SYNTHETIC BIOLOGY

IN AUSTRALIA

AN OUTLOOK TO 2030

HORIZON SCANNING

ACOLA
AUSTRALIAN COUNCIL OF LEARNED ACADEMIES

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This project has been supported by CSIRO and the Australian Government Department of Health.

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PROJECT AIMS

1. Examine the transformative role that synthetic biology might play in Australia across different sectors.
2. Consider the opportunities and challenges for advancing synthetic biology in Australia.
3. Analyse the future education, workforce and infrastructure requirements to support an Australian synthetic biology industry.
4. Examine the ethical, legal and social considerations and frameworks required to enable and support synthetic biology developments.

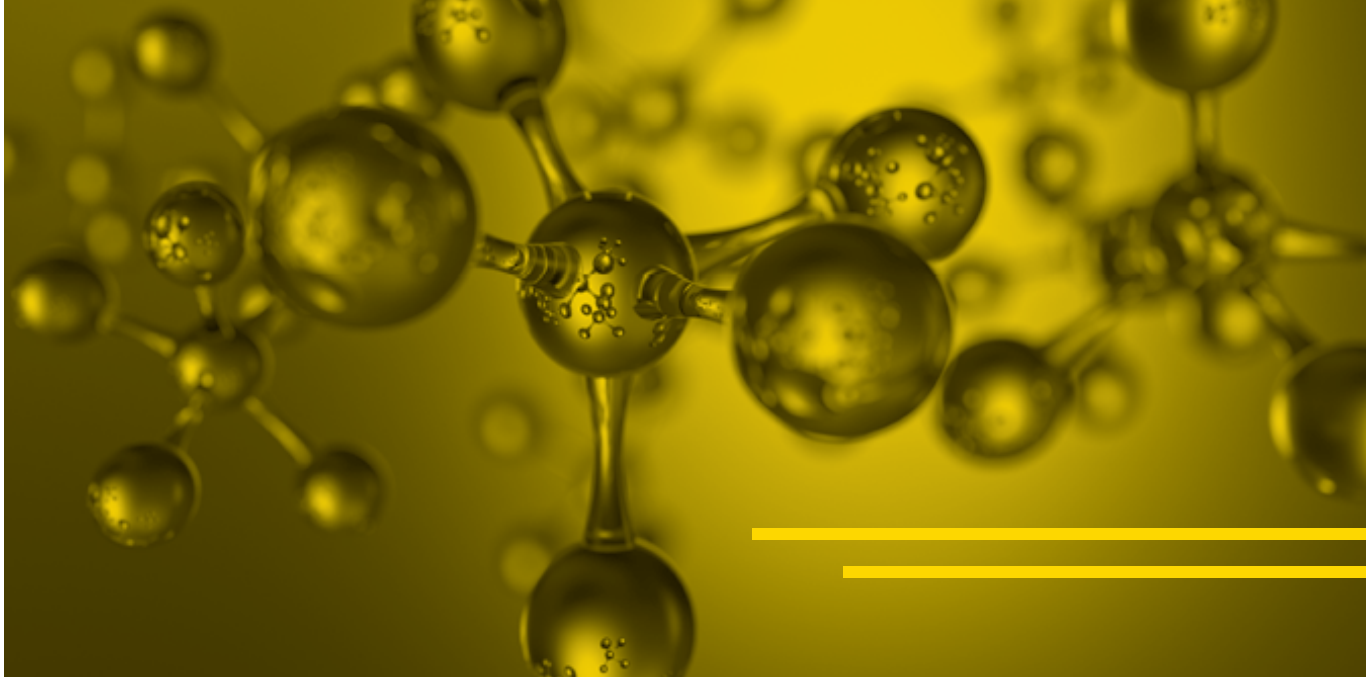
EXECUTIVE SUMMARY

The creation of novel and redesigned biological components, networks and systems is at the core of synthetic biology. Emerging from the established field of gene technology, synthetic biology applies engineering principles to biology to allow the rational design, construction and combination of nucleic acid sequences or proteins, using standardised genetic parts. This approach opens up new opportunities for us to design and create novel metabolic pathways, derive valuable biomolecules, and produce engineered organisms for use in a number of environmental, industrial, and medical applications.

Synthetic biology provides new ways to address major societal challenges in energy and food production, environmental protection and healthcare. The rapid advancement of synthetic biology as a field is being driven by major investments made by several leading research nations, including the US, the UK, China, Singapore and Korea.

Given the breadth of potential applications for synthetic biology, strategically building capabilities in areas of strength will be critical for Australia's future prosperity. The report identifies these areas as industry and energy, agriculture and food, environment and biocontrol, and health and medicine. Synthetic biology provides opportunities for the development of new industries that will produce new and improved products and services, ranging from specialty chemicals, pharmaceuticals and vaccines, to biosensors and bioremediation products, to biofuels. These industries will provide new jobs and exports and support the continued growth of the Australian economy. Our agriculture sector will be highly dependent on the adoption of synthetic biology to remain competitive and to control invasive pests and diseases. The health of Australians will be greatly enhanced by our uptake of synthetic biology applications to improve the diagnosis and treatment of disease, and to improve our diet.

Beyond the existing and developing applications discussed in this report, synthetic biology is also likely to have broad-reaching and unforeseen impacts. Diverse industries are likely to be expanded, while others will be transformed or replaced. There is substantial uncertainty surrounding the social, environmental and economic impacts that synthetic biology will have on Australia and we must be prepared for the transformative changes this field can and will have. Hence the report also considers the social, ethical and regulatory frameworks that will be needed to support its future governance and advancement.



Applications to transform the economy

Australia's strengths in several relevant fields of research and the availability of agricultural resources as feedstock for industrial biotechnology applications, give synthetic biology the potential to deliver significant benefits for Australia. These benefits can be expected across industry and transport, agriculture and food, sustainability and the environment, and health and medicine. In some cases, the use of synthetic biology will make entirely new products and services possible. In other cases, it will improve the efficiency and productivity of existing products, processes and systems. It will be important that Australia's regulatory environment anticipates the rapid advances occurring in synthetic biology.

Advanced biomanufacturing

Developments in synthetic biology at an industrial scale can be used for the production of fine and bulk chemicals, biologics and other valuable biomolecules using cell factories engineered through synthetic biology. An early success internationally which demonstrated feasibility was the commercial production of 1,4-butanediol (BDO), an intermediate chemical used in the manufacture of certain plastics, polyurethanes and elastic fibres. BDO is not a natural product and its synthesis in bacteria requires a combination of enzymes from several different organisms. Other examples include the development of microbial strains to make the high energy liquid fuels needed for aviation from renewable, low carbon, agricultural feedstocks and the production of high value biomolecules in crops, fragrances from yeast, and novel antimicrobial drugs and vaccines. As the field advances, the capture, extraction and integration of the vast amounts of data generated in the design and development of production processes will rely on artificial intelligence and machine learning to design suitable cell lines and microbial strains for use as superior cell factories.

Opportunities for agriculture

The introduction of desirable new traits to crop plants has the potential to transform Australian agriculture. Building upon earlier techniques for genetic modification, synthetic biology can provide higher levels of precision, predictability, control and sophistication

than traditional gene technology approaches to help increase crop and livestock yields and sustainability. Possible improvements include more efficient use of water, increased photosynthetic performance, better nitrogen fixation and nutrient uptake, and resistance to pests and disease. Consumer benefits may include nutritional improvements, such as increased digestibility, dietary fibre, oil quality, and the removal of allergenic proteins from milk, eggs and nuts.

Protecting the environment

The release of toxic chemicals from industrial, agricultural and mining processes can threaten environmental health, the natural balance within ecosystems and the safety and use of water and other natural resources. Synthetic biology provides sensing systems which can inform us on the state of the environment, as well as sense-and-response systems that can be used to detect contaminants and respond by producing the enzymes required for remediation.

Synthetic biology can also provide alternatives to the use of chemicals to control invasive and pest species, such as mice and weeds, by introducing genetic changes that limit the capacity of the pest organisms to reproduce. Improved resilience to the effects of climate change in key ecosystem species is also a target. Strong capabilities in ecology and population modelling are required to predict the effects of releasing engineered organisms and will be critical to the effective use and safe implementation of such synthetic biology applications.

Health and quality of life

Australia is widely recognised for its excellence in health and medical research. This capability is enabled by modern research facilities and high-quality clinical trials infrastructure. Within this context, synthetic biology has the potential to revolutionise the way biological tools are developed and used to advance the wellbeing of humans, manage human and animal health and enhance commercial opportunity in biomedicine.

