A synthetic biology roadmap for the UK

UK SYNTHETIC BIOLOGY ROADMAP COORDINATION GROUP

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Technology Strategy Board
Driving Innovation

Foreword

The excellence of the UK research community provides an opportunity for future economic growth. Deriving significant benefits also relies on the ability of business to develop products and services and on the expectation of a sizeable global market. The Technology Strategy Board highlighted synthetic biology as an emerging technology meeting all these key criteria and offering particularly strong growth potential in the UK. A coordination group was formed towards the end of 2011 to chart a suitable way forward.

The capacity of synthetic biology to develop useful applications has only become a practical option in recent years. Progress over the past decade has been driven by a combination of factors, not least an ever deepening understanding of biological systems and remarkable advances in the efficiency of DNA sequencing and synthesis. Specific applications are already emerging, but its long-term potential remains largely untapped. The sharing of understanding across the constituent biological and engineering disciplines, pooling of expertise and resources, anticipation of critical challenges and the enthusiastic commitment of all stakeholders will significantly enhance our capacity to benefit. Synthetic biology has the potential to increase prosperity and address some of the major challenges facing our planet – but much work needs to be done, and it has to be done responsibly.

Engaging the synthetic biology community in shaping this roadmap has also contributed a first step towards its realisation, through making new connections and building a shared vision. Further initiatives, such as the recent formation of a special interest group, will continue to stimulate interest and facilitate cooperation. This roadmap is not a one-off long-term plan towards a fixed point. It provides a compass-bearing for the community, helping to align interests towards future growth opportunities whilst identifying the resources and standards needed to accelerate progress in the shorter term.

As an independent panel we set out to reflect a representative view drawn from across the UK community. We believe we have achieved this, but we also recognise the need for ongoing and broadening engagement to complement what has been possible within the practical and time constraints of this exercise. Cooperation on an international scale will also help determine success. We have outlined a first step in the journey and see a leadership council helping to manage the ongoing process.

I have been impressed and delighted at the interest, energy and enthusiasm shown by those who have contributed to this roadmap and I thank them all. In particular, members of the coordination group who have worked tirelessly for six months to pull together and structure all the material.

Lionel Clarke

Chairman
UK Synthetic Biology Roadmap
Coordination Group
July 2012

A synthetic biology roadmap for the UK

Executive summary

This publication sets out a shared synthetic biology roadmap for the UK pulled together by an independent panel of experts at the request of the Department for Business Innovation and Skills (BiS).

Synthetic biology is the design and engineering of biologically based parts, novel devices and systems as well as the redesign of existing, natural biological systems. It has the potential to deliver important new applications and improve existing industrial processes – resulting in economic growth and job creation.

It is a rapidly developing technology applicable to a wide range of biological systems, and has developed over the last decade due to the confluence of a number of factors. It could help to solve a number of major global challenges including in the fields of healthcare, energy and the environment.

The UK was amongst the first to recognise and respond to the opportunities raised by synthetic biology. Publicly-funded academic studies coupled with meaningful public dialogue have established the foundations upon which the sector is now being built. Multidisciplinary expertise is already enabling the UK to make significant contributions to international research programmes, and also to assimilate and respond to global developments as they arise.

Our vision is of a UK synthetic biology sector that is:

- economically vibrant, diverse and sustainable: where businesses have successfully developed and introduced new products, processes and services – leading to significant revenues and employment
- cutting edge: leading scientific advances and with a resilient platform of underpinning technologies – delivering clear advantages in application development
- of clear public benefit: an exemplar of responsible innovation, incorporating the views of a range of stakeholders and addressing global societal and environmental challenges within an effective, appropriate and responsive regulatory framework.

Our goal is to build upon these foundations, identifying and stimulating initiatives that will help companies develop new products, processes and services of clear public benefit, and generate economic growth and create jobs. Applications could include biosensors to identify infections and diseases and trigger localised drug delivery; more personalised medicines, tailored to an individual's specific requirements; improved waste treatments and bioremediation; and more cost-effective routes to renewable chemicals, materials and fuels, leading ultimately towards more efficient solar energy conversion and storage as envisaged via artificial photosynthesis. A recent assessment by BCC research on behalf of Global Information Inc concluded that the value of the global synthetic biology market will grow from $1.6bn in 2011 to $10.8bn by 2016.

Synthetic biology is still at an early stage of development and relatively unproven, but its potential is widely considered to be very high. It is a platform and translational technology linking a broad range of foundational science with an extensive range of possible applications, some already progressing towards market. Research is moving fast, but developing specific processes to commercial scale will invariably take time and encounter new challenges. This roadmap takes a holistic view of the innovation process, to anticipate issues and facilitate progression of applications and services towards the ultimate goal of realising a clear vision for a UK synthetic biology sector.

Five core themes for the roadmap emerged from this work. They were:

- **foundational science and engineering:** the need for sufficient capabilities for the UK to maintain a leading edge
- **continuing responsible research and innovation:** including the need for awareness, training and adherence to regulatory frameworks
- **developing technology for commercial use**
- **applications and markets:** identifying growth markets and developing applications
- **international cooperation.**

An essential first stage is the building of a cohesive stakeholder community including academics, industrialists, public and private organisations. Workshops held to date have already begun this process, helping to shape the vision. Energising this growing community around the vision, supported as needed through effective resourcing and training, will stimulate the development of applications of significant value.

To accelerate the contribution synthetic biology could make towards a vibrant economy, it will be necessary to build upon the many factors that make the UK an excellent location to progress synthetic biology, whilst identifying and reducing the commonly encountered stumbling-blocks anticipated along the pathway to commercially viable products and services, particularly on behalf of smaller and start-up companies that may otherwise lack sufficient capacity or finance.

A number of factors may enhance the probability of success of a given venture, for example, being clearer on what is possible, understanding earlier in the process what is needed, gaining access to a wider range of resources including relevant training and advice, having more effective mechanisms to share ideas and best practice across the community and having access to a wider network of potential partners and sources of public and private funding.

The UK is an excellent place to progress synthetic biology because it has:

- a healthy ecosystem for new and established businesses (UK ranked* in the top 5% of countries for 'ease of doing business')
- a strong academic base in synthetic biology, linked to a very strong innovative culture and heritage across the life sciences, engineering and physical sciences
- a strong and internationally networked industrial base in application areas for synthetic biology
- agile and responsive funding agencies
- proportionate and robust regulatory frameworks that are internationally recognised and well regarded
- strong UK Government support.

*World Bank Survey 2011

Initiatives have already been taken in the UK to establish a multidisciplinary community, supported via dedicated educational programmes and facilities, including the establishment of a Centre for Synthetic Biology and Innovation. But more must be done to nurture and advance these foundations if the UK is to retain its relatively strong and innovative position on the global stage.

Our recommendations, summarised right, therefore seek to strengthen, stimulate and better integrate knowledge-generation within the UK academic research base whilst simultaneously developing routes to commercialisation. Demonstrating a consistent, long-term commitment, based around a clearly stated and broadly supported vision will be very important in ensuring the stability needed to attract ongoing investments and in assisting alignment of core research interests.

Synthetic biology in the UK operates within the existing regulatory framework and routinely takes account of social and ethical issues. Nevertheless, we highlight the need to continue practising responsible research and innovation at all stages. To ensure that practitioners continue to be fully aware of potential issues, and that regulatory frameworks remain current with leading-edge developments, it will be important to maintain effective 'open-door' mechanisms for dialogue. These, in turn, will inform, and be informed by, ongoing formal national policy and international regulatory review mechanisms.

Considering these various needs, we recommend a package of measures that should support and develop the UK-wide research and industrial communities by enhancing the availability of essential resources and information.

Specifically, we recommend the creation of a network of multidisciplinary centres, including a dedicated innovation and knowledge centre (IKC), to both strengthen and expand our foundational and applied research base and facilitate business exploitation. These should all be based within existing higher-education institutions. Investment plans for early-stage and larger demonstrator projects and for feasibility studies should also be made in the near future to facilitate industrial applications of the technology.

A variety of mechanisms should be introduced via the Technology Strategy Board, research councils and others as appropriate, to extend the UK-wide synthetic biology community. Such mechanisms may include the formation of an overarching network for synthetic biology – through the formation of a special interest group (SIG), holding an annual forum and funding competitions to support the development of novel applications. Forming a coherent, energised synthetic biology community should stimulate an innovative 'can do' culture and create an environment conducive to attracting inward investment. It should also facilitate increased levels of interaction between the research community and other stakeholders including the public.

Recommendations

1. Invest in a network of multidisciplinary centres to establish an outstanding UK synthetic biology resource
2. Build a skilled, energised and well-funded UK-wide synthetic biology community
3. Invest to accelerate technology responsibly to market
4. Assume a leading international role
5. Establish a leadership council

Realising the vision for synthetic biology should allow the UK to make a positive contribution to the global response to challenges in areas such as health and the environment. In this way, the UK may reasonably seek to build on its current strengths and assume a leading international role in synthetic biology, helping to set standards and shape future regulations. This may be achieved through a variety of mechanisms, such as participating in trans-national grant funding, hosting international conferences and continuing to foster coordinated efforts in synthetic biology through research partnerships.

Finally, a leadership council should be set up to own and oversee continual development and delivery of the vision. This will provide a focal structure for assessing progress and updating recommendations and priorities within the roadmap.

A synthetic biology roadmap for the UK

Introduction

Industry, academia, government organisations, funders and others have joined forces to produce a roadmap for the formation of a world-leading synthetic biology sector in the UK. Synthetic biology could help to tackle major global challenges in areas such as healthcare, energy and the environment and is already starting to deliver high-quality jobs. Synthetic biology's contribution to the knowledge-based bio-economy (and the wider economy) is predicted to grow increasingly in the short, medium and long term.

The UK was amongst the first to recognise and respond to the opportunities raised by synthetic biology. Publicly-funded academic studies, coupled with meaningful public dialogue, have established the foundations upon which the sector is now being built. Multidisciplinary expertise is already enabling the UK to make significant contributions to international research programmes and to assimilate and respond to global developments. Our goal is to build upon these foundations, stimulate a vibrant innovation culture within the UK and lead towards the delivery of products and services of clear economic and public benefit.

This publication sets out a shared roadmap for the UK drawn together by an independent panel of experts at the request of the Department for Business Innovation and Skills (BIS). The vision and recommendations for the UK grew out of a series of workshops attended by more than 70 people representing a broad range of stakeholders from industry, public bodies, academia and other organisations. It also draws upon the large and rapidly growing body of world literature and the numerous conferences, symposia and discussion forums that have recently focused on synthetic biology. Although specifically a roadmap for the UK, working with international stakeholders remains an essential part of implementing the roadmap (as reflected in our recommendations). We reviewed a number of thematic areas in reaching a set of recommendations, which, if advanced effectively, will establish and grow a successful synthetic biology sector.

The definition of synthetic biology we used is adapted from the 2009 Royal Academy of Engineering study.

Synthetic biology is the design and engineering of biologically based parts, novel devices and systems as well as the redesign of existing, natural biological systems. It has the potential to deliver important new applications and improve existing industrial processes – resulting in economic growth and job creation.

Our vision is of a UK synthetic biology sector that is:

- **economically vibrant, diverse and sustainable:** businesses have successfully developed and introduced new products, processes and services – leading to significant revenues and employment
- **cutting edge:** leading scientific advances and with a resilient platform of underpinning technologies – delivering clear advantages in application development
- **of clear economic and public benefit:** an exemplar of responsible innovation, incorporating the views of a range of stakeholders and addressing global societal and environmental challenges within an effective, appropriate and responsive regulatory framework.

Global trends and the role of synthetic biology

The world is becoming increasingly interconnected and the ability to generate, share and interpret data on a massive scale is accelerating our ability to understand highly complex systems. The emergence of synthetic biology as a distinct discipline through the first decade of this century is a clear example of this trend.

Potential applications of synthetic biology arise wherever biological systems play a role, or could play a role in future. Fields of increasing interest at individual and societal levels include well-being (such as prediction and prevention of diseases, personalised healthcare, improved lifestyle, employment), security (including food, water and energy security) and sustainability (meeting the challenges of managing natural resources, reducing dependence on non-renewable resources and finding ways to mitigate climate change). Objectives for envisaged synthetic biology applications in these fields include reduction in costs, extended or novel functionality and greater selectivity. However, as an emerging platform technology, the potential for synthetic biology to develop valuable applications in areas as yet unconsidered remains a significant future possibility.

Addressing these fields of interest and other global challenges will continue to generate a wealth of potential applications. There are no unique solutions to these global challenges – the issues are complex and changing, and effective responses will require a combination of scientific, technological and political options. Nevertheless, as strategies for maintaining or improving quality of life and the environment play out within an expanding global population, we expect the ongoing development of biological systems to play an important role in the global quest for solutions and to provide an expanding channel for relevant applications of synthetic biology.

