would be much easier to misuse natural pathogens. Because a pathogen has numerous characteristic properties (pathogenicity, infectiousness, host specificity), it is usually assumed to be unlikely that new pathogens could be created synthetically, but rather that existing pathogens might be modified (for example, so as to be resistant to antimicrobial agents).

The Swiss Academy concluded that '*The possibility of the abusive and criminal application of synthetic biology, for example, for bioterrorism, is negligible.*' Despite this scepticism, it is sensible to consider what steps could be taken to improve biosecurity. From the academies' perspective, the focus on synthetic biology can be informed by the previous InterAcademy Panel (IAP) statement on biosecurity, which presents principles to guide individual scientists and scientific communities, elaborating a code of conduct to reduce the risks that bioscience research could be misused (Box 1).

Subsequent to this IAP statement, individual academies have catalysed further debate. For example, the Royal Netherlands Academy of Arts and Sciences (2009) published a proposal for a national code of conduct in

<sup>24</sup> The NIH guidelines are at <http://oba.od.nih.gov/rdna/rdna.html>.

<sup>25</sup> G Poste, cited in Ball (2004).

**Box 1 Principles to be taken into account when formulating codes of conduct in the biosciences**

1. Awareness—scientists should bear in mind potential consequences of their research and refuse to undertake research that has only harmful consequences.
2. Safety and security—scientists have the responsibility to use good laboratory procedures, whether codified by law or common practice.
3. Education and information—scientists should be aware of, and disseminate information about, national and international laws and regulations, policies and principles aimed at preventing misuse of research.
4. Accountability—scientists who become aware of activities that violate the Biological and Toxins Weapons Convention or law should raise their concerns with appropriate authorities.
5. Oversight—scientists with responsibility for oversight of research or evaluation or publication should promote adherence to these principles and act as role models.

Summarised from IAP Statement on Biosecurity, November 2005. IAP Working Group was chaired by Accademia Nazionale dei Lincei, Italy, and Royal Netherlands Academy of Arts and Sciences, [www.royalsociety.org/document.asp?tip=0&id=3948](http://www.royalsociety.org/document.asp?tip=0&id=3948)

this area and the Royal Society summarised its national and international activities on reducing the risk of misuse of scientific research (Royal Society 2008c). Specifications for a code of conduct remain an active area of discussion for the bioscience community more generally and, for example, the German Research Foundation published its report on dual-use issues two years ago. The European Commission is proceeding with plans to establish a code of conduct in nanotechnology (European Commission 2008) that covers not just the dual-use issues for biosecurity but also broader aspects of research governance including biosafety, Intellectual Property Rights and scientific integrity.

In the meeting in Berlin, various specific actions for synthetic biology biosecurity were discussed that align with the general principles (Box 1). These included the following:

- Progressing education on dual use issues in the undergraduate life sciences curriculum plus

continuing effort to raise awareness across the research community. Recently, the Polish Academy of Sciences together with the US National Academy of Science hosted a workshop<sup>26</sup> to catalogue and assess current programmes at professional and graduate level for education about dual use technologies and biosecurity. Among the background papers for this meeting was a UK–Italian survey of life-science programmes in Europe that showed that only 3 out of 57 universities surveyed included a biosecurity module and only 22 out of 142 degree courses referenced the Biological Weapons Convention.

- Licensing or other management constraints in synthesising novel genetic sequences to control of the supply of sequences and gene synthesising machines. For example, in Germany businesses formed the Industry Association for Synthetic Biology ([www.ia-sb.eu](http://www.ia-sb.eu)) for the voluntary control of DNA sequence provision, subject to satisfactory completion of inquiries by the company on the customer to ascertain country of origin, nature of the laboratory and anticipated gene function.
- Ensuring that synthetic biology applications are covered within the Biological Weapons Convention.
- Considering whether there should be controls on publishing sensitive information that might aid misuse. In general, the scientific community maintains that it is better to publish openly to create the knowledge base that can counter misuse but, as noted by EGE (Appendix 2), it would be useful to define global criteria for any circumstances where publication of data on highly pathogenic organisms or toxic agents might be constrained.

Action at the national or European level must be accompanied and integrated with action globally<sup>27</sup>. The German export regulation guidelines for GMO production (German Technology Law, *Gentechnikgesetz*) might provide a model of national rules for other countries in controlling the supply of dual use goods according to the origin of the request for genetic sequence synthesis. In an international research environment, the screening of DNA synthesis orders requires centralised supervision to be effective—this raises issues for global governance and harmonisation of biosecurity standards, together with agreed disclosure of intended research protocols. The actions being discussed in Europe are consistent with what has already been proposed in

<sup>26</sup> 'Education on dual use issues' at <http://dels.nas.edu/bls/warsaw>. The survey of biosecurity education is at <http://dels.nas.edu/bls/warsaw/NAS%20PAPER%20FINAL%20sent.pdf>.

<sup>27</sup> Many in the research community are receptive. A survey gauged US researcher knowledge and attitudes about dual use (National Research Council with AAAS, survey of members, February 2009). Fifteen per cent of the 2000 respondents had taken personal action, including abandoning overseas collaboration, to avert misuse. Fifty per cent of respondents agreed with increasing restrictions on access to 'select agents', those pathogens that pose a known public health risk.

the USA<sup>28</sup>. The initiative by the Industry Association for Synthetic Biology to develop a global code of conduct<sup>29</sup> for DNA sequence screening, customer screening and ethical, safe and secure conduct in gene synthesis is a welcome step. Co-ordinated screening of potential orders requires companies to share access to international databases of sequence information (with their functional correlates). Companies producing synthetic sequences also need a national contact point to consult if they encounter suspect orders. As noted by the EGE (Appendix 2), further discussion is needed to define the responsibilities of the European Commission and national Competent Authorities in assuring the database(s) and acting on suspicious requests so as to provide a comprehensive security framework.