Cell engineering is an area of significant potential for Australia, with many different applications. One example is human cancer immunotherapy, with several Australian groups designing novel chimeric molecules to mediate aspects of immune function. Redesigned antibody molecules are being engineered into immune cells that can target tumours, bypass harmful immune responses and deliver therapeutics directly to the affected tissue.

Opportunities also exist to use synthetic biology to produce antibiotics and other molecules for which routine chemical synthesis is too complex or economically unfeasible. The ability to use genetic circuits in diagnostic devices or to synthesise vaccines and improved antimicrobial agents holds significant promise, both commercially and to benefit the health system.

A further example that demonstrates the powerful medical applications of synthetic biology is the study of brain function in people diagnosed with neuro-degenerative diseases such as Alzheimer's, Parkinson's or multiple sclerosis, where investigations are hampered by the inability to visualise the release and uptake of neurotransmitters. Biosensors with exquisite sensitivity and capable of differentiating between biochemicals would improve our understanding of the underlying pathology and greatly enhance pre-clinical models of these diseases.

Moral issues, ethics, legal and social aspects

Understanding the social context of technological innovation is important for both responsible development and technology uptake. Establishing active community engagement programs to share information with the public about synthetic biology, earn public confidence, and support appropriate governance and agile regulatory processes will be vital for innovation in synthetic biology to progress.

The emergence of synthetic biology presents an opportunity to develop community engagement approaches that are more effective than those deployed with the introduction of gene technology. Policy makers and researchers are aware of the shortcomings of previous approaches, which tended to focus on simply explaining the technology and its potential production benefits. New approaches are needed to integrate ethical, legal and social aspects (ELSA) of synthetic biology into the research and innovation process from its earliest stages. This includes acknowledgement that synthetic biology, in common with other technologies, can be used for both good and ill. The technologies and applications that are the end product of the research and innovation process need to reflect the values and concerns of the society they are to serve.

Quantitative and qualitative research in the US and the EU indicates that public awareness and understanding of synthetic biology is low. Equivalent studies undertaken in Australia show a similarly low awareness, but indicate generally positive sentiments towards how synthetic biology could improve our way of life in the future (Office of the Gene Technology Regulator, 2017).

Looking to the horizon

Maximising the future economic and societal benefits of synthetic biology will involve several complementary activities that must be delivered in parallel. These include the development of a shared vision by key stakeholders working cooperatively towards a national road mapping strategy, strategic investments in education and infrastructure, understanding both benefits and risks of synthetic biology, and earning public trust through active consideration of ethical, legal and social aspects of the field in ways that engage the wider community.

Developments in synthetic biology are poised to underpin innovations in a wide range of applications, including in areas in which Australia has been traditionally strong: food and agriculture; manufacturing; environmental monitoring and remediation; and, health and medical technologies. To remain globally competitive in these areas, Australia will need to strengthen its culture of technology development and commercialisation, including key infrastructure, effective regulation and a well-protected intellectual property base. To sustain this culture, the tertiary education of the next generation of practitioners must integrate interdisciplinary teaching and research training across science, technology, engineering and mathematics (STEM) with the humanities, arts and social sciences (HASS) disciplines.

KEY FINDINGS

1. **Synthetic biology presents a unique opportunity to address many global challenges: to meet increasing demands for energy and food; to mitigate the effects of environmental degradation; to enhance human and veterinary health and well-being. Australia is well-placed to become a leader in this emerging field with its strong science base in many essential disciplines and high-level expertise in agro-industries.**
   - Major economies including the US, UK, China, Singapore and Korea are investing heavily to advance their capabilities in synthetic biology. This interest is driven by the advantages of precision, predictability, control and sophistication that synthetic biology offers compared with previous approaches for genetic manipulation.
   - Australia has world-leading expertise in contributing fields including protein engineering, metabolic engineering and genetic circuit design. By extending capabilities in genome design and artificial gene construction, Australia has the potential to become globally competitive in synthetic biology as the field advances.
   - Without strategic national investment in synthetic biology, Australia will fall behind other leading nations, to its societal and economic disadvantage.

2. **Synthetic biology is poised to transform existing industries and create new business opportunities for Australia in health, industrial biotechnology and agriculture. Focused and coordinated efforts will allow Australia to build new globally competitive industries, and to protect the export base for existing agro-industries.**
   - Australia's capabilities in synthetic biology, allied to our expertise in health and medical sciences, agriculture and environmental management, present opportunities to develop specific applications for these industries. For example: by linking Australia's strengths in agro-industries with expertise in industrial biotechnology, synthetic biology will lead to new industries producing higher value products from agricultural feedstocks; synthetic biology will be essential to maintain and improve Australia's agricultural competitiveness in crops such as wheat and sugar cane; and scientific leadership in immunotherapy will lead to the development of new treatments and novel health products in this and related fields of research excellence.
   - Improved translation and commercialisation of synthetic biology research is essential for Australia to establish global competitiveness in

these areas of strength. Encouraging and strengthening linkages between synthetic biology research and industry must be a priority to foster this transition. Targeted support for collaborative research programs between researchers and our biotechnology industry would help forge such linkages.

- Australia's system for intellectual property protection is well regarded internationally and provides confidence for business investment. Due to the key role played by standardised, reusable components in synthetic biology inventions, the protection of intellectual property in the field differs from biotechnology more broadly, and Australia should actively engage with the organisations that will determine the international standards that will be applied.

3. **Developing effective mechanisms to proactively communicate the potential benefits and risks of synthetic biology will be critical to earning and maintaining public trust. Without effective community engagement and strong societal oversight, it may be difficult to apply synthetic biology and realise its potential benefits.**

- Social science and cultural research on community attitudes to synthetic biology in Australia is limited. Some uses of synthetic biology will be considered more acceptable than others. Social science research will be essential to the design of effective community engagement processes to identify issues early.
- Engagement processes must facilitate communication between researchers, industry, government and the community about new technologies and their benefits and risks.
- Australia will need to adopt international best practice in Responsible Research and Innovation (RRI) and ensure that ethical, legal and social considerations are integrated into the research and innovation process from its earliest stages.
- Scientists, regulators and policy makers must ensure that regulatory policies and processes have incorporated the legitimate concerns of the community.

4. **Australia's gene technology regulatory system is considered to be among the most effective and progressive in the world. The proactive approach taken to ensuring the regulatory system stays up-to-date with new genetic technologies, industry trends and international developments will be essential for the development of a thriving synthetic biology industry in Australia.**

   - To encourage innovation and responsible advancement of synthetic biology in Australia, review mechanisms must continue to ensure that new and emerging technologies are identified and regulated in a manner that is commensurate with the safety risks they pose.
   - Regulators must maintain effective communication with other countries' regulatory systems regarding applications of synthetic biology that may impact across international boundaries and harmonise systems to the greatest extent possible to ensure that Australia both protects human and environmental health and remains internationally competitive.

5. **Development and improvement of Australia's synthetic biology capability will require a skilled workforce with advanced capabilities spanning both the STEM (Science, Technology, Engineering and Mathematics) and HASS (Humanities, Arts and Social Sciences) disciplines.**

   - The advancement of synthetic biology research and development must be underpinned by strong STEM teaching at all levels of education, from primary through to tertiary.
   - The tertiary sector must recognise and meet demands for training in areas such as molecular biology, biochemistry, computational modelling and simulation, bioengineering, systems biology, bioinformatics and analytical chemistry.
   - Engineering of biology requires skills and knowledge currently derived separately through Engineering and Science faculties. A greater integration between these faculty training programs is required to gain sufficient expertise to effectively use synthetic biology to engineer biology.

- Implementation of synthetic biology solutions in society requires the integration of social and life sciences to deliver ethically and socially responsible outcomes. Integration of HASS specialties will therefore be required to provide a well-balanced interdisciplinary workforce that has competences in science communication, social science, law and ethics.
- The co-delivery of HASS and STEM subjects in synthetic biology research training would facilitate cross-disciplinary learning and promote sharing of creative, social and technical knowledge to broaden and advance the field. Graduates with these broad skills are required to service the research sector and market opportunity that synthetic biology represents.
- The successful development and implementation of synthetic biology will require multi-disciplinary teams comprised of discipline-specific experts in the fields of molecular biology, social sciences, bioengineering, programming, data analysts and analytics, as well as experts in ethics, and cultural and communication studies, who are good team players.