Synthetic biology is still at an early stage of development and relatively unproven, but its potential is widely considered to be great (and from some perspectives revolutionary). It is a platform technology with an extensive range of possible applications, a few of which are already progressing towards market, with many others under consideration.

It can take many years to develop technologically robust, safe and commercially viable solutions, yet the need for effective solutions to social and environmental challenges is increasingly urgent. This roadmap anticipates some of the mechanisms and resources we need to consider now in order to better respond to emerging opportunities and challenges.

It is too early to assess the full extent to which synthetic biology will address these challenges over the longer term. Nevertheless, the relevant global markets are substantial and growing. For example, biopharmaceuticals (pharmaceuticals

Global needs with links to synthetic biology

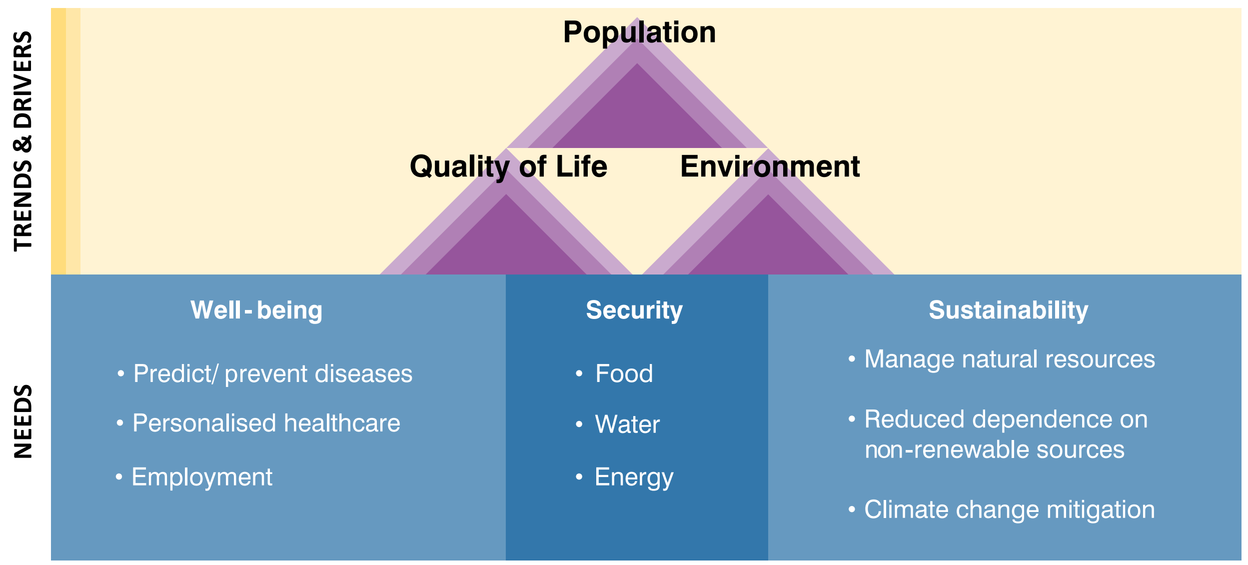

Figure 1: No unique solution can fully address the material needs of a growing global population, but technology developments in the biological sciences can play a role in responding responsibly to the underlying needs for security, sustainability and well-being. This in turn provides a number of channels where synthetic biology may make potentially significant long-term contributions.

derived using biotechnology) are now estimated to be around 20% of all medicines, effectively double what they were a decade ago. As synthetic biology starts to play an increasing role in medicines and healthcare, it is becoming possible to assess the global scale of the future market, at least in the near future. Other established markets provide further benchmarks for potential application – for example, it is estimated that 2010 revenues from industrial biotechnology in the US alone were approximately $100bn[1]. It is also estimated that €5bn may be added to the European bio-economy by 2025 from ongoing research activities[2].

Such assessments depend greatly on the assumptions used, not least the definition of synthetic biology itself and what is, or is not, appropriate to include in the definition of the market sector. One of the most comprehensive assessments available is that by BCC Research on behalf of Global Information Inc. By surveying data available from leading companies, life science research institutions, thought leaders and numerous secondary sources, they compile an assessment of global applications and forecast sales revenues over the coming five-year period. They conclude that the value of the global synthetic biology market will grow at a substantial rate, from $1.6bn in 2011 to $10.8bn by 2016. In the longer term, synthetic biology also has the potential to deliver into new, as yet undiscovered, markets in response to emerging future needs. Regardless of the accuracy of these estimates, there is strong evidence from this and the indicators above that the prospects for future growth are substantial.

1 Biodesic 2011 *Bioeconomy Update*: www.biodesic.com/library/Biodesic_2011_Bioeconomy_update.pdf

2 *Innovating for Sustainable Growth: A Bioeconomy for Europe*. Communication from the commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, Brussels 13.2.2012 COM(2012) 60 final.

UK strengths

The UK has a long tradition of world-leading intellectual activity. We have a reputation for 'punching above our weight', possessing world-leading groups that over many years have consistently delivered significant breakthroughs in a wide range of disciplines, including bioscience, engineering and ICT.

Our innovative culture is one of independent and progressive research, which has at its heart ideas and products that challenge the status quo. The UK is a healthy ecosystem for new and established businesses. We have moderate levels of corporation tax with 'patent box' arrangements for exploiting intellectual property, and generous company tax breaks to encourage research and development.

We need to reduce the risks encountered along the pathway to commercially viable synthetic biology products. This will be achieved through a variety of tailored mechanisms, including a highly skilled, flexible workforce trained by our excellent universities and colleges. Furthermore, UK research and development is protected and enabled by ethical and regulatory frameworks that are recognised around the world as robust and proportionate.

Substantial government investment underpins UK knowledge-based innovation. Total public investment in the research base, through the research councils and the Higher Education Funding Council for England (HEFCE), is around £6bn a year. The Technology Strategy Board, the UK's innovation agency, invests a further £350m a year helping 4,000 companies across all technology domains and business sectors develop new products, processes and services.

Recent UK government announcements committed £75m for the ELIXIR research infrastructure to handle the rapidly growing volume of biological data from high-throughput experiments such as DNA sequencing and £145m to improve Britain's e-infrastructure to drive growth and innovation. An investment of £380m has been made by EPSRC in cutting-edge manufacturing research with over 340 current research grants and 1100 collaborating companies. This includes a £45m recent investment in nine new Centres for Innovative Manufacturing, all working closely with businesses to

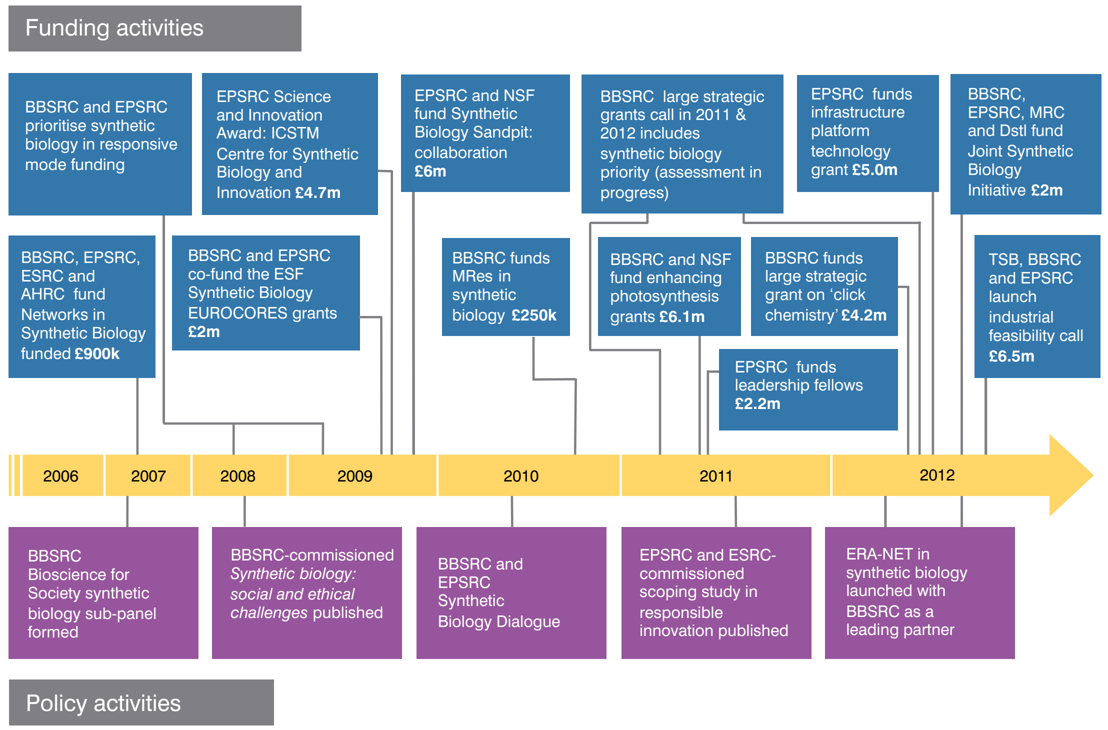

Figure 2: Funding for synthetic biology has been consistently applied by UK research councils since 2007, totalling more than £62m ($95m) to date.

Acronyms: NSF (United States, National Science Foundation) ICSTM (Imperial College of Science, Technology and Medicine), Dstl (Defence Science and Technology Laboratory), ESF (European Science Foundation), MRes (Masters in Research) and ERA-NET (European Research Area Networks) stimulate growth in a number of areas. An investment of £250m has been made by the BBSRC, including 26 strategic science programmes and 14 key national research capabilities, to meet challenges such as sustainably feeding the growing world population and finding alternatives to dwindling fossil fuels. The Technology Strategy Board is to invest £200m in seven Catapults – a network of technology and innovation centres. Other recently announced investments in supporting infrastructure include £16m in robotics (£12m from the Government to 19 universities, with a further £4m from industry) providing access to specialist laboratories, equipment and expertise across a number of sectors.

A recent study has identified that synthetic biology research is now being funded in 40 countries via more than 500 funding organisations, and carried out by a research community comprising an estimated 3000 researchers. The UK is second only to the US in publication output[3]. Publication output from Europe as a whole is comparable to the US. This places the UK in a pivotal position to influence and benefit from this internationally expanding field.

In terms of synthetic biology, there is a very significant presence in those sectors that are expected to commercialise the technology, especially in chemicals, biosciences and pharmaceuticals, advanced materials and energy. For companies in these sectors, indeed in all sectors, the UK is recognised as an excellent place to do business. It was ranked in the top 5% (7th out of 183 countries globally) for 'ease of doing business' according to a World Bank 2011 survey[4]. According to the Chemical Industries Association, it remained, in 2009, the number one inward investment destination in Europe, with almost one fifth of the total accumulated stock of foreign direct investment. In 2007/08, the UK attracted 1,573 foreign direct investment projects from 48 countries, a record-breaking performance. The UK accounts for 57% of the whole European private equity and venture capital market[5].

The UK chemical industry comprises a major sector in the UK, with over 3,000 companies in 2009 (generating an annual turnover of around £55bn). Growth in this sector in recent years has been roughly 5% a year, with the UK having in excess of 8% of the world market.

The UK has one of the most dynamic and innovative healthcare industries in the world. It has developed over 20% of the world's top 100 selling medicines (second only to the US, and more than the rest of Europe combined). Every one of the top 10 pharmaceutical companies in the world has a presence here. GlaxoSmithKline[6] has recently committed to invest more than £500m across its manufacturing sites in the UK to increase production of key active ingredients for its pharmaceutical products and vaccines. Together with AstraZeneca, these two companies alone report a combined turnover of £42bn (approximately 9% of the global market). In 2007, the value of UK pharmaceutical exports was £14.6bn, bringing in a trade surplus of £4.3bn. The pharmaceutical sector in the UK consists of around 600 companies and employs some 67,000 people. According to the Department for Business Innovation and Skills (BIS) 2009 R&D Scoreboard, pharmaceutical and biotechnology R&D expenditure in the UK in 2008 was £9.6bn. The medical technology sector in the UK consists of around 2,800 companies, employing 52,000 people and generating around £10.6bn of turnover a year.

The UK clinical and health sciences research base is second only to the US in terms of global impact. It has provided a creative crucible for the discovery of new medicines over many decades. The UK has several universities that regularly appear in the top ten of university ranking, and a strong legacy of Nobel laureates in the areas of medicine, physiology or chemistry. Over the last decade, UK university bioscience departments have generated over 200 spin-out companies[7,8].

The UK also has major strengths in advanced engineering, manufacturing and design. The potential for synthetic biology to produce high-tensile-strength and other advanced materials may well find value in application fields such as aeronautical engineering.

Bioenergy accounts for 3% of total primary energy consumption in the UK, with the majority (65%) being used in power generation and contributing towards the delivery of the UK renewables target[9]. Both Royal Dutch Shell and BP have significant global biofuel interests, and, together with their partnerships and joint ventures, promote some of the world's largest research, development and commercial renewable fuel programmes.