However, given the potential range of synthetic biology technologies, should control focus only on genetics and genomics? A case could be made that control is less necessary in a research area such as protocells, because the technical difficulty involved in such experiments means that they are likely to be confined to specialist research establishments. Moreover, the more different a synthetic biology system is from the natural system, the safer it is likely to be, because of the lack of interaction/integration with natural organisms. Paradoxically, however, it is the most unnatural systems that may be liable to provoke the most public concern.

The academies and the scientific community more generally must be involved in the continuing debate to find the right balance between self-governance and statutory regulation. In the survey conducted by Synbiosafe (Appendix 2, Ganguli-Mitra et al. 2009), synthetic biology researchers recognised it was important to prevent the public backlash that undermined agricultural GMO development. Most researchers in this survey would opt for a mix of international guidelines, national laws and self-regulation, accompanied by initiatives in education and raising awareness. The scientific community must show leadership in open public debate but few synthetic biology researchers judged the 'civil society participatory approach' as particularly robust or feasible or likely to provide the requisite flexibility to avoid the danger of constraining unforeseen advances in science and technology.

## 6.4 Intellectual property rights

Patenting is also often viewed as an ethical issue. The patentability of biotechnology inventions is well established under the European Commission's Biotechnology Directive 98/44/EC and its implementation in the European Patent Convention, using standard criteria for inventiveness. Exceptions are made for inventions contrary to morality. GMOs, microbiological processes and products thereof are patentable as a matter of principle. However, the morality clauses in European Patent Law are difficult to interpret and the EGE has probably not yet been sufficiently involved in discussion of ethical implications relating to patenting.

The Royal Society report on synthetic biology notes that there are unresolved intellectual property rights (IPR) issues in synthetic biology with some tension already appearing between scientists and their universities regarding the potential commercialisation of innovative research (for example, in biofuels). Furthermore, the magnitude of the resources needed in synthetic biology makes private sector participation in basic research essential and the private sector can be induced to invest only if to some degree it can appropriate the results of its research.

The publication by the Royal Academy of the Netherlands and the German Statement on synthetic biology identify two main problems in IPR protection in synthetic biology:

- (1) overly broad patents may create monopolies, hamper collaboration and stifle innovation by other researchers;
- (2) narrow patents may impede subsequent applications (for example, to set up a production system using standard components) because of the complexity of licensing arrangements to deal with multiple patent holders (patent thickets).

These challenges were discussed in detail at the Berlin meeting and patenting problems may seem to be accentuated in synthetic biology because of its multidisciplinary (requiring patent expertise drawn from several disciplines), compounded by the complexity of products bringing together many defined parts and their necessary interconnectedness to achieve functionality. However, an alternative case can be made (Calvert

<sup>28</sup> A US report prepared by the Craig Venter Institute together with the Center for Strategic and International Studies and MIT ('Synthetic Genomics: options for Governance', 2007 at [www.jcvi.org/research/synthetic-genomics-report](http://www.jcvi.org/research/synthetic-genomics-report)) identified three main areas for policy intervention:

- (1) Options for firms that supply synthetic DNA (including oligonucleotides)—e.g. firms must use special software to screen orders for potentially harmful DNA.
- (2) Options to regulate DNA synthesisers and reagents—e.g. owners of DNA synthesisers might be required to register their machines or be licensed to purchase reagents.
- (3) Options for legitimate users of synthetic genome technologies—e.g. education modules, previous review of experiments.

<sup>29</sup> 'Code of conduct for best practices in gene synthesis' at [www.ia-sb.eu](http://www.ia-sb.eu).

2008) that synthetic biology by encompassing entities that are discrete and isolable is, in theory, well suited to commodification, at least by comparison with intellectual property in systems biology.

In a report on IPR issues more generally, the Royal Society (2003) also warned of the consequences if patents are too broad in scope, deterring other researchers, and recommended that public authorities should make explicit to their patent offices their duty to examine patent applications appropriately. In the field of synthetic biology, there is still a concern that groups may gain a dominant, monopolistic, advantage from broad patents that then act to deter translation into products of research by other groups. For example, one US patent granted in 2003 covers 'chemical synthesis and assembly of genes and genomes' that might be construed very broadly<sup>30</sup>. EASAC reiterates the advice that patent offices should be very careful when being asked to grant broad patents. As science advances, patent offices must learn to apply more stringent examination of claims for function, novelty and inventive effort.

Assuming that appropriately delineated and focused patents are granted, there is growing interest in new routes to sharing patented information for collective benefit. One reduced-cost, approach to sharing patented information, which is already being used within the pharmaceutical industry, is the creation of patent pools. However, there may be practical problems in synthetic

biology for contributors and users of patent pools to agree on terms in joint agreements that do not exclude competition and violate anti-trust laws (Henkel and Maurer 2009).

There may be alternatives to patents, derived from the models for ownership and open sharing of information that are used in other industries. The BIOS initiative, adopted initially for agricultural biotechnology R&D from IT community practices, is one open source model for sharing both patented and non-patented technologies that might be employed as a collaborative mechanism more widely in the biosciences. In synthetic biology, the BioBricks Foundation makes its registered regulatory and structural elements freely available for use. It would be generally helpful if more researchers donated parts to the common pool and if public funders linked their support for research to the obligation to share. One problem with the BioBricks-based approach, however, is that it is not necessarily obvious if any of the parts already have rights attached to them (POST 2008). It will be necessary to become much clearer about the legal basis of all offerings within an open source platform if commercialisation is to proceed. The options for sharing standard biological parts in synthetic biology based on lessons learned from other industrial sectors are discussed in detail by Henkel and Maurer (2009).