6. **There is a need for an integrated, national infrastructure platform for synthetic biology that supports efforts to achieve international competitiveness.**
   - To bring Australia to the level of capability of other countries, there is a need for a nationally accessible facility with capabilities in high-throughput synthetic biology component assembly, analysis and testing (a Synthetic Biology Foundry). It is essential that the opportunity is taken to learn from other countries' experiences in providing such capabilities.
   - A database of Australian synthetic biology componentry with both public and private sections will provide an enabling platform for Australian synthetic biology applications and protection for Australian genetic resources.
   - Recent announcements by the Australian Government in the National Research Infrastructure Investment Plan to support Australia's national omics and high-performance computing research infrastructure and a synthetic biology scoping study is welcomed and is considered critical to achieving future advances.
   - Establishing commercial-scale production facilities for synthetic biology products would significantly assist in realising commercial impact from industrial biotechnology applications.

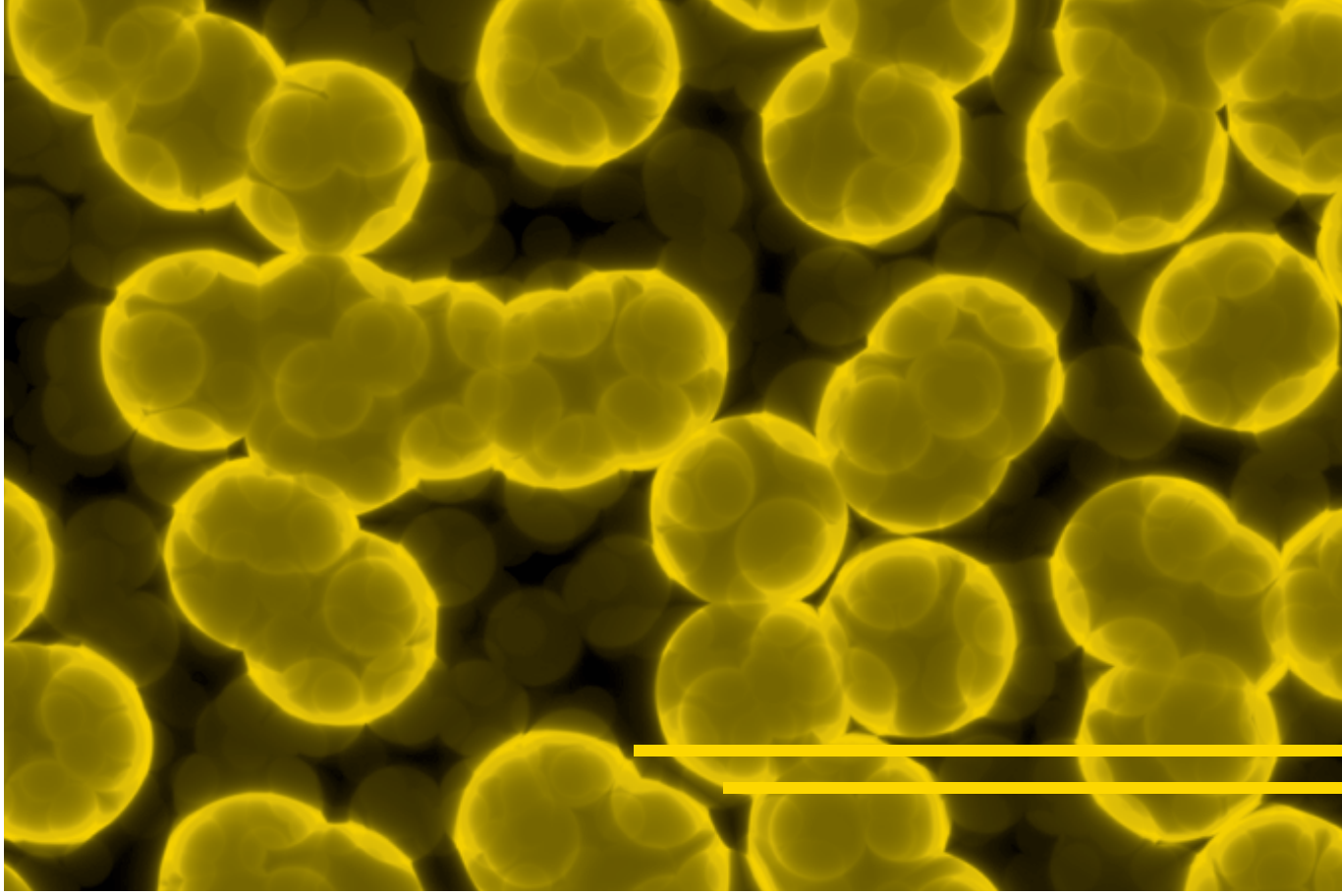
INTRODUCTION

Why synthetic biology?

Synthetic biology involves the application of engineering principles to biology, making it possible for biological systems (or components thereof) to be built to design. By customising biological systems, synthetic biology aims to provide sustainable solutions to many grand challenges of modern society, with applications in energy, manufacturing, agriculture, the environment and health amongst many others (Si and Zhao, 2016). While the term synthetic biology has no single common definition (Appendix A), defining characteristics include rational design, nucleic acid-encoded parts, standardisation and modularisation of parts, abstraction of information, high through-put construction, and improvement on entities that have naturally evolved. For the purposes of this report, synthetic biology has been defined as **'the rational design and construction of nucleic acid sequences or proteins – and novel combinations thereof, using standardised genetic parts'**. Synthetic biology is an extension of earlier genetic engineering approaches based on recombinant DNA technology.

As defined by Australia's Gene Technology Act 2000, organisms altered or developed by synthetic biology are considered to be genetically modified. Our ability to engineer biology to do useful things underpins the Fourth Industrial Revolution – the intersection of biotechnology, information technology, manufacturing, and automation. Synthetic biology builds upon earlier techniques for genetic modification to generate toolboxes with which we can advance this revolution, and as such is driving the bioeconomy (Flores Bueso and Tangney, 2018).

Synthetic biology presents new opportunities to develop industrial chemicals and fuels, cure diseases, monitor and remediate our bodies and our environment, and control invasive and pest species – the applications are limited only by our imagination. As such, synthetic biology could be considered as one of the most transformative technologies to have developed since the advancement of information technology. The two primary enabling tools for synthetic biology are reading and writing DNA. Both are



progressing more rapidly than the advances in computing power that defined the information technology revolution. This has been exemplified by the dramatic decrease in the cost to read DNA sequences, which has fallen 100,000-fold in the past 15 years.

There has been increasing global investment in development and support of synthetic biology technologies. In 2014, the UK identified synthetic biology as one of eight great technologies of the future and established three new synthetic biology research centres, training centres, provided seed funding for innovative companies and established a Synthetic Biology Leadership Council to manage the continued development of the field. The US has several education and research initiatives (ranging from high school to postgraduate level) to encourage and support a synthetic biology industry. US public agencies have conducted several roadmap studies that provide visions and recommendations to address the key challenges and deliver important applications of synthetic biology (Si and Zhao, 2016).

China recognises synthetic biology as a priority research area and the country's Ministry of Sciences and Technology has invested heavily in synthetic biology projects through its basic research funding scheme (Chen, 2014). Synthetic biology was listed as one of 22 science and technology initiatives of strategic importance to China's modernisation in a 2010 roadmap (Cao et al., 2010), and as a strategic emerging industry for development in China's 2016 Five-Year Plan (Central Compilation & Translation Press, 2016). In Singapore, the National Research Foundation

recently announced that it will launch a Synthetic Biology Research and Development Programme to advance the nation's research agenda and expertise (National Research Foundation, 2018). These are just some of the initiatives underway internationally and represent international prioritisation of technology development in this field.

Private investment into synthetic biology companies is also increasing rapidly. In 2017, fifty of the top synthetic biology companies raised US$1.7 billion in capital for technology development (compared to approximately US$175 million in 2009), with the number of synthetic biology companies and overall venture funding increasing (Synbiobeta, 2018).

Developments in synthetic biology are poised to underpin innovations in a wide range of applications, including in areas in which Australia has been traditionally strong: manufacturing, food and agriculture, environmental monitoring and remediation, and health and medical technologies. Health and medical science are traditionally disciplines where advanced technologies have a very high uptake rate. This is therefore likely to be one of the important areas where synthetic biology delivers early impact. However, Australia will need to strengthen its culture of technology development and commercialisation, including key infrastructure, effective regulation and a well-protected intellectual property base, to remain competitive in these areas. Further, there will be risks associated with not sufficiently attending to social and ethical concerns related to synthetic biology. Policy makers, regulators, scientists and social scientists will need to proactively engage the community and different interest groups to develop dialogue and build consensus on both benefits and risks and on the regulation of the field.