In 2010, the energy supply industry in the UK contributed approximately 4% of GDP (£60bn), 10% of total investment, 52% of industrial investment, and directly employed approximately 173,000 people[10].

The UK energy research community also produces recognised high-quality research[11] across a variety of energy technologies. The Biotechnology and Biological Sciences Research Council's (BBSRC) Sustainable Bioenergy Centre is a £27m investment in bioenergy research. The centre brings together six world-class research groups and 15 leading industrial associates.

UK biotechnology built on strong heritage

The UK has a strong heritage in biotechnology which underpins not only world-class academic research, but also a vibrant biotechnology industry.

The discovery by James Watson and Francis Crick of the structure of DNA in 1953 and seminal follow-up work by Crick in 1961 that cracked the DNA-to-protein code, laid the foundations on which all synthetic biology designs now rely. UK expertise led to the discovery of reverse transcriptase (now an indispensible part of molecular biology) and the development by Frederick Sanger in 1977 of a vastly improved sequencing method. This led to huge scientific advances including the Human Genome Project.

In the 1990s, Professor Shankar Balasubramanian and Professor David Klenerman of the University of Cambridge invented Solexa sequencing: an ultrafast method for sequencing DNA that improved cost and speed by 1,000 to 10,000 fold on previous technologies. Solexa was sold to Illumina for $600m in 2007 and is the global market leader in next generation sequencing. This expertise has continued to the present day. Oxford Nanopore Technology (ONT) has developed a new sequencing technology based on fundamental research from the University of Oxford which works by running a strand of DNA through a tiny hole called a nanopore. Developments like these are leading to a point where DNA can be sequenced in real time, opening up exciting new possibilities for medicine and biotechnology.

3 *Synthetic Biology: Mapping the Scientific Landscape*; Oldham, P; Hall, S; Burton; G. (2012), PLoS ONE 7,4

4 World Bank. *Ease of doing business survey 2011.* www.doingbusiness.org/rankings

5 UKTI. *Chemicals – the UK advantage.* 2009.

6 www.gsk.com/media/pressreleases/2012/2012-pressrelease-994808.htm

7 Royal Society (2010). *The scientific century. Securing our future prosperity.* http://royalsociety.org/policy/publications/2010/scientific-century/

8 Office for Life Science and UK Trade and Investment (2010). *Life science. The UK: collaboration for success.* http://webarchive.nationalarchives.gov.uk/20110120011807/bis.ecgroup.net/publications/uktradeinvestment/uklifescience/10579.aspx

9 UK Bioenergy Strategy, 2012

10 UK Energy In Brief 2011, DECC.

11 Report of the International Panel for the 2010 RCUK Review of Energy

Synthetic biology

Synthetic biology is the design and engineering of biologically based parts, novel devices and systems as well as the re-design of existing, natural biological systems. The step change in the synthetic biology approach is to engineer biological systems to perform new functions in a modular, reliable and predictable way, allowing modules to be reused in different contexts. It has the potential to deliver important new applications and improve existing industrial processes across many sectors including healthcare, energy, pharmaceuticals, materials, and remediation – resulting in economic growth and job creation.

Synthetic biology has developed over the last decade. The field arose from the confluence of a number of factors. First, the revolution in molecular biology that has occurred over the last 60 years and in which the UK has played a leading role. A significant development was DNA sequencing, which during the 1990s and early 2000s yielded the genome sequences of a handful of important species. From the standpoint of synthetic biology, efficiency gains from next-generation sequencing have led to industrial-scale enterprises with potential to open up nature's vast reservoir of biological information and, with it, identification of novel biological parts. Coupled to this, the development of reliable, chemically based, DNA synthesis is allowing the alteration and construction of DNA sequences, their use in existing biological chassis, and the possibility of building whole genomes from scratch. Second, the development of our understanding of biological systems and how to manipulate them is advancing at pace through systems biology, bimolecular sciences and related fields. This all means that we can now attempt the design and engineering of biological systems with increased confidence and success.

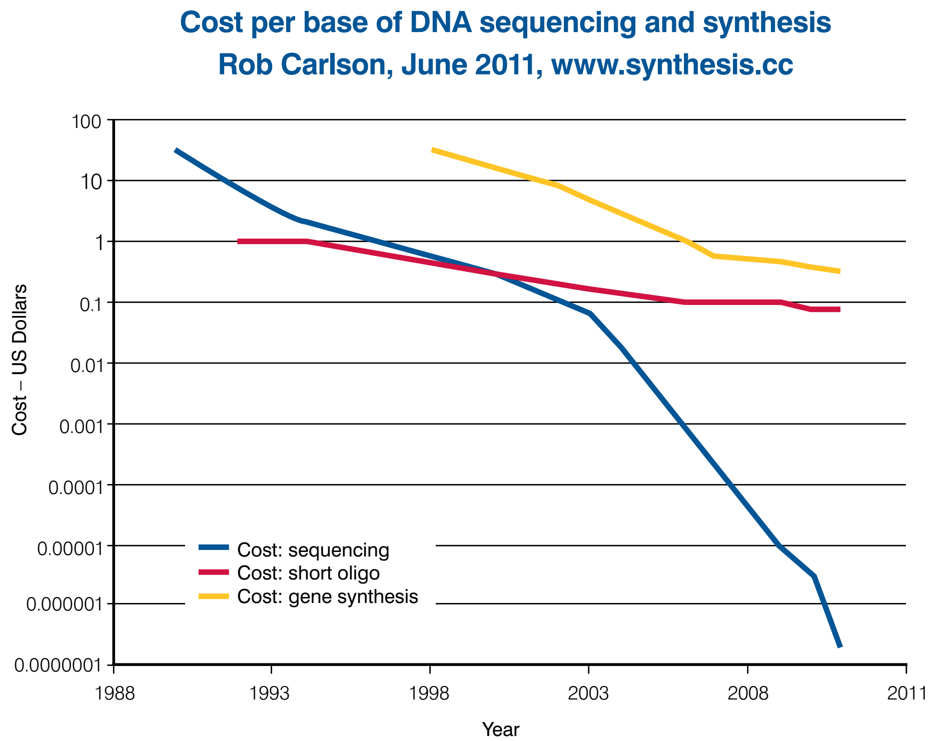

Figure 3: The cost of DNA sequencing has plummeted over the past two decades whilst more modest reductions have been achieved to date in synthesis

Importantly, synthetic biology is a translational field that takes foundational research from a range of fields (for example, biochemistry, systems engineering, molecular biology, plant sciences, chemical engineering, informatics, microbiology) and integrates and builds upon these findings through the application of engineering design principles. This is possible because biological systems are inherently modular and biological function – usually expressed through proteins and RNA – is primarily encoded in DNA. In addition, biological control and regulatory elements can be defined (for example, logic gates, feedback systems, amplifiers and oscillators). An objective of the field is therefore to utilise the diversity of biological parts (genomes and metagenomics, synthetic parts/components) to build new biological devices and systems with defined function.

'Clicking' DNA and RNA

Professors Tom Brown (University of Southampton) and Andrew Turberfield (University of Oxford) are leading a collaboration developing a technique for producing DNA and RNA structures more efficiently and on a larger scale than is possible using current enzyme-based technologies. They have 'clicked' DNA and RNA segments together using a chemical method which could allow long strands of DNA to be produced in large amounts for industrial-scale applications. The ability to 'click' DNA together opens up the possibility of producing new DNA structures decorated with a variety of useful chemical modifications for industrial uses in the UK bioeconomy, including in clinical applications, for example to 'switch-off' disease genes.

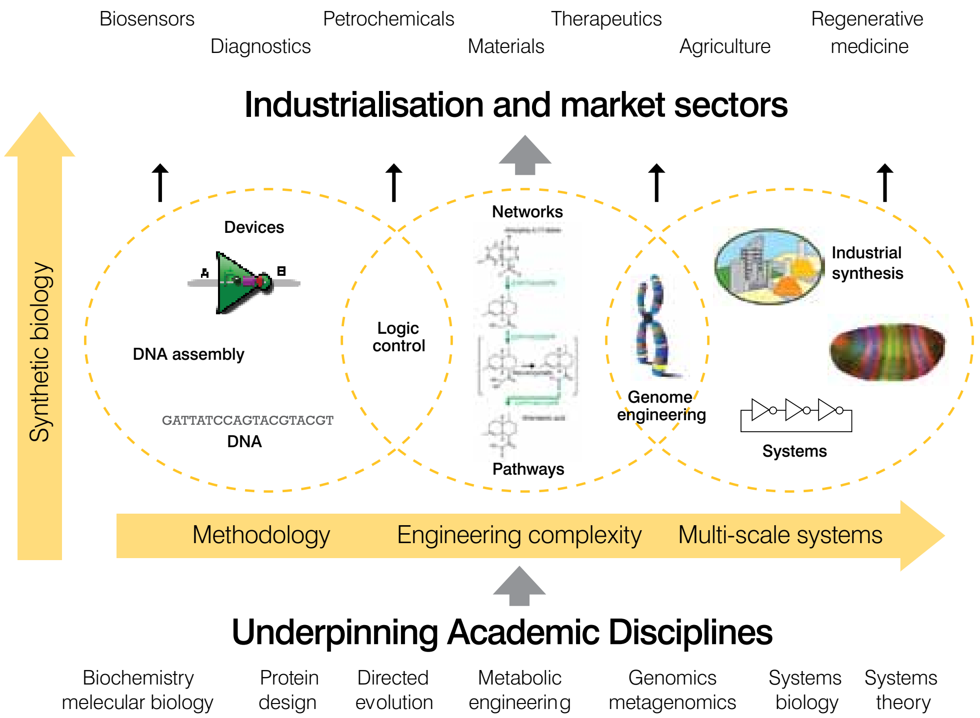

Figure 4: Synthetic biology is both a platform technology (building a systematic basis for design – combining biological, engineering and computational capabilities) and a translational technology (providing the link between a wide range of underpinning disciplines – ranging from biochemistry to systems theory – and practical applications in a wide range of different market sectors)

The engineering concepts of modularisation, characterisation and standardisation are central to the field. Here, modularisation is defined as the process of breaking down a biological system into a series of well-defined, standard parts or components (for example, a gene, protein, a pathway, a microbe in a culture). Characterisation is the process of defining the behaviour and function of these parts in particular contexts in order to understand how they can be used in human-defined design. Standardisation means that the design process is based on well-defined standard modules that can be interfaced to produce a device or system. It is accepted that interfacing biological parts will be challenging, and issues relating to context dependency, predictability and robustness will need to be tackled. The standardisation of components and processes generated significant advances in mature engineering disciplines, and a major challenge for synthetic biology is to put biological systems' engineering on the same footing.

Synthetic biology comprises a translational process achieved through the deployment of platform technologies, within a framework of robust engineering principles and practices. These platforms harness informatics (for example, databases, Bio-CAD software), analytical technologies (DNA synthesis and assembly, sequencing, metabolic and proteomic profiling) and biological technologies (for example, host cell systems) in the process of systematic design. Another key component of the translational process is interplay between experiment and theory, and the application of a synthetic biology design cycle. The cycle comprises the following steps: specification, design, modelling, implementation, testing and validation. These approaches are central to enabling the creation of industrial products when integrated with new scale-up methodologies, and industrialisation is one important end point of synthetic biology. Another important end point is the contribution that synthetic biology will make to the fundamental understanding of bioscience, which, combined with rapid and significant developments across the related underpinning biosciences themselves, will stimulate further generations of industrial products made using this approach.

Synthetic biology is now poised to have an important industrial future in a range of fields. Figure 4 illustrates how the underpinning academic disciplines contribute to the methodology to create devices, networks and systems as part of the synthetic biology translation process. This leads to industrial processes which, in turn, leads to products.

A technology roadmap

The primary purpose of this technology roadmap is to establish a vision for synthetic biology in the UK, and to identify the processes that must be applied to realise it. It provides a framework within which to consider future options and coordinate actions. Because synthetic biology is an emerging and fast-developing sector, the purpose of the roadmap is not to provide a detailed project plan but, more importantly, to determine those core elements that need to be put in place as a secure platform upon which innovative developments may build in future. The process of generating the roadmap is itself an integral part of opening up stakeholder discussion, seeking consensus and starting the process of building an informed, energised and effectively supported UK-wide community.

This roadmap has been produced during 2012 by an independent panel of experts at the request of the UK Department for Business Innovation and Skills. It incorporates material generated during two UK roadmap workshops attended by 70 participants representing a broad range of stakeholders from industry, public bodies, academia and other organisations. The workshops followed a process established through extensive experience by the Institute for Manufacturing (IfM) in Cambridge, ensuring substantial engagement of all participants and generating a wealth of valuable material and insights. The roadmap has also been heavily informed by the large and rapidly growing body of world literature and the outputs of the numerous conferences, symposia and discussion forums that have focused on synthetic biology in recent years.