From the public policy perspective, it is also worth noting that patenting is not the only way to control

**Table 2** *New approaches to collaborative activity in biosciences with features that may serve as models for synthetic biology R&D*

Initiative	Scope
EMBL: European Bioinformatics Institute, EU, 1998 ( <a href="http://www.ebi.ac.uk/industry/ind-prog-index.html">www.ebi.ac.uk/industry/ind-prog-index.html</a> )	Bioinformatics forum for interaction with users in life sciences industry, for research and training; aims to maximise benefits from innovation.
Division of Signal Transduction Therapy, University of Dundee, UK, 1998 ( <a href="http://www.ppu.mrc.ac.uk/technologies/dstt.php">www.ppu.mrc.ac.uk/technologies/dstt.php</a> )	Collaboration with pharmaceutical companies who share rights to exploit certain results while also contributing to basic research and dissemination of fundamental knowledge into public domain.
InnoCentive, USA, 2001 ( <a href="http://www.innocentive.com">www.innocentive.com</a> )	First global web community for open innovation marketplace, connecting public and private sectors.
Biomarkers Consortium, NIH–FDA–pharmaceutical sector, USA, 2006 ( <a href="http://www.biomarkersconsortium.org">www.biomarkersconsortium.org</a> )	Biomedical research partnership to develop and validate efficacy and safety markers in treatment of disease.
Innovative Medicines Initiative, European Commission-pharmaceutical sector, EU, 2008 ( <a href="http://www.imi.europa.eu">www.imi.europa.eu</a> )	Pre-competitive research collaboration to tackle bottlenecks in pharmaceutical R&D.
Health Commons, supported by MIT, USA, 2009 ( <a href="http://www.sciencecommons.org/projects/healthcommons">www.sciencecommons.org/projects/healthcommons</a> )	Virtual marketplace to share data, knowledge, materials and services to accelerate research.
Sage bionetwork, USA, 2009 ( <a href="http://www.sagebase.org">www.sagebase.org</a> )	Seed money from private sources to build integrative, open access platforms and databases for complex predictive models of disease. Constitution of this Commons is being drafted to cover formal standards, rules and rewards.

<sup>30</sup> US patent 6,521,427 issued to Egea Biosciences in 2003, cited by May (2009).

development of a field: the creation of standards can also determine R&D directions. Thus, the interface between standard setting and IPR may become critical for synthetic biology policy-making. EASAC encourages the academies to help to take forward clarification of the options for freedom to operate in building an open, standardised, co-operative research environment while encouraging investment and avoiding infringing existing rights. Lessons can be learned from a wide

range of other public-private research partnerships, many of which include significant commitment to open innovation. Some examples are listed in Table 2, mainly drawn from biomedical research, to illustrate the range of initiatives that may serve as potential models for data sharing in synthetic biology. However, many of these initiatives still have questions to answer relating to where the value is created in R&D, and how it should be rewarded.

## 7 Summary of issues and recommendations

The initial discussions that led to this EASAC project identified three main objectives for the report, which are as follows.

- (1) Clarifying scientific strengths and weaknesses, with the aim of developing critical mass in Europe, across fields and across R&D communities—noting where there is scope to increase resources and standardise methodologies, and where there are realistic prospects for innovation. Scalability – filling the current translational gap between basic research studies and industrial applications – may be a particularly important element in building the critical mass.
- (2) Raising awareness of the opportunities and challenges—both within the scientific community and with the public. It is important to evaluate what could be the possible benefits as well as the safety and ethical concerns to provide balanced information to policy-makers.
- (3) Exploring how science can inform policy development in governance of the technologies and promotion of EU competitiveness.

### 7.1 Previous recommendations at Member State level

The publication from the Royal Netherlands Academy and the German Statement make some recommendations for national attention that provide a useful foundation for considering what then should be attended to at the EU level:

- (1) *Sustained investment in basic research is vital*—recognising that most application-oriented programmes are still at the design stage, there must be increasing public investment in synthetic biology, possibly in connection with existing related initiatives in genomics, nanomedicine and systems biology and the efficient use of available infrastructure.
- (2) *Investing in interdisciplinary research to generate synergies is also essential*—recognising that this also has implications for education and training, for example in Master's level degree programmes.
- (3) *Commercial exploitation depends not only on excellent research but also on the appropriate strategic, legal and societal framework and on mechanisms to ensure fast knowledge transfer to industry*—this requires patent protection (under same conditions as applied previously to recombinant gene products and gene fragments). There must also

be expansion of research into, and communication about, the social aspects of synthetic biology.

- (4) *The existing legislation for biosafety and biosecurity is adequate*—but developments are diverse and dynamic so continuing monitoring of advances in the science and technology is needed, together with establishing clear criteria for assessing and managing risks in contained use and deliberate release, for both human and environmental protection. The voluntarily agreed systems (self-regulation) to reduce risk of misuse are important; if additional rules are needed these must be subject to international agreement.
- (5) Consideration of ethical issues must continue—ensuring that Academy scholarship helps to clarify and focus the discussion of synthetic biology.

### 7.2 EASAC recommendations for the EU

Drawing on this analysis at the national level and the EASAC Working Group deliberations, key issues for Europe in providing the multi-national strategic framework for supporting synthetic biology are outlined in Box 2.

However, to what extent should a specific policy focus on synthetic biology be developed? It is not yet clear if such a policy focus would advance the field or, alternatively, would risk creating additional barriers by making new distinctions from other fields. In considering whether to develop a specific strategy for synthetic biology, public policy-makers, at national and EU level, need also to consider the following:

- (1) their role in stimulating synthetic biology research activity – relative to other funders and other funding priorities;
- (2) their responsibilities for policy issues associated with security, ethics and public dialogue—clarifying who else shares the responsibilities;
- (3) the desired balance between national priorities and international co-ordination.