Structure of the report

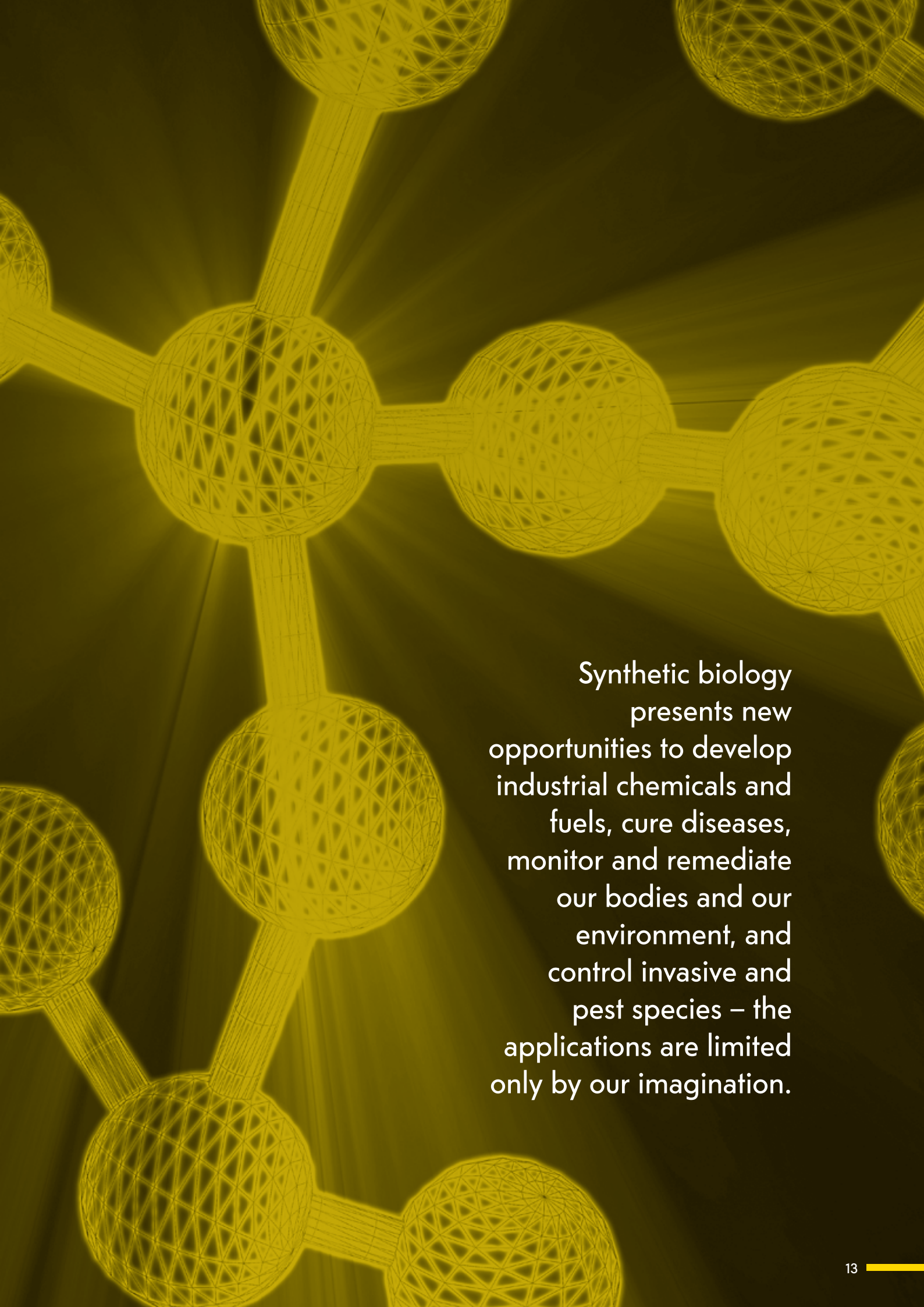
Chapter one provides an overview of the core features of synthetic biology. The chapter introduces examples of what we consider as synthetic biology and provides an overview of the complexity of the field.

Chapter two examines the emergence of synthetic biology in Australia, involvement in international synthetic biology initiatives and activities and our national research outputs. Drawing on information collected through a survey conducted for this ACOLA study, chapter two also reviews the requirements to strengthen Australia's synthetic biology sector.

Chapter three analyses synthetic biology opportunities and challenges, technological advances, and economic prospects across four broad areas in which synthetic biology is most likely to deliver opportunities in the Australian context. The areas examined are industry and energy, agriculture and food, environment and biocontrol, and health and medical applications.

Chapter four reviews social scientific, ethical and legal research on synthetic biology. It gauges the degree of public understanding and examines the importance of adequate public engagement, current regulatory regimes and the international regulatory landscape. The chapter also considers intellectual property issues that arise from the advancement of synthetic biology.

The final chapter summarises the key messages developed throughout the report and closes with scenarios of how synthetic biology may address future global challenges.



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CHAPTER 1
WHAT IS SYNTHETIC BIOLOGY?

1.1 Introduction

Advances in DNA sequencing and synthesis technologies have accelerated the development of synthetic biology as a field, providing the capability to both read (sequence) and write (synthesise) longer DNA sequences, more efficiently and at a faster rate. This has increased the complexity of projects that can be attempted, to the point where whole genomes, and even wholly new organisms can be synthesised. Genome synthesis started with re-synthesis of relatively small known viral and bacterial genomes in the 2000s and has progressed to an attempt to synthesise a heavily modified version of the yeast genome, which is orders of magnitude more complex than early genome synthesis (see Yeast 2.0 project in Appendix A.2.5). Genome synthesis is just one aspect of synthetic biology.

1.2 The emergence of synthetic biology

Synthetic biology evolved from the more established field of genetic modification (sometimes known as gene technology or genetic engineering). The 1953 discovery of deoxyribonucleic acid (DNA) as the molecule that encodes an organism's genetic information paved the way for the first exploration of recombinant DNA technology in the 1970s (Figure 1). In 1974, based on these early discoveries, geneticist Wacław Szybalski commented "*up to now we are working on the descriptive phase of molecular biology... But the real challenge will start when we enter the synthetic phase ... We will then devise new control elements and add these new modules to the existing genomes or build up wholly new genomes.*" (Sybalski, 1974). This is considered the first reference to synthetic biology as it is defined today and was remarkably long sighted: it was two decades until synthetic biology emerged as a field; and almost four decades until we began to build new genomes (Vickers, 2016).

Early genetic modification based on recombinant DNA technology involved the simple transfer of existing DNA sequences from one organism to another (including across species boundaries), thereby transferring the biological components – and traits – encoded by that DNA. Over the

following decades, the technology became increasingly precise and reproducible, and recombinant DNA research initiated a flourishing biotechnology sector. Eventually, researchers moved beyond working with existing DNA sequences and began to modify sequences for new functionality, for example, by combining sequences in novel ways or synthesising entirely new biological components and providing greater capacity to program biological behaviours.

Synthetic biology emerged as a new field in the early 2000s (Figure 1). A key player in this emergence was Massachusetts Institute of Technology (MIT) professor Tom Knight, a computer scientist and electrical engineer who conceived the philosophical approach of applying electrical engineering concepts to biology. This involved treating biology like an integrated circuit, with the aim of simplifying complex biological systems so that they are understandable and simple enough to engineer. This requires collection and characterisation of DNA-encoded parts that are modular, behave predictably and can be used to build more complex systems. While there were problems with this approach in the biological context (Kwok, 2010) relative to classical engineering, it effectively served as a framework for the field of synthetic biology to develop.

The first DNA parts standard, the BioBrick standard, was described and introduced in 2003. Soon after, the first international repositories of standard biological components were established, providing a source of genetic building blocks and supporting the development of technical standards (BioBricks Foundation, 2017a). By applying the core engineering principles of 'decoupling, standardisation and abstraction', it was foreshadowed that the parts-based approach would facilitate the development of synthetic biology as a platform technology whose engineered pathways could be predicted (Endy, 2005).

In 2004, the First International Meeting on Synthetic Biology at MIT was held and has since evolved into the international SB conference series. Since 2004, the global synthetic biology community has also sought the involvement of undergraduate students, particularly through the international genetically engineered machine (iGEM) competition that challenges teams of students from around the world to develop useful tools using synthetic biology and contribute their novel components to the open repositories. iGEM, and other international synthetic biology competitions, have played a significant role in advancing the field of synthetic biology (Appendix B).