Fundamental to the roadmap study, as applied in the workshops, has been the need to consider the activity as a whole, taking an integrated overview of all key influences upon and stages within the process, whilst informing the discussion with essential details and knowledge from experts representing a broad cross-section of stakeholders. Our intention throughout has been to identify early the steps that must be taken along the journey, to avoid delay in anticipating and responding to the opportunities and challenges that lie ahead, and to recognise that there are many other stakeholders whom we would encourage to engage in further shaping the way forward as the community develops.

The workshops considered the roadmap landscape as a whole, across a range of timeframes, stretching out towards a post 2030 vision. This was populated in detail from both a 'top-down' perspective, considering trends and drivers, and a 'bottom-up' perspective, considering enablers, capabilities and technology, leading to consideration of value-creation opportunities and value-chain perspectives. Key outcomes are summarised in the A3 fold-out 'UK Synthetic Biology in the UK: Roadmap Landscape' graphic at the back of this publication. The individual elements captured in this diagram are not intended to represent a comprehensive set of activities with precise timings, but rather to represent, through their entirety, an illustration of the broad landscape, the options available and the timescale that must be considered. It is clear that synthetic biology should not be approached in a sequential, piecemeal fashion, but as an integrated whole, addressing issues across the entire landscape in the short term, whilst maintaining a long-term perspective.

By focusing on value-chain perspectives, and considering the various processes that apply when nurturing ideas to market, for example, from academia through SME/start-up companies to large industry, we were better able to identify key needs that should be addressed in nurturing the emergence of a vibrant future industry. Important considerations identified in the workshops included the need to be clear what should be the main areas of focus, recognising the need for genuine market pull for products and for selecting key categories in which the UK can excel, and how to accelerate progress – reducing development time to market – acknowledging the essential role of public funding.

A wide spectrum of applications can be envisaged, each specific application having its own particular trajectory in scope and time, from concept through to commercialisation. Although each individual application will face its own very specific development programme issues, a number of generic success factors could be identified from the many worked examples we considered. By addressing those generic factors, we can create a more broadly supportive operating environment and facilitate progress across the entire range of potential applications.

A fundamental challenge is to reduce the development time and cost to market. Effective links between academia and industry are important throughout, although the balance of engagement will shift towards industry as the concept steps towards market deployment. Taking an integrated approach to the whole is critical to rapid development, but, in practice, development and scaling-up of a concept tends to be stepwise as new challenges emerge. This approach is captured schematically in figure 5, opposite. There are many different ways of clustering and defining the various stages, but this is not critical to the scheme. For illustration, we consider progression through four stages, namely from the initial capability (foundational and enabling science and engineering) to innovation of the concept (technology providing capability) to initial value creation (proof of the application) and finally to value capture (scale-up and market growth).

To facilitate progression within each stage, and from one stage to the next, a number of things need to be in place. These can be broadly split between generics that provide a supportive environment – regulatory frameworks, education and skills, stakeholder participation, multidisciplinary funding – and those that provide a more specifically technical underpinning such as availability of dedicated resources, access to an expert community and links between academia, industry and government. Moreover, the critical role of demonstration as a rate-limiting step in progressing through every stage from the scientifically possible to the technologically real has been clearly identified by the Technology Strategy Board[12]. The benefits of international cooperation apply equally to generic and technological issues.

Starting from these broad insights and the wealth of information gathered from the workshops and other mechanisms as outlined above, we explore in more detail the issues and requirements arising, clustered broadly under five main themes.

12 *Emerging Technologies and Industries – Strategy 2010-2013*, TSB February 2010. www.innovateuk.org see under publications/strategy

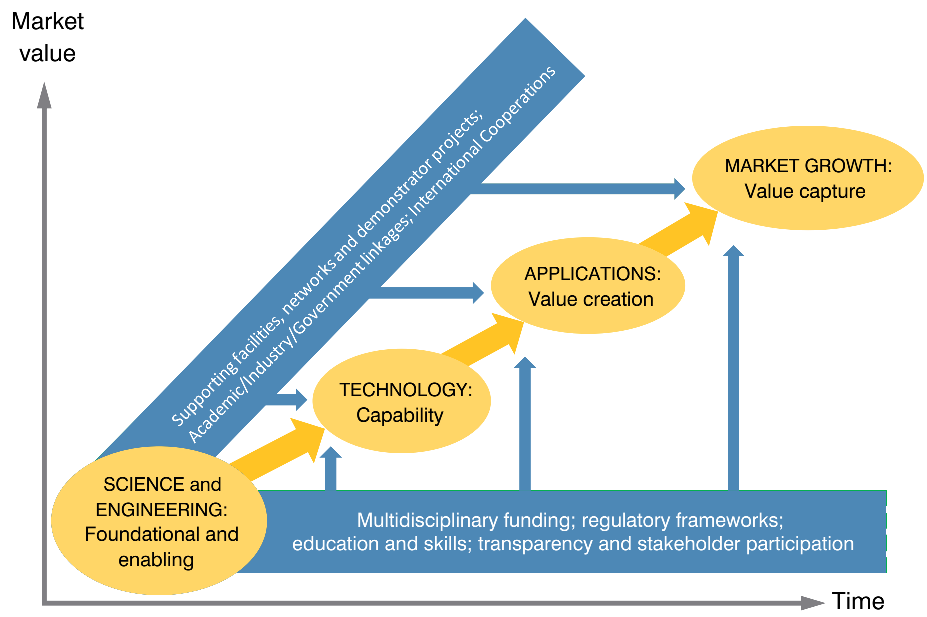

Figure 5: Facilitating progression of an idea through to market in terms of speed and likelihood of success can be achieved by generating a more receptive and supportive operating environment and providing access to critical resources relevant to each stage of development. The precise requirements for any specific idea will be unique, but addressing these generic challenges will enhance the overall synthetic biology translation process

Themes

A number of recurring ideas, observations and issues emerged that we consider directly relevant to the generation of a UK roadmap for synthetic biology. We have gathered these into five core themes.

The first theme 'foundational science and engineering' relates to the underpinning technological potential of synthetic biology and the need to establish sufficient and accessible capabilities within the UK to maintain a leading edge.

The second theme 'continuing responsible research and innovation' is the recognition that the ground-breaking opportunities and benefits arising from synthetic biology also come with the potential for unintended consequences, which can be avoided through awareness, training and adherence to prevailing regulatory frameworks.

The third theme 'developing technology for commercial use' recognises that it can be very difficult to take an idea from the laboratory environment through to a fully-scaled industrial product or service. Steps need to be taken to help overcome the more challenging hurdles so that important opportunities do not fail for readily avoidable reasons.

The fourth theme 'applications and markets' is the identification of future growth markets and the development of suitable applications that would gain from more effective interactions between the academic and industrial communities.

The fifth theme we consider here is 'international cooperation'. Realising the vision for synthetic biology should allow the UK to play a positive role in the international response to global challenges, including helping to set standards and suitable operating frameworks.

It will be clear that these core themes are mutually linked and must be addressed collectively to achieve a successful outcome.

A synthetic biology roadmap for the UK

Theme 1: Foundational science and engineering

Synthetic biology is an emerging area arising out of the confluence of several core disciplines. It integrates knowledge, principally from biology, engineering and chemistry, to create new products and processes. A by-product of this process is increased understanding of biological systems. The UK already possesses world-class expertise within these core disciplines – this provides the strong foundation upon which synthetic biology is being built. A strong message that emerged from the road mapping workshops was that innovation in academia and multidisciplinary confluence are key drivers of the field.

Bacterial logic gates

Professors Richard Kitney and Martin Buck (Imperial College London) have demonstrated that we can build 'logic gates', like those used for processing information in computers and microprocessors, out of harmless gut bacteria and DNA. Logic gates are fundamental building blocks in silicon circuitry. The researchers have replicated these logic gates using biological parts and showed that they behaved like their electronic counterparts. The new biological gates are also modular, which means that they can be fitted together to make different types of logic gates, paving the way for more complex biological processors to be built in the future.

To date, UK research funding for synthetic biology has come principally from the Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC). The funding has supported community networks to initiate research partnerships, a specialist centre, strategic funding for technologies and applications, and high-risk/high-reward studies to explore potential in new areas. International collaboration has resulted in funding to UK universities from a range of sources including the EU, the Gates Foundation and joint programmes with the US National Science Foundation. These grants are important because they establish collaboration with other leading international groups and show the quality of the UK academic base in synthetic biology.

Multidisciplinary centres and funding

There is a need to capitalise on these investments and the research undertaken. The UK has one funded centre in synthetic biology at Imperial College and several other large-scale investments also developing platform technologies (Southampton and Oxford; Warwick) and applications including second generation biofuels (Nottingham). A recent development is the formation of a consortium for synthetic biology comprising Imperial College, Cambridge, Edinburgh and Newcastle universities and King's College London. This aims to further establish a significant infrastructure and resource for synthetic biology within the UK and in support of international collaborations[13]. In addition to these specific examples, there are many other significant groups actively engaged in directly related research, funded by various research councils, industry and other funding bodies (the BBSRC and EPSRC alone support more than 30 different higher education institutions in related fields). For the UK to fully leverage its capabilities as a basis for industrial growth, it will be important to coordinate support for synthetic biology research centres and corresponding research agendas that can facilitate the integration of the UK's research and training capability in the field, ensure good access to leading-edge equipment and generate more opportunities to interface with industry.

It has already been proposed that an innovation and knowledge centre (IKC) for synthetic biology should be established as an important mechanism towards driving technology towards commercialisation. This is described in more detail in theme 3. It is, however, essential to establish how the hub will integrate with the research centres – the concepts of multidisciplinary research centres and a commercialisation centre must be developed as an integrated whole. Concentration of research funding into academic centres of excellence is a feature of synthetic biology investment in the US, China and EU. The UK centres are necessary to build on our strong foundations and to create bioengineered solutions to underpin the UK bioeconomy. Recognition of the social sciences' and humanities' research effort in synthetic biology, together with potential applications in the biomedical arena, may lead to an increase in strategically coordinated research councils' funding.

In 2007, the UK research councils established seven research networks in synthetic biology to bring together different disciplines, to develop a common language and to develop potential research projects. The networks integrated a strong social and ethical dimension into their activities and involved ten universities with considerable researcher outreach. The grants for the existing seven networks have recently come to an end. The roadmap workshops have identified the need for continued multidisciplinary networking activities. These include academic-to-academic networking; academic-to-industry networking; and a number of supporting activities. A pan-UK network could bring together the work of the seven previous networks under a common umbrella. This would provide a

13 www.epsrc.ac.uk/newsevents/news/2012/Pages/syntheticbiology.aspx

forum for the research centres, as well as smaller research groups in other institutions, to discuss a range of topics, exchange best practice and act as a showcase for the presentation of work with applications in a range of industry sectors. It is envisaged that the network should use traditional formats and virtual communication, such as social networking, to build an integrated synthetic biology community. The plant sciences 'GARNET' model[14] provides an example of a pan-UK network that undertakes tasks that mirror those required in synthetic biology. As discussed under theme 3, these networking concepts could be taken forward by the recently formed special interest group (SIG).

Training

The UK has been very proactive in the area of education and training relating to synthetic biology over a number of years. For example, in the session on education and training at the Fourth International Meeting on Synthetic Biology (SB4.0), UK universities were singled out (along with some US universities) as leaders in this area. This activity has taken a number of forms. There are now a number of programmes in operation. These include undergraduate final-year options, MScs and MRes/PhD programmes. In addition, UK teams have been highly successful at iGEM[15] (an international undergraduate competition) over a number of years. There may now be a need to streamline the existing education and training programmes and, where appropriate, to introduce new courses to address the industrial translation process and, more generally, to meet the needs of industry.

It is important to recognise that specialist training is required to produce professional, responsible synthetic biology researchers. The road mapping workshops identified the need to build, maintain and develop the skills base and to enhance interdisciplinary graduate training. It is also important to recognise that synthetic biology training and education needs to take place at all levels – from school outreach (potentially including more practical engagement and learning, as for example being promoted elsewhere via iGEM High School[16]) to undergraduate and postgraduate training and beyond – and that mechanisms need to be tailored to meet the needs of specific student groups. Hands-on experience of synthetic biology should start at the undergraduate level with taught modules given by teams of research-active staff with direct experience of 'wet-lab' biology, engineering design and modelling, and expertise in the ethical and societal aspects of synthetic biology. Such courses should attract students drawn from a number of disciplines, for example biology, engineering and chemistry.

Postgraduate training must be intrinsically multidisciplinary. In addition to the experience derived from existing programmes in synthetic biology around the world, it is important to learn from programmes in associated areas, for example, systems biology. Suitable students should be identified to study at, or in association with, the research centres. In this regard, it should be noted that many of the most successful research centres in synthetic biology around the world have, from their inception, included a multidisciplinary training environment. Students should follow the one-year MRes plus three-year research project model that has been very successful in a number of areas. The approach also includes cross-disciplinary co-supervision, together with professional internships within UK companies and summer schools. In addition, students should be educated in societal and ethical issues, and opportunities for technical and management training should be explored. Short courses for existing industrial personnel should be envisaged.