The EGE has urged the European Commission to propose and implement a robust governance framework and to raise the issues for governance in relevant global fora. However, there is a countervailing view, expressed in some of the discussion in the academies' publications, that seeking new governance mechanisms is premature. As yet, there is no consensus on whether synthetic biology will be a transformational technology and, if so, whether it can or cannot be accommodated within the current

## **Box 2 Synthetic biology: what issues do policy-makers at the EU level need to consider?**

- Research capacity. Where are the priority areas for the EU/Member States to compete given that the USA established an early lead in some key research directions? Should funding be invested in new dedicated synthetic biology initiatives or aligned with other programmes in genomics, nanotechnology etc?
- Higher education. How will the new interdisciplinary skills and lifelong learning be delivered to address the urgent needs for training the next generation of scientists?
- Protection of innovation. What can be patented and can the open exchange of pre-competitive information be maintained? Is there anything special about the IPR issues for synthetic biology?
- Public engagement. How can dialogue with the scientific community be encouraged, avoiding hyperbole and communicating based on sound science? What lessons have been learned from previous difficulties in engaging on social and ethical issues in emerging technologies?
- Biosafety. What are the new issues for human and environmental protection and what are the options for managing containment in laboratory and production facilities and for deliberate release? What can be expected from self-regulation? Can legislation be introduced without reducing the flexibility to encourage future science and manage future developments?
- Biosecurity. How to appraise the potential for abuse at the State, organisational or individual level at a time when the progressive deskilling of biotechnology facilitates its wider application? In addition to the issues for controlling production, there are considerations relating to the adequacy of surveillance and public health infrastructure to respond to deliberate attacks and accidents.
- Global governance and regulation. How best should the EU contribute to the international framework for policy development?

regulatory framework. It is also important to acknowledge that safety can be engineered into the applications of synthetic biology. Nonetheless, the EU must continue to review science and technology developments and be prepared to act if voluntary codes or current regulatory procedures appear insufficient. The member academies of EASAC have an important continuing role in alerting EU and national policy-makers to such developments. Furthermore, it seems entirely reasonable to develop practical recommendations on the need to invest in basic

and interdisciplinary research accompanied by review of risk management procedures that will be consistent with many of the recommendations made by EGE, but do not require policy-makers to judge now whether synthetic biology is ethically different or conceptually distinct from other scientific fields.

In developing our recommendations, EASAC aims to address three goals: (1) to confirm what more needs to be done in those Member States who are already most active in synthetic biology; (2) to identify options for building capacity in other Member States; and (3) to establish the policy options for a coherent strategy at the EU level covering research, education, innovation and regulation.

### **(1) Research capacity building**

There is a significant agenda for what might be advised about extra investment in synthetic biology by Member States and the European Commission (DG Research), while avoiding misuse of research:

- Core disciplines. In some areas there is a need to strengthen the traditional disciplines such as physiology and microbiology. The case can also be made for highlighting more explicitly the key role of the chemistry–biology interface in advancing synthetic biology. In some of these disciplines, Europe remains ahead of the USA and Asia and there is enormous potential to enhance European competitiveness. Moreover, progress in synthetic biology depends not only on input from the laboratory-based sciences but also on the social sciences and humanities. Therefore, academic funding bodies must recognise the need for broadly based support.
- Centres of Excellence. One option is to establish integrative Centres of Excellence in synthetic biology—where research is already internationally competitive in chemistry, biology, medicine, engineering and the other relevant disciplines. These could help to foster interdisciplinary perspectives by tackling the current obstacles to bridging the disciplines and attracting new support by research funders. Centres of Excellence can also serve as a focal point to seek collaboration with industry and others involved in delivering the products and services resulting from synthetic biology.
- European Commission funding. A good case can be made for new European funding to bring together synthetic biology research from the smaller laboratories across the EU, where there is already demonstrable excellence. In addition, synthetic biology can capitalise on other areas of research already strongly funded by the European Commission, such as epigenetics and epigenomics. Synthetic biology approaches may well be fruitful,

for example, in helping to clarify epigenetics with regard to cell reprogramming and molecular memory systems; and this application of synthetic biology in the new Network of Excellence EpigeneSys is a valuable initiative. We advise that, overall, funding for synthetic biology should be at least as high in the Seventh Framework Programme as in the Sixth and this funding should be allocated for laboratory work as well as for support actions. An increased focus on synthetic biology should be included as part of the current strategic discussions about the Eighth Framework Programme. DG Research should also consider the opportunities afforded by synthetic biology in its strategic support for the current portfolio of Technology Platforms and Joint Technology Initiatives.

- Education and training. It is essential to commit to training the next generation of scientists to bridge between engineering and biology disciplines while also teaching the information and skills needed from chemistry, physics and informatics. This is required at all levels in higher education from undergraduate through to PhD programmes. Centres of Excellence can help to provide the necessary multi-disciplinary training and motivation in new Master's and PhD programmes. Options for creating the 'European Graduate School in Synthetic Biology' might be developed based on the original European Molecular Biology Organisation (EMBO) model in the 1980s as well as extending current initiatives in several Member States relating to 'molecular life sciences'. Co-supervision across national boundaries is one way to create additional flexibility in provision of training to motivate students. Although opportunities have been insufficiently exploited throughout higher education for biologists to improve their ability to think quantitatively and for engineers to be given insight into the techniques employed in the biosciences, nevertheless some Member States already provide Master's courses in synthetic biology. It is important to share best practice from those Member States who have already introduced such courses, in order to build comparable teaching capacity across the EU.
- Translational steps towards innovation. Although there is much to be accomplished in fundamental research, it is also vital for the European Commission to support the translational research and reduction to practice that will provide proof of concept in the envisaged applications. There is often a gap between work on the fundamental technologies (such as the design of minimal genomes and model circuits) and the engineered biological applications. There must be an appropriate commitment of resources to refine and optimise the tools and this will require developing additional models for supporting translational science. However, it is also important

not to finalise the tools too early in development of applications lest there is risk of inflexibility in standardising platform technologies. Public sector financial support across the R&D continuum might also help to counter any concerns that 'big business' will monopolise the outputs.