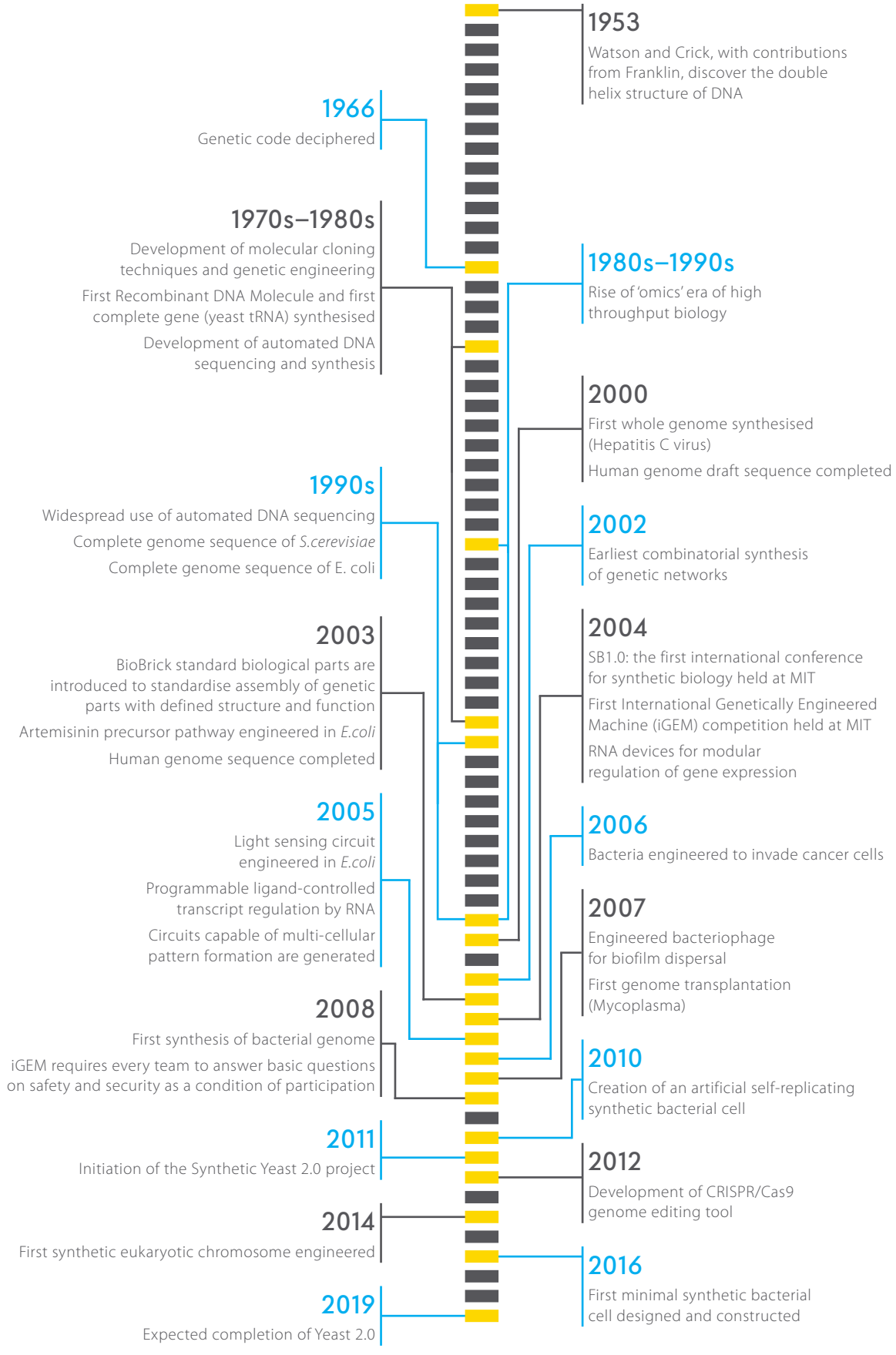


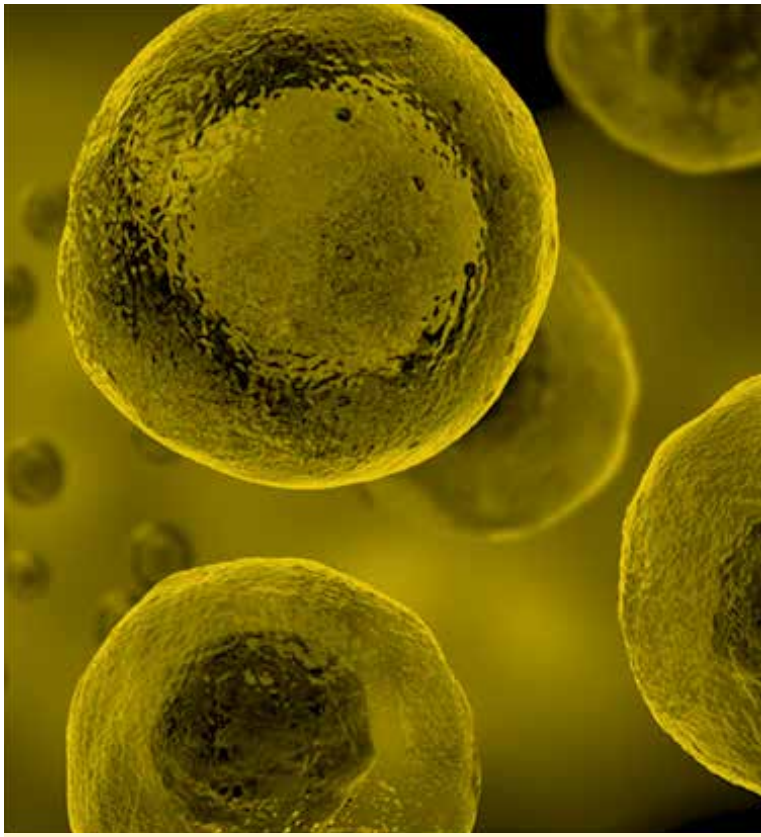
Figure 1: International timeline of events defining the emergence of synthetic biology.

1.3 Core features of synthetic biology

A feature of synthetic biology is that the engineering steps are mediated by genetic manipulation of DNA-encoded parts. Synthetic biology therefore depends heavily on technologies for reading, writing and editing DNA sequences. Improved accessibility, technological advances and the falling costs of both reading DNA (using sequencing technologies) and writing DNA (through chemical synthesis) are some of the driving forces behind the evolution of synthetic biology. Furthermore, synthetic biology capability is greatly supported by new, more sophisticated tools that increase the speed, ease and precision of genetic manipulation, such as CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated) genome editing systems.

1.3.1 An engineering approach

In synthetic biology, engineering principles – in combination with standard experimental scientific principles – are applied to the design and construction of biological parts, devices or systems. Embedded in the engineering approach are the concepts of abstraction and standardisation as well as the use of iterative design-build-test-learn (DBTL) cycles (Figure 2). The design and build phases of this process most obviously embody synthetic biology; systems biology (in particular, omics analysis and modelling) is applied in the test, learn and design phases. Although they are commonly applied together, systems biology is not synthetic biology, and vice-versa: they are different fields (refer to Box 1 for more information).



Box 1: Systems biology and synthetic biology – two distinct fields

Systems biology and synthetic biology are two distinct fields commonly applied together. In the DBTL cycle, cellular behaviour in the test phase is characterised using systems biology at different levels of biological complexity (genomics, transcriptomics, proteomics, metabolomics are all examples of tools employed for measurement). Analysis and modelling of results using computational systems biology approaches contributes to the learn-design phases of the iterative cycle. Systems biology is also frequently used for the analysis of natural biological systems and thus covers a much broader range of applications. In contrast, synthetic biology is used in the build phase.