Any course in synthetic biology will have a high content of engineering and physical science. Hence, synthetic biologists aiming to practise in industry may benefit from professional as well as academic qualifications (compare chartered status in engineering). Accreditation of courses, in this context, would be carried out by the appropriate professional institutions (for example, the Institute of Engineering and Technology).

14 See www.garnetcommunity.org.uk/
15 See http://igem.org/Main_Page

16 iGEM High School is now in its second year and expanding internationally: http://igem.org/High_School_Division

Theme 2: Continuing responsible research and innovation

It is crucial that this technology continues to be developed in a socially responsible fashion, and that relevant stakeholders, regulators and the public are engaged in research and innovation processes from the outset. Responsible research and innovation encompasses, but is not confined to, operating within an effective risk regulatory framework. The UK needs to be, and to be seen to be, leading the way in frameworks and methodologies for responsible innovation. The UK has already initiated public dialogue in synthetic biology and encouraged interaction between regulators and funders.

Since synthetic biology is a new field, there is much uncertainty surrounding both the risks and benefits of its research and applications. While stringent risk management is crucial for responsible research and innovation, inescapable uncertainty must be acknowledged and accounted for. The aim of responsible research and innovation is not simply to predict and proactively manage negative outcomes, but also to shape decision-making procedures that recognise such uncertainty across the whole life cycle of innovation. To foster successful innovation, governance must be flexible, transparent, open to wider participation, and responsive to emerging evidence and changing social priorities.

Public acceptability

Public acceptability is widely recognised as a crucial issue for synthetic biology, but it cannot be adequately dealt with through communication aimed at reassuring the public. Prior public controversies on emerging technologies demonstrate that it is essential for debates to go beyond the community of experts to open up discussions about the purpose of innovation and about uncertainties and complexities surrounding both the benefits and risks associated with particular applications. Research has shown that 'the public' is not a singular pre-existing mass that accepts or rejects particular technologies according to fixed preconceptions. The direction taken by innovation pathways, and their perceived social consequences, themselves shape public responses. The responses and decisions of many and varied social groups – alongside those of academic researchers and firms – help to determine technological pathways and the realisation of benefits. These include institutions involved in health, safety and environmental regulation, intellectual property, research funding, and capital investment, as well as intended users and beneficiaries, and civil society groups. New social groups also emerge alongside innovation (new pressure groups may come into being when, for example, a new drug is developed to extend the life of patients with a specific terminal cancer). All of these groups need to be actively engaged, throughout the process, in the governance of synthetic biology research and innovation.

In the UK, public acceptability was recognised as crucial from an early stage and led to a large-scale synthetic biology dialogue in 2010. Findings from the dialogue showed there was support for synthetic biology but that this was conditional. While there was great enthusiasm for the possibilities of the science and its application, there were also fears of control and misuse and concerns about how to govern this novel area when there is uncertainty over its outcomes. One of the key findings of the dialogue – which is consistent with a large body of social science research – was the emergence of these five key questions that synthetic biologists should be willing and able to answer[17]:

- **what is the purpose?**
- **why do you want to do it?**
- **what are you going to gain from it?**
- **what else is it going to do?**
- **how do you know you are right?**

To build on this successful dialogue, it is crucial that these questions are at the forefront of ongoing decisions about the commercialisation, translation and regulation of synthetic biology. Indeed, BBSRC, on behalf of the UK research councils, posed those questions in the closing session of the Six-Academy Synthetic Biology Symposium II in Shanghai in October 2011[18]. Although addressing health, environmental and security risks is important, this will not in itself lead to broad public acceptability unless innovation in synthetic biology is demonstrably directed towards:

- new products, processes and services that can bring clear public benefits including, but not limited to, employment, improved quality of life and economic growth
- solutions to compelling problems that are more effective, safer and/or cheaper than existing (or alternative) solutions.

Integrating social sciences, humanities and arts researchers can help with understanding of, and engagement with, such issues and thus foster responsible innovation. The UK is at the forefront of experimenting with such cross-domain collaborations: the seven synthetic biology networks included social scientists, artists, philosophers, and legal scholars; and the Imperial College Centre for Synthetic Biology and Innovation (CSynBI) was set up as a joint centre between scientists and engineers at Imperial College and social scientists at the BIOS research group[19].

17 BBSRC/EPSRC (2010) Synthetic Biology Dialogue. Swindon, Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC), p.7. Online at: www.bbsrc.ac.uk/web/FILES/Reviews/1006-synthetic-biology-dialogue.pdf
For a summary of how these same issues recur throughout all the ScienceWise Dialogues, see Chilvers, J and Macnaghten, P. (2011) *The Future of Science Governance: A review of public concerns, governance and institutional response.* London: Sciencewise-ERC. Online at www.sciencewise-erc.org.uk

18 Six Academies Synthetic Biology Symposium II – Shanghai 12 – 14 October 2011, www.sibs.ac.cn/synbio/programme.asp
19 BIOS – a centre for Biological Sciences originally based at the London School of Economics (LSE) and now based in King's College London

Regulating synthetic biology

Building a culture of responsibility, evaluating health and environmental risks at all stages from the planning stage onwards, and increasing awareness of those risks are integral to good practice in synthetic biology research and innovation and in the subsequent development of synthetic biology products, processes and services. Regulatory authorities recognise that synthetic organisms may have unintended harmful consequences; in certain circumstances they could transfer DNA to other organisms, and unanticipated interactions between synthetic organisms and the environment or other organisms could cause unintended harm to the environment and public health. Such risks are currently covered by relevant conventions and legislation, and active review processes exist to ensure these remain informed by, and responsive to, emerging developments in synthetic biology. Biosecurity issues also arise from the risk of deliberate actions intended to cause harm by people who pay no heed to legislative regulations. Additional measures may be required for such scenarios and these have been seriously considered in numerous studies in recent years[20,21].

At present, synthetic biology is regulated by conventions and legislation that was established to regulate the use of genetically modified organisms (GMOs). Regulations for the 'contained use' and 'deliberate release to the environment' of GMOs are determined at the EU level through directives which are then transcribed into UK law. In the future, certain applications of synthetic biology could conceivably entail the deliberate release of modified organisms to the environment. If this were to be the case, the legislation relating to the deliberate release of GMOs would apply. Under this system, decisions on research trials are made at the national level, whereas decisions on marketing applications are made at the EU level. Currently there are some problems with the operation of the EU clearance processes, and this could act as a barrier to commercialisation of certain synthetic biology products. The UK government is currently engaged in EU negotiations with the aim of enabling more effective operation of the current regulatory system. The *Cartagena Protocol on Biosafety to the Convention on Biological Diversity* is an international agreement which aims to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity, taking also into account risks to human health[22]. There are 163 countries party to the *Cartagena Protocol*, including the UK.

Work in research laboratories involving the genetic manipulation of organisms is required to comply with Contained Use Regulations[23]. All persons carrying out such work must notify the Health and Safety Executive (HSE), and for higher risk work must have consent before they proceed. The controls required are based on an assessment of the risks of potential for harm to human health and for damage to the environment. Any work with a substance produced by synthetic biology processes, which is not itself a genetically modified organism, but is potentially hazardous to human health (for example toxic or allergenic), would require risk assessment and appropriate controls to protect the workers and any other persons who might be affected[24].

Regulations are kept under constant review by the regulators, be they the HSE or the Home Office, recognising that science continues to develop and regulation needs to reflect those changes. The principles underlying current regulations are that they:

- place the protection of human health and prevention of harm to the environment as the first priority
- take a risk-based approach, requiring proportionately more stringent controls for higher hazard work
- allow novel work to be carried out, without unduly hindering innovation, but for GM work require that risk assessments are reviewed and for higher-risk work that the regulator gives consent before the work begins.

Questions have been raised about the extent to which the risk assessment framework for genetically modified organisms will be appropriate for synthetic biology (due, for example, to the larger number of genes transferred and the possible use of synthetic genes with no wild-type comparator)[25]. The current general consensus among regulators and scientific institutions is that existing GM regulations are broadly adequate and could be adapted for synthetic biology, but that regulators need to keep a watching brief as synthetic biology research develops.

The regulatory framework for the release of genetically engineered organisms remains contested, most visibly in Europe, but also in the United States and around the world, albeit relating to technologies that precede and are different from synthetic biology. What is contested is not so much 'Is it risky or not?' but rather: 'What counts as risk?' and 'Who decides?' It will be crucial, as synthetic biology progresses, to continue developing a robust regulatory and enforcement regime involving scrutiny, evaluation and modification of existing regulations to address issues such as indirect, delayed, and cumulative long-term effects, including accumulated effects of approvals for different organisms; and appraisal of risks which consider how the technology will be used in practice, in real-world conditions. The latter includes the potential for 'dual use' at a time of increasing global uncertainty. (Science is primarily used to benefit humanity, but particular scientific technologies can be misused, presenting scientists and others with an ethical quandary known as the dual-use dilemma[26].) It is also essential to ensure that a broad range of scientific experts and other stakeholders continue to be involved in scrutinising and contributing to the questions asked in risk assessments. This must include international collaboration, which will be essential to allow the UK to realise the full benefits of its synthetic biology sector.

In addition, in order to ensure that the spirit and not just the letter of the legislation is followed, it is important that researchers and regulators work together to ensure that all novel entities and methods produced through synthetic biology are encompassed by these GMO regulations, or are replaced with alternative legislation providing appropriate risk safeguards.

In summary, responsible research and innovation for synthetic biology requires:

- that inescapable uncertainty is acknowledged and measures are put in place to ensure safe, rapid and effective responses to any unforeseen problems
- that the UK maintains and develops its regulatory and enforcement regime for environmental, health and security risks relating to synthetic biology and that it does so from an international perspective
- that 'engagement' means genuinely giving power to a wide range of diverse social groups, including those who will be the end users or presumed beneficiaries of the technologies, taking their concerns seriously, and enabling them to participate throughout the whole pathway of technological development.

Public dialogue on synthetic biology

Synthetic biology has enormous potential but also raises questions around ethics, social justice and biosecurity. In 2010, the Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC) published the results of a joint public dialogue on synthetic biology (with support from Sciencewise-ERC, the UK's national centre for public dialogue in policy-making involving science and technology issues).

The dialogue explored people's hopes and fears for synthetic biology, aiming to ensure that the research funded by the two councils sits comfortably with society. Four workshops in England, Scotland and Wales were attended by 160 members of the public. An additional 41 interviews were carried out with consumer groups, industry and scientists, focusing on the issues and the development of the science. The dialogue revealed that most people are supportive of the research but with conditions on how and why it is conducted. The results of the dialogue have influenced how BBSRC and EPSRC think about funding research in synthetic biology.

Checks and balances

The Biotechnology and Biological Sciences Research Council (BBSRC) has a number of checks and balances in place to ensure that the researchers it funds are aware of any ethical and social issues that their research raises, and that they respond to these appropriately. Applicants are required to consider the ethical issues raised by their grants, for instance, the need to use animals in an experiment or the potential for misuse. If any issues are identified by the peer reviewers or grant committees then BBSRC can draw on a broad range of expertise via its Bioscience and Society Strategy panel and from third parties like the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). BBSRC will not start paying grants until all issues have been resolved.

20 *NIH Guidelines for Research Involving Recombinant DNA Molecules*

21 *Addressing biosecurity concerns related to Synthetic Biology*: Report of the National Science Advisory Board for Biosecurity (NSABB), April 2010

22 http://bch.cbd.int/protocol/

23 Directive 2009/41/EC on the contained use of genetically modified micro-organisms; GMO (Contained Use) Regulations 2000

24 The Control of Substances Hazardous to Health Regulations 2002.

26 Rodemeyer, M (2009) *New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology* Woodrow Wilson International Center for Scholars; Dana GV, Kuiken T, Rejeski D, et al. *Synthetic biology: Four steps to avoid a synthetic-biology disaster. Nature* 2012 483(7387): 29.

26 Parliamentary Office of Science and Technology, Postnote, July 2009, Number 340

A synthetic biology roadmap for the UK

Theme 3: Developing technology for commercial use

In this third thematic area we consider how to advance synthetic biology technologies so that they are fit for use in a broad range of potential applications and markets. Implicit in this activity is the desire to increase growth in the UK economy, generating wealth and creating jobs, consistent with the ongoing practice of responsible research and innovation outlined in theme 2. Below, we set out some of the opportunities available in the UK to accelerate the development and uptake of this powerful technology. The work draws on the overarching framework of the Technology Strategy Board's Emerging Technologies and Industries Strategy, other roadmaps and literature, sector expertise and the outputs of the two roadmapping workshops. A key element is the iterative process of matching the commercial requirements of a number of potential markets to the performance that is, or could be, achieved by the technology.

Synthetic biology is still at a relatively early stage of emerging from the science base, but it has truly disruptive potential. Already it allows some things to be done that were not previously possible. Many more things will follow. Even now it is beginning to offer totally new opportunities for existing businesses and new entrants. Below are some of the ways in which those opportunities can best be realised.