- Research priorities. It is not the purpose of the present report to specify priorities for EU-funded research in synthetic biology. The individual outputs from the academies, cited throughout this report review particular research areas where the European contribution to synthetic biology might be fruitful and we emphasise that it is important to advance mammalian synthetic biology. The EASAC Working Group identified two other general topics where further EU support is warranted. First, investment in research to generate the tools (for example, expanding the library of interoperable parts) for use by the scientific community in developing safe biological systems. This requires wider debate on 'what is safe'. Secondly, the development of biological systems with enhanced genetic stability, because the drift of genetic information that characterises any natural biological system is a handicap for production-oriented applications.
- Forming a new professional society. The present relative lack of an organised synthetic biology community across the EU might usefully be addressed by the creation of a new scientific society. Although such an organisation should, preferably, come into being from 'bottom-up' initiatives, it might be quicker if 'top-down' interests were also expressed. EASAC invites the European Commission to consider what role it could play in facilitating the formation of a new organisation.

## **(2) European competitiveness**

Individual Member States have already achieved a leadership position in some of the tools used in synthetic biology. For example, Germany is strong in oligonucleotide and synthetic gene supply companies (such as the company Gene Art). Member States have also initiated major research centres in synthetic biology. For example:

- Germany, the Cluster of Excellence in Biological Signalling Studies at the University of Freiburg and the Center for Synthetic Microbiology, a joint venture of the University of Marburg and the Max Planck Society;
- UK, the Imperial College London Institute of Systems and Synthetic Biology;
- The Netherlands, the new/redistributed funding at Delft University (Department of Bionanoscience), University of Groningen (Centre for synthetic Biology)

and Eindhoven University of Technology (Institute for Complex Molecular Systems);

- Italy, the Synthetic Biology laboratory in Rome and Synthetic Biology in Mammals laboratory in Naples;
- Spain, the Centre for Genomic Regulation in Barcelona.

Small and medium-sized enterprises (SMEs) are also being established in metabolic engineering/synthetic biology<sup>31</sup>.

However, new sources of activity will provide increasing global competition within the next generation. For example, Asian universities fielded 14 iGEM teams in 2008 and 24 in 2009, now only slightly less than the number of entrants from EU Member States, although it is noteworthy that all finalists in 2009 came from the EU.

In considering the potential for newer Member States to contribute to EU competitiveness in synthetic biology, one starting point is the present state of their biotechnology industry. A survey<sup>32</sup> of the SMEs biotechnology sector in newer Member States and candidate countries showed that Hungary, Poland, the Czech Republic and Estonia are the most successful. Despite a highly educated workforce, historically many other newer Member States and candidate countries lack appropriate support structures for SMEs and funding for IPR and technology transfer. However, EU Structural Funds have been increasingly used in the newer Member States for support of translational activity, particularly in SMEs. EASAC welcomes this innovation funding, and we emphasise that policy-makers need to understand that this must be a long-term strategy and that synthetic biology should be supported in this way.

EASAC also emphasises the applicability of synthetic biology to transform traditional industry sectors—for example in the production and use of silk, other fabrics and dyes. Although there may be concomitant implications for regulation of innovation (for example, in this case, for engineered silk, see section 5.4), policy-makers and manufacturers must appreciate that the alternative to innovation is often market loss. We recommend that DG Enterprise and Industry consider the implications of synthetic biology when supporting its industrial sectors: the biotechnology and chemical sectors are obvious customers but there will be others.

### **(3) Governance of research**

It is difficult for policy-makers to determine if there are new issues for synthetic biology in R&D governance

because it is not yet clear where the technology boundaries are. EASAC advises that the scientific community should help EU regulators define these boundaries and, thereby, reduce one source of uncertainty in policy-making. For the specific policy areas discussed previously:

- **Biosafety.** EASAC observes that the existing legislation provides an adequate framework as long as synthetic biology remains an extension of recombinant DNA technology. The recent updating of the US NIH guidelines on recombinant DNA provides a useful model for corresponding updating of EU research procedures. Existing legislation may need to be re-considered, if there are significant advances in modifying the basic chemistry underpinning genetic information machinery and processes, although we re-iterate that one advantage of synthetic biology is the flexibility to engineer additional safety features (for example, by producing synthetic systems within the cell that do not communicate with the endogenous systems). Nonetheless, until a synthetic organism is demonstrated to be harmless, it should be handled with high safety requirements adopted from those already in place for other research and subject to the well-established systems of regulation in place at EU and national levels.
- **Biosecurity.** The initiative by the Industry Association for Synthetic Biology to construct a global code of conduct for companies for DNA sequence screening, customer screening, and ethical, safe and secure conduct in gene synthesis is welcome. Additional security roles for the European Commission and Member State Competent Authorities in (1) supporting the infrastructure for an international database of DNA sequence and function and (2) acting on suspicious requests for synthesising sequences require further discussion. We recommend that the European Commission take a lead in initiating global discussion on database infrastructure roles and responsibilities. EASAC also welcomes initiatives by academies and the InterAcademy Panel in constructing individual researcher and institutional codes of conduct in the biosciences that will help to promote both biosafety and biosecurity. Widespread adoption of such codes has implications for education and training programmes to raise awareness across the research community (including those parts of the community who are relatively new to research in the biosciences). In the public debate on these codes of conduct, potential implications have also been noted for the open publication of information that might, potentially, aid misuse. EASAC emphasises

<sup>31</sup> For example, in the UK Novacta Biosystems ([www.novactabio.com](http://www.novactabio.com)) is working on engineered lantibiotic peptides as next generation therapy for *Clostridium difficile* infection, and Biotica ([www.biotica.com](http://www.biotica.com)) is working on polyketide antibiotics, antivirals and anticancer agents.