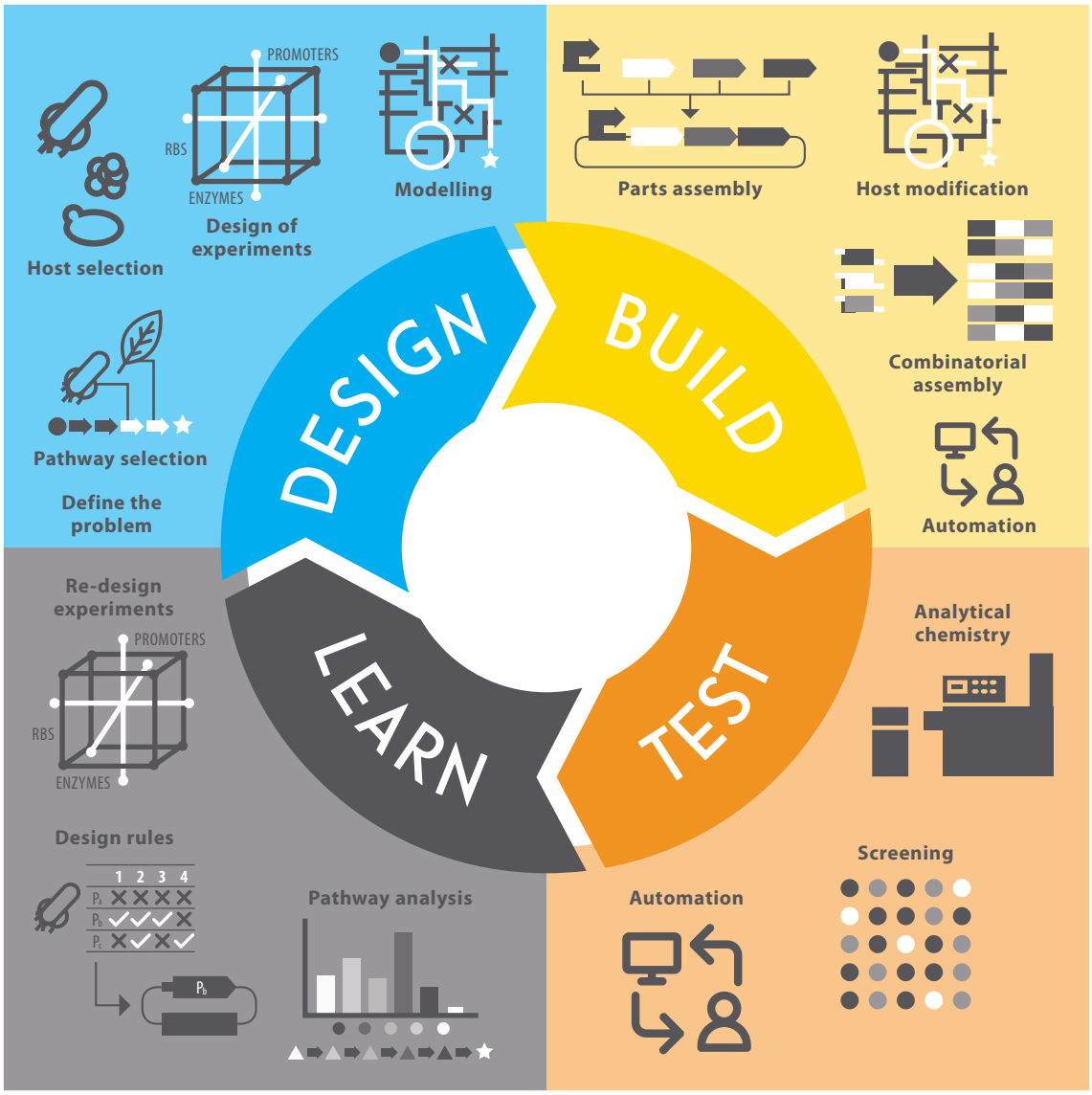


Figure 2: Iterative design-build-test-learn (DBTL) cycle.

The 'design' process defines the problem and develops an initial design; modelling is often used to assist this. The 'build' process is where components are selected, synthesised and assembled to incorporate into the preferred host. The 'test' phase is where the design is validated. The 'learn' component scrutinises the test data, which can inform further iterations of the cycle. Each cycle provides new learnings, which are integrated into the models used to assist the 'design' phase. Adapted from: Petzold et al., 2015.

The synthetic biology philosophy applies the idea that biological systems can be *abstracted*, that is, broken down into simpler parts that can then be encoded and re-assembled, in a standardised way, to form novel genetic devices and more complex arrangements including circuits and systems (Figure 3). This abstraction of genetic sequences to parts, devices and circuits allows representation and manipulation of different levels of complexity without focusing on unnecessary detail. Synthetic biology encompasses multiple levels of complexity: the simplest level comprises parts such as DNA sequences with a defined function (e.g. a gene or a regulatory element). These parts can then be combined into operational devices that contain, for example, genes under the control of regulatory DNA that function together to achieve a defined outcome, such as a biosynthetic pathway. Devices can be further integrated into genetic systems of varying complexity (Figure 3).

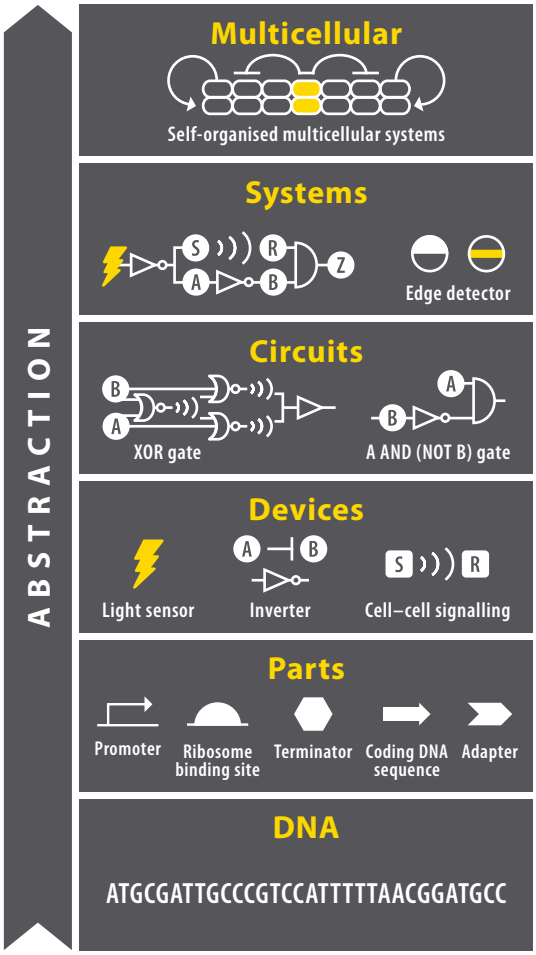


Figure 3: Abstraction in synthetic biology and engineering at different scales.

Functional DNA units are abstracted to parts, which include genes and regulatory elements, which can be combined to produce devices: novel assemblies of defined function. Work on even larger scales can be envisaged by combining devices into genetic circuits, which can be integrated into even more complex systems. For example, when engineering microbes to produce useful chemicals such as polyhydroxybutyrate (PHB; used for biodegradable plastics), it is useful to start the production phase after the microbial growth phase to overcome any growth defects or toxicity caused by production. He et al. (2017) combined a cell-to-cell communication device with a growth arrest device to start PHB production only when cells had both reached high density and stopped dividing. Notation used to depict genes and regulatory DNA elements provides an example of the Synthetic Biology Open Language (SBOL) Visual (Box 2). Adapted from: Federici, Rudge, Pollak, Haseloff, & Gutiérrez, 2013.

An important enabler for the effective engineering of abstracted parts is standardisation: parts, devices, circuits and systems must conform to standards that allow them to be combined in predictable and reliable ways (Box 2).

Through abstraction and standardisation, synthetic biology aims to transform DNA parts into a 'plug and play' toolkit, where components, of all levels of complexity, from parts to systems, can be reused in multiple different contexts for distinct applications. To date, only a small proportion of biological components are sufficiently characterised to support such an approach. Among these, are many well-characterised DNA sequences called promoters, which control when a gene is turned on or off. In many cases, synthetic biologist can choose from a library of promoters, and have reasonable confidence regarding under what conditions and to what level their gene will be expressed. Many genes (DNA sequences that typically encode proteins) are also well-characterised; however, as the primary effectors of function in biological systems, different applications require a great diversity of genes. As a result, many synthetic biology projects must custom pick poorly characterised genes from nature and must determine their behaviour in the new synthetic system. A smaller number of higher order components including devices and circuits have also been characterised. A survey of the literature in 2015 identified 189 genetic logic gates for integrating multiple biological inputs into a single output (Wang et al., 2015).

The DBTL process, although developed initially for other engineering disciplines, is particularly relevant for synthetic biology. Synthetic biologists use iterative cycles of designing genetic modifications, carrying out these modifications, and analysing and learning from these results to improve the design. It is through this iterative approach that functional characterisation of components and system improvement is effectively achieved. Ultimately, once sufficient characterisation is achieved, it will become possible to move more quickly to implementation and deployment (Vickers, 2016).