Seeing the opportunity

The UK possesses outstanding expertise in its science and engineering base as well as imaginative businesses that are both well established and newly formed. The science is rapidly advancing and markets are changing almost as quickly. This is true, not just in the core synthetic biology technologies, but also in the supporting technologies such as rapid sequencing, microfluidics and bioCAD. It can be difficult for individuals in businesses to stay abreast of scientific developments across the entire field and to determine how these can be best applied to the opportunities they see in their own organisations and markets. No individual or group of individuals is likely to be fully aware of all of the most promising business opportunities. An opportunity exists, therefore, to bring those at the cutting edge of science together with innovators in business to find the best fit between commercial opportunity and scientific potential, and to help them to work together to develop their ideas: to energise the new product supply chain, and to inform the science base.

Creating the industrial translation process

Synthetic biology is, by definition, an applied approach. It draws on a range of fundamental fields in the life sciences, as described in the synthetic biology section and outlined in figure 4. The industrial translation process takes the idea through a development process from laboratory to market, as schematically captured in figure 5. Output from the initial science and engineering phase may take any of a wide range of forms, such as newly characterised bioparts within the registry, new industrial hosts or chassis, or new assembly methods.

The next step in the translation process is the development of the industrial engineering methods appropriate for the applications being developed, and ultimately the development of biofactories.

All of the stages in the translation process lead through to products and, ultimately, to market. It is essential to develop processes whereby industrialists and academic researchers can more effectively collaborate to define application projects and requirements in terms of industrial techniques and the market, including societal benefits. These collaborations are likely to be different in relation to projects with large companies and projects with SMEs.

Accelerating the journey to market

Most modern technological products and services exist in complex, and global, supply chains, and it takes time to introduce and have adopted radically different propositions. Each organisation along the chain has to evaluate the impact a new technology may have on its operations, and has to satisfy itself that it can assure the quality and delivery of the commercial offering. It has been shown that one of the best ways to speed up this process is to create 'demonstrators' that show what is on offer in a compelling way[27]. Helping innovating organisations to produce demonstrators of various kinds will advance the technology more quickly to market. In some cases the type of demonstration needed will be demonstration of scale, and access to production capability to assist scale-up will be important. Some of the facilities needed already exist in the UK. In other cases, demonstration will require access to cutting-edge laboratory equipment, and it is important that critical equipment is located within the UK – it should be made easier for businesses to access the expertise and facilities within the university sector. This could be particularly valuable in highly specialised areas or where a combination of biology and electronics or material sciences is used.

Reducing the commercial and technical risk

It is a regrettable fact that new product introductions often fail, even where the products themselves can deliver benefits for consumers and have economic potential[28,29]. A proven method of bringing more products to market sooner is to help reduce the risk of technical failure, and to share the financial risk. This can be done by bringing people from different organisations and with different capabilities together to work jointly on collaborative projects. These organisations can find better solutions to problems, and share the research and development costs, reducing the burden on any individual one of them. In the next stages of the development of synthetic biology, whilst companies may perceive that there is little or no technical risk in specific project areas, they certainly perceive that there is commercial risk.

A three-component approach, comprising input in both cash and kind, has been found to be effective. The three components of this hybrid model are industrial resources, public resources and university resources. The public funding contribution would normally be in terms of cash or the de-risking of the investment to make it more attractive to other potential funders (such as venture capitalists). The main university contribution is in terms of research facilities and highly skilled research personnel. Industry may contribute cash or know-how. The public and university components of the model act as a catalyst to counteract common causes of failure of application projects as seen from industry, for example through provision of training, mentoring and expansion of partnering opportunities. Larger industries may also separately fund their own 'in-house' research to address their internal investment criteria.

In his keynote speech at the University of East Anglia 'What's the Good of Government?'[30] the Minister of State for Universities and Science David Willetts said: 'The Government can bear the big risks of scientific innovation, which are too great for any individual company.' This is not to be interpreted as being an argument for a 'blank cheque' from government for innovative companies, but it does highlight the potential for government to be an early adopter and to stimulate demand for potentially valuable innovations that initially entail a high degree of risk. One such mechanism potentially available to government might be use of the Small Business Research Initiative (SBRI) scheme. SBRI could be used to procure synthetic biology developments that potentially meet the strategic and operational needs of government departments and the interests of society that they serve whilst simultaneously serving to de-risk commercial developments for emerging private sector customers – thereby creating new commercial markets as well. BIS has increased the funding for SBRI through the package of support for SMEs announced in the Innovation and Research Strategy[31] to be delivered through the Technology Strategy Board.

Since the launch of the programme in 2009, SBRI has awarded 914 contracts worth £78m to technology based SMEs. Some 55 per cent of these contracts have been awarded to either micro (fewer than 10 employees) or small (fewer than 50 employees) companies, typically the sort of companies that the public sector has the greatest difficulty in contracting with. The additional funding is expected to enable the Government to build on this success, and promote awareness and take-up of SBRI across departments. Synthetic biology could be considered a candidate technology for the future use of the SBRI approach[32].

Building a community of practitioners

The UK has numerous well established networks in the academic and business domains, and these have much to contribute to a community of practice in this space. Complex problems are often best addressed by bringing a combination of experienced and fresh minds to bear on the topic. Applying a variety of mechanisms to build a networked community will be particularly important in synthetic biology because of the wide range of disciplines involved – science, engineering, social, regulatory and others – and the need to develop common standards and protocols.

Creating momentum – critical mass

When businesses cluster together they can collectively be more effective. Examples from the digital industry are well known and include Silicon Valley, Silicon Fen, and Tech City. With today's communications it is no longer essential for clustering businesses to be located together, but providing a nucleus for the activities of various protagonists can add value. The UK is fortunate in that three of the world's top 10 life sciences universities (Cambridge, Oxford, Imperial) are relatively close geographically and, indeed, the span of

Biotica/Amyris: from therapeutics to renewable fuels

Polyketides are compounds from bacteria and fungi that hold great promise in areas ranging from clinical medicine to biofuels. Biotica, a company co-founded by Professor Peter Leadley, of the University of Cambridge, has signed a non-exclusive deal with Amyris, an integrated renewable products company, that will see Amyris use Biotica's polyketide engineering technology to make a range of compounds that are either difficult or impossible to make by conventional methods. The agreement between Biotica and Amyris could bring new routes to renewable fuels a step closer.

27 Technology Strategy Board, *Emerging Technologies and Industries Strategy* 2010-13 (Feb 2010) www.innovateuk.org see under publications/strategy

28 Source: Stevens, G.A. and Burley, J., *3,000 Raw Ideas = 1 Commercial Success!*,(May/June 1997) Research Technology Management, Vol. 40, #3, pp. 16-27.

29 Robert G Cooper, *Winning at New Products*, 3rd Edition, p10-12 (Basic Books, 2001)

30 See www.bis.gov.uk/news/speeches/david-willetts-whats-the-good-of-government-2012

31 See www.bis.gov.uk/assets/biscore/innovation/docs/i/11-1387-innovation-and-research-strategy-for-growth.pdf

32 See www.innovateuk.org under publications/about our programmes

academic establishments working in synthetic biology and related disciplines across the UK as a whole is relatively compact.

A characteristic of synthetic biology is the need for multidisciplinary centres. Establishing a UK-wide network of academic, industrial and other organisational interests will benefit from the presence of a backbone of potentially several multidisciplinary centres, including an innovation and knowledge centre (IKC) for synthetic biology. Reviewing the options and proposing an optimum configuration for the UK is a clear requirement emerging from this roadmap.

Intellectual property

The way in which intellectual property (IP) rights are treated will play an important role in encouraging the development of synthetic biology in the UK. At a fundamental level, the concept of 'ownership' of living organisms raises ethical issues that are approached differently in different territories. At a technology level, there is a balance to be struck between that which may reasonably be protected and that which would encourage greater enterprise through being made available as open source. The BioBricks Foundation[33] represent this latter approach, seeking to ensure that standard biological parts they create are made freely available in the public domain. Conversely, it is also recognised that the formation of a fully reliable and characterised library of parts will require significant investment that may reasonably justify a level of intellectual property protection. Related issues arise when considering more complex entities assembled from these basic parts such as devices and systems. Finding where to draw the line between what is publicly available and what is protected by IP remains a subject of ongoing debate. Nevertheless, there is clearly a regime in which specific applications are developed, optimised and commercialised for which IP ownership will be vitally important. It is vital to establish an appropriate and more consistent approach to determining what is, or is not, suitable as a basis for protection as intellectual property in this field of synthetic biology. To be broadly useful and effective, this will need to be addressed at an international level.

We have identified the importance of improved academic/industrial partnerships, and indeed the links between different scales of industry in developing synthetic biology in the UK. Establishing suitable mechanisms for IP capture and ownership will be highly influential in promoting the desired working environment. A common approach is to consider the development of ideas sequentially, capturing IP along the pathway and, for example, if the patentable idea is developed within academia, to consider translation to industry via licensing (compare the Lambert Review model from 2003[34]). Alternatively, taking the more integrated approach we have explored in this roadmap, it is clear that industry plays a significant role in helping identify and access end markets, and in so doing may help shape and focus the early-stage and application development processes. The recent 'patent-box' initiative, which provides a tax break for corporate income earned through the exploitation of a patented invention, provides a strong incentive to industries to get more involved in the development of qualifying IP within the UK, and has already had an important influence on the recent decision by GlaxoSmithKline to increase their investments in the UK[35].

Important technologies for development

It will be important to invest in the development of technologies that work across a wide range of applications. This will include the development of accurate and reliable characterisation methods for defining bioparts and the development of different types of hosts or chassis (ie cells used in the synthetic biology process). Particularly relevant here is the development of new industrial strains of hosts. New wet-lab assembly techniques will need to be optimised for industrial application. Biopart characterisation, host development and assembly methods could be incorporated within a web-based information environment containing bioCAD tools, a registry of bioparts (with their associated metadata) and a registry of models. Industrial engineering methods, applicable to the specific applications, will need to be developed, leading ultimately to the development of biofactories.

Amyris: anti-malarials and more

Amyris is a US-based company that is using synthetic biology to produce high-performing alternatives to oil-based fuels and chemicals. Amyris was founded in 2003 by four post-doctoral researchers from the University of California Berkeley. Their founding product was Artemisinin, a highly effective anti-malarial medicine traditionally derived from plants using a slow and expensive process. The Amyris team used synthetic biology to engineer the pathway for producing an Artemisinin precursor in yeast which could then be converted into the drug relatively easily. Amyris granted a royalty-free licence for the technology to Sanofi-aventis to develop the production process to a commercial scale. Using building-blocks derived from its yeast-based platform and renewable feedstocks, Amyris is now developing a slate of different products for the fuels and specialist chemicals markets.

33 http://biobricks.org/

34 www.hm-treasury.gov.uk/lambert_review_business_university_collab.htm

35 www.gsk.com/media/pressreleases/2012/2012-pressrelease-994808.htm

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Theme 4:
Applications and markets

One of the exciting things about synthetic biology is the wide range of applications to which it might be put. Its potential is truly as a platform technology, capable of realising benefit in a very wide range of markets. The full breadth of applications is clearly articulated in the literature and was reinforced by the workshops we held. Below is a summary of some of the key opportunities that have been identified and from which the UK is well placed to benefit. Many of these benefits could be realised using renewable and potentially low-carbon biological materials.

Medicines and healthcare

An increasing proportion, currently an estimated 20% (up from 10% in 2002[36]), of all medicines are biopharmaceuticals – in which the active pharmaceutical ingredient (API) is a large biological molecule, such as a protein (as in insulin) rather than a small molecule (as in aspirin). Such large and complex molecules can be very difficult and/or expensive to extract from natural plant materials or make using conventional chemical processes. Synthetic biology has the potential for a step-change reduction in the difficulty of production, potentially making expensive drugs, both biopharmaceuticals and small molecule APIs, more available to patients, and also benefiting the industry. BCC Research identify around 20 drugs based on the use of synthetic biology that are currently under development or clinical evaluation[37]. We know of others. Cells could potentially be designed for use as therapeutic agents to deliver delicate drug molecules (that would otherwise be metabolised by the body before reaching the diseased area) in a targeted way. It is even possible to envisage the use of a cell as a biosensor to detect a biomarker for a disease and then, from within the same cell, to switch on the production of a desired drug. If brought to fruition, this could truly revolutionise the treatment of chronic illness. Other applications include vaccines and gene therapies. Synthetic biology technologies could also be used as enabling tools to help researchers identify and interrupt disease pathways more quickly.

Fine and speciality chemicals

Although it is not possible in all cases now, the technology has the theoretical potential to produce many of the chemicals or materials currently derived from petrochemical feedstocks using fermentation/industrial biotechnology routes and renewable feedstocks. Industrial biotechnology could be a key application area for synthetic biology, providing the platform to deliver benefits to many different sectors. Potential applications include cosmetics, flavours, fragrances, lubricants, additives, polymers and rubbers, surfactants, biopharmaceuticals and detergents. In some cases, synthetic biology may already provide advantages over existing routes, and, in the longer term, alternative routes to materials currently derived from fossil hydrocarbons may become increasingly attractive.