<sup>32</sup> 'Biotech in the new EU Member States: Policy Recommendations' published by EuropaBio and Venture Valuation, September 2009. Available at [www.europabio.org/positions/general/IndecsHPolicyrecommendations.pdf](http://www.europabio.org/positions/general/IndecsHPolicyrecommendations.pdf).

the importance of academic freedom to publish but we note that there are other voices (e.g. the EGE) who question the assumption that all research can be published. EASAC recommends that the scientific community work harder to make the case that an open publication strategy is appropriate unless there are overwhelming security reasons not to publish.

- IPR. EASAC reiterates the principle that patent offices are advised to be careful when being requested to grant broad patents that might deter other research. EASAC also supports proposals to examine the potential value of alternative models for owning and sharing information. We suggest that academies are well placed to catalyse further discussion on the options that will facilitate researcher freedom to operate in an open, standardised, co-operative research environment while, at the same time, encouraging public and private investment in research.

#### **(4) Product regulation**

In addition to the issues appertaining to the management of research, the scientific community can help the statutory regulatory authorities to understand any implications for the control of product approval. For example:

- Medicinal products. The EMEA and Member State authorities should review the safety and efficacy of drugs and devices resulting from synthetic biology protocols using the same procedures as when reviewing products of other origin. It will be necessary to consider which products fall within the remit of the Directive on Advanced Therapy Medicinal Products<sup>33</sup>. Researchers will also need to be aware of the provisions of the EU Tissue and Cells Directive and the Clinical Trials Directive.
- Environmental products. The EGE document describes potential environmental applications in bioremediation (for example, for heavy metals, pesticides and radioactive material). Such applications must be considered within the scope of the EU legislation (Directive on the deliberate release into the environment of genetically modified organisms, 2001/18/EC, implemented in all Member States) which is likely to include the requirement for ecological impact assessment.
- Chemical and energy products. As discussed previously, the methods of synthetic biology may

be used to create a new generation of biofuels for energy and biofeedstocks as precursors for chemical synthesis. This use of synthetic biology for generating alternative energy sources should be taken into account in EU renewable energy policy development<sup>34</sup>. As the EGE emphasise, new energy sources must be evaluated for (1) risk to health of the general population, (2) safety of workers exposed in production processes, and (3) protection of the environment.

#### **(5) Societal engagement and market development issues**

The European Commission made a good start in the Sixth Framework Programme in supporting work to identify and analyse societal attitudes, expectations and issues in synthetic biology. It is essential that this surveying and comparative analysis continues at the EU level. Further understanding of the public environment for synthetic biology and further involvement of other stakeholders (including trade associations and NGOs, Appendix 2) in discussion about synthetic biology impact will be aided by the following:

- Provision of balanced descriptions in lay language of what synthetic biology encompasses, what scientific advances are now occurring and what may be in prospect for new applications. EASAC acknowledges its continuing role to use the present report to create clear and accurate messages for a wider public readership. Moreover, the communication of information at the European level must be accompanied by national efforts to provide accurate and relevant information, and the member academies of EASAC have a role in this regard as well. There is an important collective responsibility to ensure that an environment is created in which the public can realistically assess the alarmist assertions sometimes made in media accounts of synthetic biology research. In engaging with, and encouraging, public debate about the opportunities and challenges, the academies, with the scientific community more broadly, have a particular responsibility. This is to ensure that regulations are not introduced that will – either intentionally or inadvertently – stifle research. EASAC also now recommends that the European Commission consider how it can best create a platform for the sharing of information about synthetic biology with all stakeholders. The recent initiative by DG Sanco (March 2010) to organise a workshop on synthetic biology in support of a dialogue on risk assessment is a valuable first step.

<sup>33</sup> Directive 2001/83/EC covers tissue engineered products, advanced somatic cell therapy products and gene therapy products. The information that is required to be supplied in human cell-based medicinal products is discussed at [www.emea.europa.eu/pdfs/human/cpwp/41086906enfin.pdf](http://www.emea.europa.eu/pdfs/human/cpwp/41086906enfin.pdf).

<sup>34</sup> Such policy has been initiated by the Directive on the promotion and use of energy from renewable sources, 2009/28/EC (April, 2009).

However, debate on governance issues must be well integrated with discussion on potential benefits and clarification of the policy issues for supporting R&D. This communication model should be adopted by other Directorates-General relating to other industrial applications. At the same time, the European Parliament should also consider how it could help to promote stakeholder education and engagement.

- Initiatives in scenario modelling (led by DG Enterprise and Industry with DG Research and sector-specific Directorates-General, including those with responsibilities for Energy, Environment and Security) to develop a range of forecasts for future economic impact of the applications of synthetic biology to inform public debate and help underpin well-prepared product regulatory procedures.
- As the field progresses, the European Commission should support continuing discussion on what is distinctive about synthetic biology and whether new issues are raised thereby for the regulation of the scientific procedures or applications.
- In the longer term, the European Commission should also contribute to economic studies of cost-effectiveness of the emerging synthetic biology innovations in the respective industry sectors, and to the use of economic outcome data to inform public debate and market development.