Box 2: Standardisation of parts

A standard can be applied at different levels in synthetic biology. Several approaches to standardisation of modularisation that facilitate simple or high-throughput assembly of parts have been developed, including diverse toolkits based on a build strategy known as Golden Gate cloning as well as designated standards including BioBricks and BglBricks (Knight, 2003; Anderson et al., 2010). The BioBrick standard is used for the iGEM competition (Appendix B). International standards are an active matter of discussion in the synthetic biology community because such standards will facilitate sharing of parts and may accelerate progress in the field.

An open-source standard for parts annotation and graphical representation called synthetic biology open language (SBOL) has been developed and can be used in combination with various different standards (Galdzicki et al., 2014; Quinn et al., 2015).

Synthetic biology practice varies considerably with respect to use (or otherwise) of standardisation approaches. No consensus has been reached on the adoption of an international standard. Similarly, there is no standard for minimum requirements for characterisation of parts; although recently a data acquisition standard was proposed to facilitate a comparison of parts characterised in different laboratories (Sainz de Murieta, Bultelle and Kitney, 2016).

Open sharing is a strong feature of the synthetic biology community and requires repositories for parts (both standardised and non-standardised). Sharing is supported by open or universal Materials Transfer Agreements. Different repositories adopt different standards for sharing. The Registry of Standard Parts and Addgene are two of the best-known. The Registry compiles parts developed through the iGEM competition and uses the BioBricks standard, whereas Addgene accepts DNA componentry of many different types. There remains a tension between open source sharing, favoured by many sectors of the community, and intellectual property protection, which can encourage investment.

1.3.2 Interdisciplinarity

Synthetic biology is fundamentally an applied field where its outcomes are intended to solve problems and be applied for useful outcomes in a real-world context. As a field, it was recognised very early on that earning a social licence to operate would be critical for the field to make an impact. The lessons learned from history and observation of previous social responses to earlier genetic technologies have driven synthetic biology's relatively proactive approach to involvement of social sciences during technology development and application. Engineering biology for real-world applications requires not only an understanding of the technical specifics and challenges (obtained from a solid foundation in engineering and biological sciences), but also an appreciation of deeper and embedded legal, safety, social and ethical issues, as well as the resulting regulatory and policy implications. These considerations exemplify why synthetic biology will be the field for which effective integration of STEM and HASS disciplines is necessarily required for successful development and implementation (Chapter 4). The essential concepts of interdisciplinarity have been embedded in the growth of the field and are exemplified by the 'Human Practices' element of the iGEM competition (Appendix B).

In addition to the influences of engineering, synthetic biology draws heavily on tools developed by other disciplines. From biology, it applies knowledge of the macromolecules (for example, DNA and proteins) that determine genetic traits. From information science, it uses ideas

Table 1: Society's grand challenges.

Society's grand challenges	Potential solutions and impacts
Health and wellness	• A variety of synthetic biology approaches are being applied in the emerging field of cancer immunotherapy, with novel chimeric molecules being designed to stimulate, or in some cases suppress, specific aspects of immune function. • 'Smart' vaccines based on the delivery of nucleic acids, transcribed from synthetic RNA sequences, which are designed to elicit antigen-specific immune responses when activated by the body's immune system. • Implantable biosensing and response devices which can monitor human health in real time and respond to problems using engineered genetic circuitry.
Food production in a populous world	• Development of new crop varieties with greater genetic diversity that are more highly resistant to pests and diseases, exhibit greater tolerance to extreme weather, can be grown in marginal environments or have enhanced functionality or nutritional quality. • Development of smart plants that sense and respond to environmental conditions or report soil nutrient contents so that farmers can optimise application of fertilisers, decreasing the cost of production.
Energy and mitigation of climate change	• Advanced manufacturing using synthetic biology to produce a range of pharmaceuticals, nutraceuticals (e.g. vitamins), industrial chemicals and chemical building blocks from renewable agricultural substrates using low carbon-emitting processes. • Sustainable production of biofuels and oils from renewable feedstocks such as synthetic-biology-developed crop species, reducing the use of fossil fuels and resulting carbon emissions. • Developing artificial photosynthesis, based on microorganisms developed by synthetic biology and using atmospheric carbon dioxide and hydrogen produced by renewable electricity, to bypass the need for land, water, nitrogen and other nutrients to build high-energy carbon bonds for fuel and chemicals.
Environmental protection and remediation	• The emergence of cell-free synthetic biology will enable enzymatic biosensors to be produced with improved sensitivity and specificity to toxic chemicals and other toxins, extending the range of biosensing and bioremediation applications. • Production of specialised microorganisms capable of sensing and degrading toxic chemicals, pollutants and the bioremediation of contaminated land sites. • Gene drives to limit or eliminate populations of insect species that transmit disease, such as malaria-carrying mosquitoes and other invasive pests such as rodents and feral cats. • Development of smart plants (see above) that reduce over-fertilisation and agricultural chemical run-off, thus minimising environmental damage from farming
Biosecurity	• Gene-editing systems designed to deactivate critical genes in a pathogen or pest species. • Using synthetic biology to rapidly develop therapeutics and vaccines against new zoonotic diseases.

based on networks and logic gates. Synthetic biology applications also commonly rely on knowledge and understanding derived from chemistry, mathematics, modelling, systems biology and other data-intensive technologies. Furthermore, most synthetic biology is conducted at the sub-microscopic or molecular scale and thus has affinities with nanotechnology. Recently, there has been an emphasis on robotics, artificial intelligence and machine learning, which are required for development of high throughput combinatorial parts engineering (Section 3.3).

1.3.3 A focus on applications and problem solving

Although some synthetic biology investigations provide an improved understanding of the natural world, generally synthetic biology has a strong focus on providing workable solutions in a wide range of application areas (such as energy, industrial chemicals, agriculture, environment, and health). Potential applications of synthetic biology in Australia are outlined in Table 1 and discussed in further detail in Chapter 3.

1.4 What is and what isn't synthetic biology

Synthetic biology technologies exist on a continuum of genetic technologies from basic gene manipulations to highly complex, modular, and abstracted engineering (Figure 4). Where this continuum transitions into synthetic biology is a grey area and the definition of synthetic biology is somewhat subjective (see Appendix A). Early definitions revolved around the philosophical construct that cellular components could be treated like electrical circuits, with similar levels of reproducibility, modularisation and abstraction. This provided for a relatively narrow circuit-based definition; the phrase 'synthetic biology' is used much more broadly nowadays, partially in response to more advanced technological developments.

It is easiest to demonstrate where technologies sit on this continuum by using examples. Most people would agree that introduction of a single gene into an organism – for example, taking the human insulin gene and putting it into a bacterium to get the

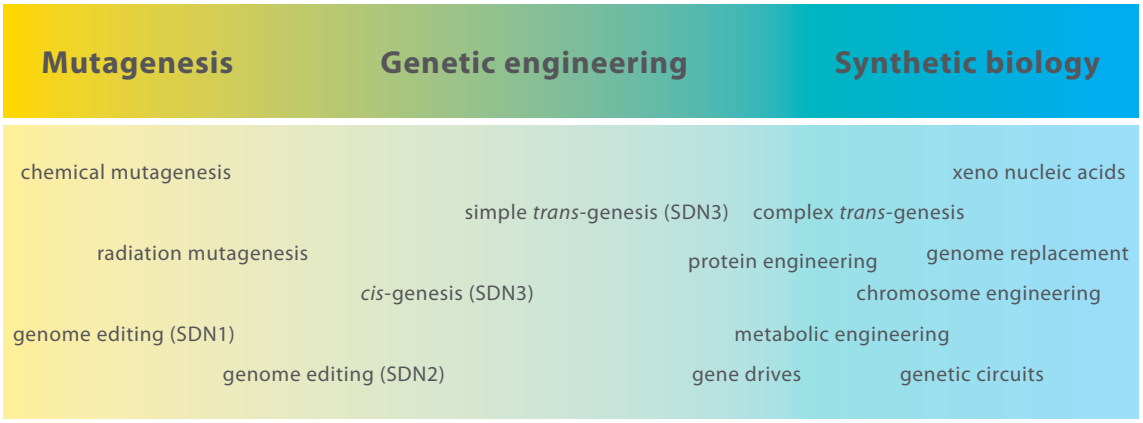


Figure 4: A continuum demonstrating the gradation between genetic engineering and synthetic biology.