In the short to medium term, industrial biotechnology is an area that could derive particular benefit from synthetic biology, with opportunities for economic growth. To help drive this process, it will be important for the Industrial Biotechnology Leadership Forum and the Synthetic Biology Leadership Council to ensure their work is aligned.

Energy

The production of biofuels using biological conversion processes is well established. Bioethanol is the product of fermentation by yeast. In addition to yeast, a variety of different micro-organisms, including bacteria and cyanobacteria, are being investigated for fuel component production capabilities. Modification of such organisms to improve production economics or to produce different fuel or chemical component characteristics is being explored by many universities and companies, for example modifying yeast to produce iso-butanol[38], or farnasene[39], whilst engineered clostridia may be used in the industrial production of n-butanol[40].

Longer-term options include direct conversion of sunlight to fuels such as hydrogen. Such 'solar fuels', produced via 'artificial photosynthesis', may be achieved using entirely inorganic materials, or by applying synthetic biology to produce

TMO Renewables

One of the cornerstones of the TMO process is the ability of its proprietary microorganisms to produce ethanol from a wide range of non-food lignocellulosic feedstocks. TMO has achieved this by employing a synthetic biology approach to develop strains that can convert such feedstocks to fermentable sugars with greater efficiency, thus maximising ethanol yields and lowering one of the economic barriers that previously restricted the manufacture of cellulosic ethanol. Using synthetic biology techniques will facilitate the development of additional improved strains for use in the production of other renewable fuels and chemicals.

36 EvaluatePharma *World Preview 2016: Beyond The Patent Cliff*, p8 (June 2011)

37 BCC Research, *Synthetic Biology: Emerging Global Markets*. November 2011.

38 Gevo: http://blogs.nature.com/news/2012/05/butanol-hits-the-biofuels-big-time.html

39 Amyris: *Renewable Chemicals Digest*, 25 June 2010.

40 Green Biologics: www.greenbiologics.com/

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some form of hybrid system. Such an approach would have the benefits of direct photon capture, with the captured energy stored in chemical bonds via conversion of water or carbon dioxide. A number of academic groups in the UK are working in this field, including Imperial College and Glasgow (see box)[41].

Environmental

Synthetic biology technologies could be useful in bioremediation[42], for the digestion of otherwise difficult to dispose of materials, or for the absorption and retention of impurities, such as arsenic or radioactive elements, in water. It could become possible to mine waste streams using novel organisms to seek out, and concentrate up, rare elements from distributed sources such as waste effluent streams or landfill. The technology could also find application in CO_2 capture.

Sensors

Biological systems can be highly sensitive and can detect extremely low levels of target substances with extremely high selectivity and specificity[43]. This fact could be used to design sensor systems that could be used in healthcare applications to detect the early stages of time-critical conditions such as sepsis, or to give early warning of the presence of undesirable bacteria, viruses or other pathogens or poisons. They may also be used to check for contamination of drinking water, for example by arsenic[44].

41 *Solar Fuels and Artificial Photosynthesis*, Royal Society of Chemistry (www.rsc.org/solar-fuels) Jan 2012

42 Victor de Lorenzo, *Current Opinions in Biotechnology*, 2008, 19, 579.

43 Ahmed Khalil and James Collins, Nature Reviews Genetics 11, 367-379 (May 2010)

44 *Development of a Set of Simple Bacterial Biosensors for Quantitative and Rapid Measurements of Arsenite and Arsenate in Potable Water.* Stocker, J. et al. Environ. Sci. Technol, 2003, 37, 4743-4750

The artificial leaf

Professor Richard Cogdell and Professor Lee Cronin (University of Glasgow) are taking a synthetic biology approach in a bid to create an artificial 'leaf' capable of converting the sun's energy into a carbon-based liquid fuel. The researchers hope to use chemical reactions similar to photosynthesis but in an artificial system. Plants are able to take solar energy, concentrate it and use it to split apart water into hydrogen and oxygen. The oxygen is released and the hydrogen is locked into a fuel. Their research aims to use synthetic biology to replicate this process.

Agriculture and food

Agriculture is a powerful route for producing large volumes of biological materials (such as for food, clothing or paper) or smaller compounds (such as sugar). Synthetic biology has the potential to make food crops less vulnerable to stresses such as drought, saline water or pests and diseases; and/or to create new plants that can produce, in the field, large volumes of substances useful to man.

Core and underpinning technologies

In addition to the synthetic-biology-derived products mentioned above, a thriving industry would have to draw upon a range of core and underpinning technologies such as DNA design, DNA synthesis, rapid sequencing, bioparts, microfluidics, enzyme evolution or other manufacturing technologies, and bioCAD or other ICT tools. Technology development in these areas could itself provide a basis for possible new industries, with DNA sequencing an example of a successful UK development in underpinning technology.

The global value of these combined markets has been estimated by BCC to be $10.8bn by 2016[45], up from $1.6bn in 2011. Products generated using synthetic biology techniques are expected to account for $9.5bn of this, with $1.3bn arising from the market for underpinning technologies.

45 BCC Research, *Synthetic Biology: Emerging Global Markets*. November 2011. Summary: http://bccresearch.blogspot.co.uk/2012/05/global-market-for-synthetic-biology-to.html

Theme 5:
International cooperation

Realising the vision for synthetic biology should allow the UK to play a leading role in the international response to global challenges, including helping to set standards and suitable operating frameworks. In this way, the UK may reasonably seek to build on its current strengths and assume a leading international role in synthetic biology.

Coordinated international cooperation

The UK is an important international player in synthetic biology through a major role in organising the Six-Academy Synthetic Biology Symposia. The six academies are the US's National Academy of Science and National Academy of Engineering, the UK's Royal Society and Royal Academy of Engineering, and the two equivalent Chinese academies. These meetings have played an important role in development and direction. We should continue to build upon the six academies initiative and at the national level seek further coordination between national learned societies with interest in the field (for example, the Biochemical Society, the Royal Society of Chemistry, Society for General Microbiology, the Institution of Engineering and Technology and the Institute of Physics).

International collaboration should also be encouraged and supported through the research councils. Mechanisms such as 'ideas labs' and 'sandpits'[46] joint with the US have been very successful at funding high-quality innovative science in synthetic biology. On a smaller scale, partnering awards have also been effective in seeding international collaborations. These mechanisms can be complemented by the work of the Foreign and Commonwealth Office (FCO), Science and Innovation Network and British Council funding scholarships and meetings. The FCO has a further role to play helping to promote UK science to foreign investors. We should aim to have a co-ordinated approach to international engagement, ensuring that we proactively engage partners to result in the greatest benefit to UK synthetic biology research and to UK plc.

The UK academic community should continue to be very involved in the organisation of international conferences in synthetic biology (both in the UK and abroad). These may approach the subject from a variety of different perspectives, as exemplified by the enGENEious conference organised by students in June 2012[47] through to plans for the UK to host the next (6th) international conference in synthetic biology (SB 6.0)[48] in 2013. A UK–organised Gordon Conference in the field could have a strong impact.

Engagement with international policy and funding bodies

Active engagement with international bodies will remain a very important element in the development of synthetic biology and in realising its potential. Despite a range of differences in approaches at national and regional levels, significant commonality also exists. Learning from this diversity of approaches, sharing best practice and seeking common standards where appropriate will all contribute positively towards the establishment of effective applications on a global scale.

The question of intellectual property in synthetic biology should be discussed internationally, as it is not currently well defined. For this reason, there should be continued engagement with the Organisation for Economic Cooperation and Development. There should be encouragement of collaboration on studies relating to IP, in terms of industrialisation, as this is clearly an important issue. The patent situation for existing biological components and their use in research is in many cases unclear, and joint work would help to clarify this situation. The World Health Organisation should also be engaged in the areas of international healthcare, funding and governance. Joint work should be undertaken on regulations, ensuring a robust international regulatory framework for synthetic biology.

European (including UK) funders have collectively funded transnational projects in synthetic biology through the European Science Foundation EUROCORES initiative[49]. More recently, an ERA-NET in synthetic biology (ERASynBio) was launched[50] which aims to enhance European synthetic biology by co-ordinating national funders. The BBSRC has a strong role in the strategic development and infrastructure planning for this. The EU framework programme provides a route for large investments in synthetic biology. The next framework program, Horizon 2020, will provide in the region of €80m for European science with an emphasis on creating a knowledge based bioeconomy (KBBE), including a role for synthetic biology. This should be linked to the EU bioeconomy initiative. The UK should maintain its high involvement in the development of Horizon 2020 to ensure appropriate support for synthetic biology research.

Joint funding between the UK and US should continue to be explored and excellent collaborations and the networks generated through ideas labs and sandpits should continue to be supported. Opportunities to jointly fund with other non-EU countries leading on synthetic biology should also be explored.

46 www.epsrc.ac.uk/newsevents/news/2009/Pages/syntheticbiologysandpit.aspx

47 http://engeneious.chem.ox.ac.uk/

48 http://sb6.biobricks.org/

49 www.esf.org/activities/eurocores.html

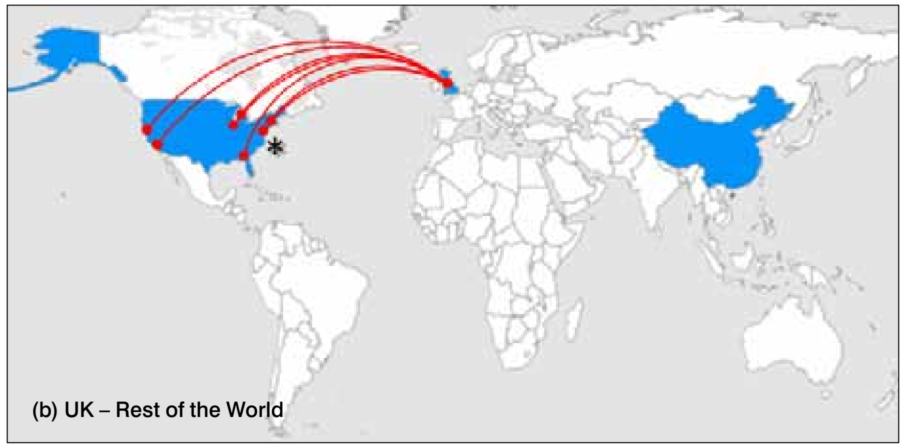
50 http://netwatch.jrc.ec.europa.eu/nw/index.cfm/info/Net/NetId/860D14FB0023C80D84EE1BBABCF12015

International synthetic biology links to the UK

Policy links

Funding links: ESF EuroSYNBIO grants with UK partners

Centres involved in UK – EU FP7 funded projects



Policy links: Six Academies symposia participants
*The US is also an observer in ERASynBio

Funding links: BBSRC – NSF Enhancing photosynthesis grants
EPSRC – NSF Synthetic biology sandpit grants

Figure 6: International synthetic biology links to the UK:

a) Links between the UK and Europe. Further information about these international links is available at: ERASynBio www.erasynbio.net/; EuroSYNBIO www.esf.org/activities/eurocores/running-programmes/eurosynbio.html; and UK-EU FP7 funded projects http://cordis.europa.eu/home_en.html

b) Links between the UK and the rest of the world. Further information on these international links can be found at: Six Academies http://blogs.royalsociety.org/in-verba/2011/04/15/; BBSRC - NSF Enhancing Photosynthesis - http://www.bbsrc.ac.uk/news/food-security/2011/110927-f-increasing-food-and-fuel-production.aspx; EPSRC-NSF sandpit /www.epsrc.ac.uk/newsevents/news/2009/Pages/syntheticbiologysandpit.aspx

Establishing international standards

The establishment of international standards is seen as an essential step in the translation/industrialisation process for synthetic biology, and some work is on-going in the UK, US and Europe, for example in relation to biocomponents. In the US, the technical standards work mainly revolves around synthetic biology open language (SBOL). The work under SBOL relates to the definition of DNA sequences and their unambiguous transmission. Another aspect of the work is to achieve data format compatibility with a range of BioCAD software packages, such as Gene Designer. The European work on standards involves two aspects: the development of standard laboratory and other protocols for biopart characterisation and assembly (including metadata), and the development of a comprehensive information standard called DICOM-SB. This standard is designed to be an extension of the highly successful DICOM standard for biomedicine. In the jargon, what is being developed is a new piece of the standard. This will be directly compatible with all aspects of the original standard, which is widely used by industry.

As globally-applicable applications develop, so needs for further standardisation are likely to emerge. Involvement of the British Standards Institution in developing international standards (with ISO as appropriate) would significantly contribute towards providing the consistency required to establish working systems and assist UK synthetic biology companies to compete globally.