These recommendations are challenging because the field of synthetic biology is still in its formative stages

and overlaps with other emerging technologies. Furthermore, the science is progressing rapidly. It is relevant for the European institutions to consider the implications of synthetic biology in their current strategy development for related innovation areas, for example in biotechnology and nanotechnology. Furthermore, in the view of EASAC, synthetic biology will become important for the EU strategy for 2020<sup>35</sup>. This strategy has highlighted key drivers that include 'smart growth' (developing an economy based on knowledge and innovation) and 'sustainable growth' (promoting a more resource efficient, greener and more competitive economy). In both these respects and in the efforts to engage with society, developments in synthetic biology are of great importance for the EU.

At the end of this project, EASAC confirms its view that the academies, collectively, have an important role to identify developing trends while also emphasising what is still uncertain in synthetic biology. The timetable for societal impact is very difficult to forecast: a contribution by metabolic engineering can realistically be expected within the short term but some of the other methodologies reviewed in this report can only be anticipated to deliver in the longer term. Nonetheless, it is important to prepare for these longer-term advances and to manage expectations about their impact. And, to reiterate the point made at the beginning of this report, whatever the uncertainties about particular applications, we are certain that synthetic biology will also be of critical importance in contributing to the better understanding of natural biological systems.

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<sup>35</sup> European Commission "Europe 2020: a European Strategy for Smart, Sustainable and Inclusive Growth", available at [http://ec.europa.eu/europe2020/index\\_en.htm](http://ec.europa.eu/europe2020/index_en.htm).

## Appendix 1 Academy sources and Working Group composition

A first draft of this report was compiled from information discussed and published by individual academies as follows:

- The Royal Society: (1) 'Synthetic Biology Scientific Discussion Meeting Summary', August 2008 (Royal Society 2008a); (2) 'Report on the third joint Royal Society-Science Council of Japan workshop on new and emerging technologies', September 2008 and (3) 'Opportunities and challenges in the emerging field of synthetic biology', symposium July 2009, co-organised with the US National Academies and the Organisation for Economic Co-operation and Development.
- The Royal Netherlands Academy of Arts and Sciences, together with the Health Council of the Netherlands and the Advisory Council on Health Research, report 'Synthetic biology: creating opportunities', September 2008.
- The Swiss Academy of Sciences Forum on Genetic Research, 'Fact sheet on synthetic biology', January 2006.
- The German Academy of Sciences Leopoldina, together with the German Academy of Science and Engineering and the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), workshop on Synthetic Biology, Berlin, February 2009 and Statement, November 2009.

The member academies of EASAC appointed experts to the EASAC Synthetic Biology Working Group in January 2010. The Working Group met in March 2010, with further discussion occurring by email. The Working Group report was completed in May 2010 and was independently reviewed by additional experts nominated by EASAC.

### Members of the Working Group

Volker ter Meulen (Chairman), German Academy of Sciences Leopoldina and EASAC

Bärbel Friedrich, Institute of Biology, Humboldt University, Berlin, Germany

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Peter Leadlay, Department of Biochemistry, University of Cambridge, United Kingdom

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George Thireos, Director of Research, Biomedical Research Foundation of the Academy of Athens, Greece

Jean Weissenbach, Director, Genoscope, France

Robin Fears (Secretariat), EASAC, United Kingdom

## Appendix 2 International activities in synthetic biology: analysing ethical and societal implications

Apart from the work of the European academies in analysing the status of synthetic biology, various other national and international bodies have been active in addressing capacity building and governance issues. Some examples are listed in Table 3, to illustrate the range. These other sources of information helped to provide the background

**Table 3 Issues analysis and other initiatives in synthetic biology**

Organisation and initiative	Primary focus
European Commission (DG Research), NEST Pathfinder initiative <sup>36</sup> and Framework Programme 6-funded projects:	
Toward a European Strategy of Synthetic Biology (TESSY) <sup>37</sup>	Inventory of resources, roadmap, analysis of strategic sustainability
Synbiology <sup>38</sup>	Analysis of current research (EU, USA)
Synbiosafe <sup>39</sup>	Ethics, safety and security
Emergence <sup>40</sup>	Education, infrastructure and standards
EMBL/EMBO, Conference on Systems and Synthetic Biology, 2008 <sup>41</sup>	Scientific and social implications
European Science Foundation meeting and Eurocores project, EuroSynBio, opened for applications for research funding, 2009 <sup>42</sup>	Supporting engineering and molecular research in complex biological systems and societal context
Kavli Futures Symposium, Ilulissat Statement, 2007 <sup>43</sup>	Identification of fundamental, applied and social research needs
US Woodrow Wilson Center report on synthetic biology <sup>44</sup>	Anticipating and addressing concerns for laboratory and environment
International Risk Governance Council report on synthetic biology, 2008 <sup>45</sup>	Analysing applications, risks and governance
UK Biotechnology and Biological Sciences Research Council report, 2008 <sup>46</sup>	Analysing societal impact, risks and regulation
UK Lloyd's Emerging Risks Team Report 2009 <sup>47</sup>	Analysing risks and governance issues with implications for insurance sector
European Group on Ethics of science and new technologies (EGE) 2009 <sup>48</sup>	Analysing issues for biosafety, biosecurity, industrial applications, IPR, societal engagement and research support

<sup>36</sup> 'Synthetic biology, a NEST pathfinder initiative' at <ftp://ftp.cordis.europa.eu/pub/nect/docs/5-nect-synthetic-080507.pdf>.

<sup>37</sup> TESSY final report 'TESSY achievements and future perspectives in synthetic biology', December 2008, at [www.tessy-europe.eu/public\\_docs/TESSY-Final-Report\\_D5-3.pdf](http://www.tessy-europe.eu/public_docs/TESSY-Final-Report_D5-3.pdf).

<sup>38</sup> 'An analysis of synthetic biology research in Europe, the United States and Canada' at [www.atg-biosynthetic.com/nect-project.html](http://www.atg-biosynthetic.com/nect-project.html).

<sup>39</sup> Output as commentary paper 'Synbiosafe e-conference: online community discussion on the societal aspects of synthetic biology' (M. Schmidt, H. Torgersen, A. Ganguli-Mitra, A. Kelle, A. Deplazes, N. Biller-Andorno) Syst Synth Biol, doi:10.1007/s11693-008-9019-y.

<sup>40</sup> 'Emergence: a foundation for synthetic biology in Europe', at [www.synbio.org.uk/synthetic-biology-index/1105-emergence-foundation-in-europe](http://www.synbio.org.uk/synthetic-biology-index/1105-emergence-foundation-in-europe).

<sup>41</sup> 'Systems and synthetic biology: scientific and social implications', Heidelberg, Germany, November 2008 at [www.embl.org/aboutus/sciencesociety/conferences/2008/programme.html](http://www.embl.org/aboutus/sciencesociety/conferences/2008/programme.html).

<sup>42</sup> European conference on 'Synthetic biology: design, programming and optimisation of biological systems', St Feliu de Guixois, Spain, November 2007 at [www.functionalgenomics.org.uk](http://www.functionalgenomics.org.uk); EuroSynBio call for proposals on [www.esf.org/activities/eurocores/programmes/eurosynbio.html](http://www.esf.org/activities/eurocores/programmes/eurosynbio.html).

<sup>43</sup> International discussion meeting in Ilulissat, Greenland. Statement 'Synthesizing the future – a vision for the convergence of synthetic biology and nanotechnology' accessed at [www.royalsociety.org/page.asp?id=7493](http://www.royalsociety.org/page.asp?id=7493).

<sup>44</sup> Report 'Synthetic biology' by D. Caruso, Hybrid Vigor Institute, at [www.science.progress.org/wp-content/uploads/2008/11/syntheticbiology.pdf](http://www.science.progress.org/wp-content/uploads/2008/11/syntheticbiology.pdf) for Woodrow Wilson Center ([www.wilsoncenter.org](http://www.wilsoncenter.org)).

<sup>45</sup> Report 'Synthetic biology risks and opportunities for an emerging field' by J. Calvert and J. Tait at [www.igrc.org/IMG/pdf/RGC\\_ConceptNote\\_SyntheticBiology\\_Final\\_30April.pdf](http://www.igrc.org/IMG/pdf/RGC_ConceptNote_SyntheticBiology_Final_30April.pdf).

<sup>46</sup> Report 'Synthetic biology social and ethical challenges' by A. Balmer and P. Martin on [www.bbsrc.ac.uk](http://www.bbsrc.ac.uk).

<sup>47</sup> Report 'Synthetic biology: influencing development' by Lloyd's Emerging Risks Team, July 2009, on [www.lloyds.com](http://www.lloyds.com).

<sup>48</sup> 'Opinion on the ethics of synthetic biology', EGE, November 2009, at [www.ec.europa.eu/european\\_group\\_ethics/docs/opinion25\\_en.pdf](http://www.ec.europa.eu/european_group_ethics/docs/opinion25_en.pdf).

for EASAC inquiry in elucidating what public policy-makers need to know to provide a supportive framework for synthetic biology R&D.

Apart from the ethical issues raised about creating life, research funders, NGOs and advisory groups have discussed other ethical issues associated with synthetic biology. Concerns relating to trade and global justice have been expressed. For example, the synthesis of artemisinin might move production from developing countries to developed countries—but this type of concern is by no means confined to the products of synthetic biology.

It is also worth noting that in the recent work of the European Commission-funded Synbiosafe project (Ganguli-Mitra et al. 2009), a survey of researchers involved in synthetic biology revealed a prevailing view that synthetic biology raises no particular ethical issues in itself and that any social implications are exclusively related to specific practical applications, for example, manipulation of the human genome. It is not clear if these researchers' perspective is shared more widely across the EU, although some initial public expectations are being elucidated (chapter 4). Other commentators have raised concerns that synthetic biology raises new ethical issues in creating artificial life and in blurring the boundaries between animate and inanimate. However, bioethicists themselves differ in their views on this: some perceive a need for 'synthetic bioethics', others see little novelty in synthetic biology ethical issues. This debate might be helped by greater clarity in definition. Semantic problems arise in part because researchers use terms and metaphors (such as 'living machines') that appear to blur the boundary between living and non-living matter.

As there is extensive discussion on ethical issues in synthetic biology in the publications already cited (in particular the German Statement and the Royal Society publication described in footnote 21) as well as in the sources listed in Table 3, the EASAC Working Group did not address these ethical matters in further detail. However, as noted elsewhere in this report, EASAC suggests that the academies should support further analysis and debate on ethical issues, perhaps through the mechanism of the Standing Committee on Science and Ethics of the All European Academies (ALLEA).

## List of abbreviations

AAAS	American Association for the Advancement of Science
ALLEA	All European Academies
CIA	Central Intelligence Agency
DNA	Deoxyribonucleic acid
DG Enterprise and Industry	European Commission Directorate General for Enterprise and Industry
DG Research	European Commission Directorate General for Research
DG Sanco	European Commission Directorate General for Health and Consumer Protection
EASAC	European Academies Science Advisory Council
EGE	European Group on Ethics in Science and New Technologies
EMBO	European Molecular Biology Organisation
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GM	Genetically modified
GMOs	Genetically modified organisms
IAP	InterAcademy Panel
iGEM	International Genetically Engineered Machine
IPR	Intellectual property rights
IT	Information technology
MIT	Massachusetts Institute of Technology
NGO	Non-governmental organisation
NIH	National Institutes of Health
R&D	Research and development
RNA	Ribonucleic acid
SMEs	Small and medium-sized enterprises
XNA	Xeno-nucleic acid

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