International involvement in education and training

International summer schools are an effective method of enabling UK scientists to engage with and train in an international environment. Effort should be devoted to establishing international summer schools for synthetic biology. These could be targeted at specific countries or regions, for example within the EU (as is being done through ERASynBio) or with the US, or left open to all nations, allowing the dissemination of UK synthetic biology practice more widely.

Higher degree coordination needs to be addressed. What is envisaged is the creation of a joint group to share best practice in creating curriculums for synthetic biology at various levels. However, it is not recommended to plan and implement any form of joint PhD programme involving multiple universities – experience has shown that this is extremely difficult to achieve because of the problem of aligning higher degree regulations. A more practical possibility is the coordination of, for example, PhD programmes where students rotate through various laboratories (often in different countries), but are registered at a single university. One mechanism to increase international collaboration would be to allow students to undertake research rotations or research visits to institutions within different countries (similar to the British Council ERASMUS scheme).

As noted previously in theme 1, iGEM has been very influential in getting synthetic biology recognised internationally. It is a highly prestigious student competition. Last year, around 130 teams from universities all over the world took part and there has been good UK representation with UK teams winning a number of medals and awards at the final. Due to its expanding popularity and size, opportunities to participate now take place at regional levels, not only globally. Participation in the competition by UK universities should be encouraged to inspire the next generation of synthetic biologists.

Establishing international markets and supply-chains

The establishment of international markets and supply chains requires a number of components to be put in place. Depending on the nature of the project and whether or not it involves an SME, it will be necessary to seek industrial support, funding or partnership. If the project is university based, then a partnership with a large company with international links may be most appropriate. This can most effectively be done via some form of licensing or cooperative research agreement. However, large industries are well placed to identify appropriate research groups to partner with anywhere in the world, so ease of working together in addition to world-class expertise will be important factors in their selection. Smaller companies may require more specific support to access international markets, for example by being assisted in developing some form of showcase programme that would in turn attract the required external investment or partnership.

An important question is how to develop and fund a trained workforce to support a solid research base. There is no doubt that with knowledge-based industries it is the quality of the workforce that is a key factor in attracting companies to particular locations (the area around Massachusetts Institute of Technology is a prime example of this phenomenon). The UK is major research player; hence it is important to put mechanisms in place to attract international companies to locate in the UK to undertake industrial activity in synthetic biology, for example by the creation of research campuses built around our universities and research institutes.

With sectors like synthetic biology there could be a tendency for the technology to move abroad once any form of volume market has been established (as seen with next-generation sequencing), although it should be noted that there are also many examples of high-tech companies retaining a key presence in the UK. By considering the opportunities arising whilst the sector is still at an early stage, as in this roadmap, it may be possible to establish a 'silicon valley' type environment for synthetic biology in the UK that attracts inward investment and secures a critical mass from which growth may continue to flourish locally.

However, reflecting the increasingly interconnected nature of global markets and the rapidly growing interest in synthetic biology internationally, it is also important to consider the nature of this core technology in synthetic biology and the opportunities that increasing globalisation may generate. One approach could be to focus on producing new generations of the technology and providing vehicles for full commercialisation, using licensing deals to provide revenue streams as specific new technologies are rolled out. Another would be to take a positive approach towards stimulating appropriate end market activities, for example, agreeing with EU partners to establish a 'lead market initiative' in synthetic biology, or working with the UKTI or FCO to initiate specialist trade missions for the sector.

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Realising the vision

Realising our vision will require an integrated approach today guided by a long-term view. Success will stem from the enterprise and enthusiasm of individuals and stakeholder groups within the UK community, nurtured within a supportive yet clearly structured national operating environment, itself set within the international context.

The following recommendations address a number of critical success factors derived from consideration of the material summarised in the five themes. These need to be taken forward as a whole if the sector is to thrive. The purpose of this roadmap is to chart options for a way forward, but not to pre-empt the outcomes of more detailed follow-up studies that must necessarily take place, continuing to engage experts and the broader community as appropriate.

This roadmap was requested by the UK Department for Business Innovation and Skills (BIS), and there is a role for government in translating the UK's world-leading synthetic biology science base into a commercially vibrant and viable sector. It should begin with the government adopting this roadmap and strategic intent.

A cross-Whitehall strategy group appropriately linked to the role of the proposed leadership council should be established to detail how and where the government will support the development of this sector with the aim of delivering economic growth and employment in the UK.

The important role of public investment

Examples from many different administrations have highlighted the need for public investment to unlock the potential of emerging technologies. Initial investment by the US Department of Defence in DARPANet (Defence Advanced Research Projects Agency), led to investment in the first network to speed up communications between its university researchers involved in defence research.

DARPA realised that connecting universities and the network had wider applications, and moved the project into the National Science Foundation. NSFNet led to public sector investment in servers, high-speed networks and initial operations, without which the Internet would not have been developed as it is.

With suitable infrastructures in place, innovative applications can flourish – such as the development of HyperText Mark-up Language (html) by Tim Berners-Lee leading directly to the meteoric expansion of the world-wide-web.

Recommendations

The following section summarises the main recommendations arising for immediate consideration by BIS. Further details and examples may be found under the relevant themes.

1. **Invest in a network of multidisciplinary centres to establish an outstanding UK synthetic biology resource**

   Facilitating communications and learning, and networking experts across disciplines with customers, public and private interest groups are common themes running through this roadmap. One key element will be to provide access to cutting-edge resources for both the academic community and industry. A single multidisciplinary centre already exists within the UK, but there is now a need to establish a number of additional centres to boost the national research capacity and diversify our expertise, stimulating innovation and facilitating the interfaces with industry and other key stakeholders. Innovation and knowledge centres (IKCs) already provide an established mechanism for integrating cutting-edge academic science with business. Embedding an IKC within this overall structure will provide the important function of academic/business integration.

1.1 Sufficient resources should be deployed within the UK to ensure availability of research capacity and a full spectrum of essential facilities including sequencing and synthesis, CAD and robotics commensurate with the needs of the innovation community.

1.2 This multi-centre network should be coordinated to provide 'one-stop' access to critical resources and expertise, enhancing developmental opportunities for academia and industry alike, including leveraging capabilities in other relevant institutions (such as the European Bioinformatics Institute) as appropriate.

1.3 Centres within this core network should also provide an effective training environment and venues for conferences and other essential stakeholder interactions.

1.4 A process should be initiated immediately to help define this proposed infrastructure, as follows:

- establish the overall requirements of the multi-centre network in line with the roadmap objectives and concurrent plans to establish a synthetic biology IKC
- undertake an audit and prepare an inventory of resources currently available
- determine essential resource requirements, based on the inventory and what is needed to meet the roadmap objectives
- define an appropriate configuration (and optimal number) of centres that will deliver the whole concept
- estimate overall costs and timescales
- report to the proposed leadership council in autumn 2012.

2. **Build a skilled, energised and well-funded UK-wide synthetic biology community**

   Complementary to recommendation 1 above, which focuses on boosting our foundational and applied research base, attention should be given to developing a skilled, energised, responsible and well-funded community. This will involve stimulating cross-disciplinary interactions and sharing best practice, encouraging innovative research proposals and facilitating the development of valuable applications. Together with the provision of further guidance on responsible research and innovation and other training initiatives, an increasingly secure and confident 'can-do' culture should be established.

2.1 Community building. Develop a synthetic biology special interest group (SIG) to facilitate interactions across the community by fostering coordinated efforts, showcasing events and engendering a greater awareness of funding mechanisms to pursue opportunities.

2.2 Embedding responsible innovation. Public sector investment in synthetic biology should take into account social, ethical and regulatory issues and increase awareness of responsible innovation via training programmes. This will include on-going stakeholder engagement and dialogue with wider social groups.

2.3 Training. The next generation synthetic biology community needs to comprise researchers with (a) depth within core disciplines and the ability to work in cross-disciplinary collaboration; and (b) high-level, broad interdisciplinary synthetic biology expertise. Training should also integrate broader societal and business contexts and understanding. Doctoral training should be included as an important element within the multidisciplinary centres. Further training mechanisms include:

- identified students to have cross-disciplinary supervision and experience of working in industry through professional internships. Students should be educated in societal and ethical issues and provided with opportunities for technical and management training
- summer schools and short courses: targeted to meet the common and different needs of industrial and academic researchers. Courses could include introduction to core principles, training in platform technologies, and business development.

3. Invest to accelerate technology responsibly to market

An essential activity in commercialising disruptive emerging technologies is to undertake an iterative process of matching technology with potential market opportunities, and demonstrating that the potential benefits can be achieved in order to attract the investment required. This can be hard to justify for companies where the precise value proposition or business model is still unclear. The UK should invest to help innovators to create new products, processes or services using synthetic biology in a responsible way. Because synthetic biology is at an early stage it is possible that it may find application in a myriad of ways as yet unconsidered. An open-ended innovative approach to early-stage research must also be preserved and stimulated and not constrained to market situations as currently understood.

3.1 Help companies evaluate the potential of synthetic biology in their markets, linking outstanding science to real-world commercial opportunities, for example by:

- facilitating access to expertise and facilities
- setting strategic targets that could stimulate market demand.

3.2 Technology Strategy Board, with research council partners and other investors, should invest in:

- small-scale feasibility studies to test out ideas in a wide range of application areas
- larger-scale R&D projects to demonstrate the technology for promising applications.

3.3 Help companies embed best practice use of synthetic biology technology in their organisations through targeted programme of Knowledge Transfer Partnership (KTPs).

3.4 Ensure provision of an impartial resource to help innovators in the area to evaluate the ethical, social, regulatory and business issues raised by their proposed innovations, such that the maximum benefits of the technology can be achieved.

3.5 Promote the use of responsible innovation across the sector by:

- increasing levels of interaction between the synthetic biology research community and risk regulatory bodies, ensuring that the legislative framework continues to adequately encompasses novel entities as they arise
- translating the principles of continuing responsible research and innovation into the funding mechanisms and related activities recommended in this roadmap.

4. Assume a leading international role

International collaboration is an essential factor underpinning progress in synthetic biology, reflecting the increasingly knowledge-based and interconnected nature of 21st-century society. Clear economic benefits derive from increasing scientific activity between countries, and this expectation lies behind a range of initiatives, including joint research programmes in synthetic biology between funders in the US and Europe and China. Whereas the UK is considered to lead synthetic biology in Europe, our total research funding is significantly lower than in the US. On the other hand, overall research effort across Europe including the UK is comparable to the US, placing the UK in a prime position to continue its leading international role, for example in helping to establish international standards, both technical and regulatory. A number of mechanisms should be invoked to promote this position.

4.1 The British Government should play a leading, proactive role in promoting synthetic biology internationally, particularly in the US, China and within the EU (for example through the EU Bio-economy Initiative and Horizon 2020).

4.2 The UK should work with other countries on the development of IP frameworks that establish a more constructive balance between the benefits of open information exchange at the foundational level and the opportunity to protect valid proprietary developments.

4.3 The UK should work with other countries on the development of regulations and a governance model for the field that is robust and proportionate and adopted internationally.

4.4 The UK should establish mechanisms to promote the UK as a centre for international conferences in the field and help coordinate international activity in advanced training in synthetic biology.

5. Establish a leadership council

The range of potential synthetic biology applications and the corresponding number of bodies involved in different aspects of synthetic biology mean there is a need for one body to be a visible point of coordination. We envisage this to be a leadership council. We propose that the leadership council owns and oversees the continual development and delivery of the vision and roadmap.

5.1 The leadership council should act as a focal point for the development of the synthetic biology sector in the UK, bringing together key interested stakeholders representing a wide diversity of interests, including: industrialists; leading academics; regulators; social scientists; the research councils; Technology Strategy Board; learned societies; NGOs; other stakeholders; and relevant government departments.

5.2 It should provide an exemplar of openness and transparency with two-way stakeholder engagement as a core principle.

5.3 The group should meet three times a year, with at least one meeting held in public. The activity of the council should be supported by ongoing dialogue via social media.

5.4 There is a need for a leadership council to be a visible point of coordination, however there are many bodies in this field, each with a different remit. We would encourage and expect members of the leadership council to work with, and where appropriate sit on these other bodies.

5.5.The work of the leadership council should be supported by sub-groups, appointed by the council, which will deliver discrete pieces of work, for example engagement, regulation, or international collaboration. We would encourage membership of these groups to be broader than that of the leadership council, and to incorporate a much wider cohort of stakeholders.

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Footnote

This roadmap draws upon materials and inputs generated by participants in the two workshops and also reflects ideas drawn from a wide range of other relevant sources. It seeks to reflect a representative view drawn from within the UK community, but does not purport to represent the totality of views that may exist within the UK – further engagement as an ongoing process is a specific recommendation. Nor does it necessarily represent the views of those bodies with whom individual coordination group members are affiliated. Information on markets and trends has been drawn from publicly-available data to illustrate possible futures for synthetic biology, but should not be interpreted as a recommendation and no liability may be accepted by the contributors to this study in regard to any investment decisions taken on the basis of this material.

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