**SDN refers to site-directed nuclease techniques: SDN-1 involves the unguided deletion or replacement of one or a few nucleotides; SDN-2 involves deliberate, guided changes to one or a few nucleotides; SDN-3 involves inserting a new gene or other genetic elements (see OGTR, 2016 for more information).*

bacterium to make insulin – is not synthetic biology. And most would agree that artificial synthesis of highly modified chromosomes to make synthetic organisms is definitely synthetic biology. These are two examples on opposite ends of the continuum; in the middle sits individual pathway reconstruction to make complex secondary metabolites, a process that would be considered synthetic biology, if standardisation, abstraction, and design-build-test-learn (DBTL) cycles were used to optimise the pathway. Further examples of what does – and does not – constitute synthetic biology are provided in Appendix A.2.

It is important to differentiate between tools that are commonly used to achieve synthetic biology outcomes and the outcomes themselves. Many of the tools used in synthetic biology are often used for other non-synthetic biology applications. One set of such tools are site-directed nucleases (SDNs) that allow researchers to cut DNA at precisely defined locations. The best known of these tools, CRISPR-Cas, has revolutionised many applications in biotechnology due to its ease of use. A DNA cut allows changes to be introduced at the disrupted site, which can range from small modifications indistinguishable from natural selection at one extreme (not synthetic biology), to entirely re-engineered genomes at the other (synthetic biology).

Finally, some tissue engineering practitioners are starting to refer to their field as synthetic biology. Tissue engineering that does not meet the definition of synthetic biology used here, as it does not include design of novel nucleic acid or protein sequences, has not been considered in this report.

Box 3: The advantages of synthetic biology over genetic engineering

Synthetic biology offers advantages of precision, predictability, sophistication, control and openness over genetic engineering:

Precision: Synthetic biology utilises the latest recombinant DNA technologies to achieve maximal precision in the construction of components and modules and their insertion into the genome.

Predictability: The re-use of standard components and modules offers improved predictability in the function of synthetic biology constructs.

Sophistication: The modularity of synthetic biology components permits more complex and sophisticated constructs to be built.

Control: Genetic circuits used in synthetic biology promise greater control over the activity of introduced genes.

Open standards: Current synthetic biology initiatives are based on open standards for biological components. This is an aspirational goal, as an international standard is not yet in place.

CHAPTER 2
SYNTHETIC BIOLOGY IN AUSTRALIA

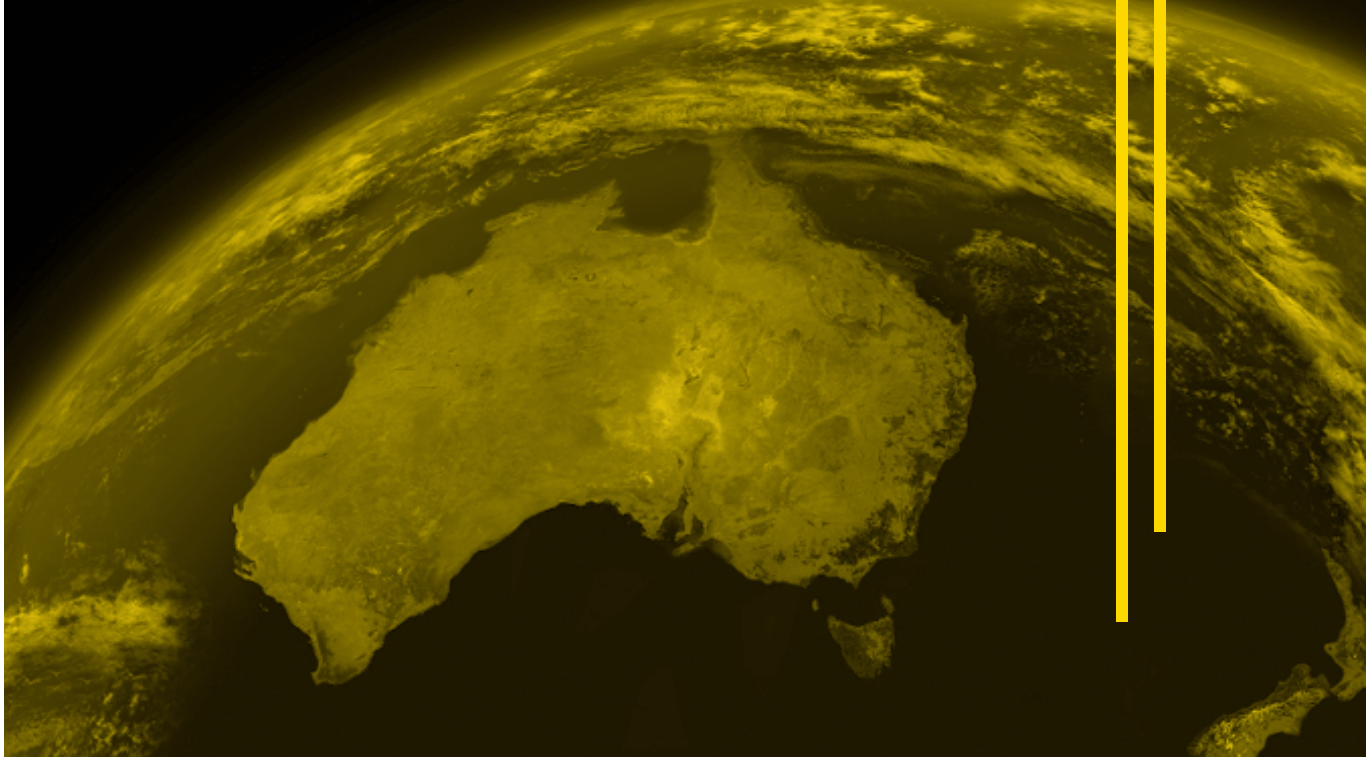
2.1 Introduction

As the field of synthetic biology advances, Australia is well positioned to positively contribute and become globally competitive. The country's research sector has expertise in key contributing fields such as protein engineering, genetic circuit design and development of non-natural cellular componentry, and in applications including biocatalysis, biosensors and metabolic engineering. This chapter assesses the state of synthetic biology in Australia with respect to research strengths, skills and training, involvement of industry, and infrastructure. Opportunities are highlighted, and gaps in Australia's existing capabilities are identified.

2.2 Australia's position in the global synthetic biology community

Historically, engagement in the iGEM competition (Appendix B) has reflected national engagement with synthetic biology as a field. In 2007, the first Australian team, from the University of Melbourne, participated in the iGEM competition – one of 88 teams (up from five in the inaugural 2004 competition) (iGEM, 2017). During this time, the global synthetic biology field was gaining momentum. In 2008, international activities included the Fourth International Meeting on Synthetic Biology (SB4.0) taking place in Hong Kong, the UK Biotechnology and Biological Sciences Research Council (BBSRC) and the UK Engineering and Physical Sciences Research Council (EPSRC) identifying synthetic biology as a research priority, and creation of the first entirely synthetic genome (Clarke et al., 2012; Clarke and Kitney, 2016; BioBricks Foundation, 2017b).

Several years elapsed before the Australian synthetic biology community self-organised, with the establishment of Synthetic Biology Australasia (SBA) in 2014 (Box 4). In 2016 the first SBA conference was held in Canberra in collaboration with CSIRO, with 120 people in



attendance. In recognition of the rapidly developing field, CSIRO established the Synthetic Biology Future Science Platform in the same year (Box 4). The second SBA conference was hosted by Macquarie University in Sydney in 2017. Approximately 180 attendees participated, highlighting the increasing involvement of Australia's synthetic biology community. These conferences include both social sciences (social, ethical, legal, regulatory, policy) and laboratory science and will convene biennially going forwards, with the next to be hosted by the University of Queensland in Brisbane in 2019. Through execution of Memoranda of Understanding with international organisations, SBA is also active in networking the Australian and international communities, most recently with the Asian Federation of Biotechnology at the SB7.0 conference in Singapore in 2017.

Box 4: Australian synthetic biology initiatives

Synthetic Biology Australasia
synbioaustralasia.org

Synthetic Biology Australasia (SBA) is non-profit society established in 2014 to support the developing synthetic biology research field in Australia, New Zealand and the broader Australasian region. SBA acts as a community hub to advance the development of collaborations within academia and between academia and industry. The society also engages in public outreach, education and training in synthetic biology. Membership is open to all interested stakeholders.

CSIRO Synthetic Biology Future Science Platform
research.csiro.au/synthetic-biology-fsp

CSIRO's Synthetic Biology Future Science Platform is a multi-year, multi-disciplinary A$13 million investment to catalyse innovation and develop capability to advance Australia's synthetic biology capacity and competitiveness in a responsible way. The synthetic biology future science platform has three aims: build foundational capabilities to advance synthetic biology; drive national coordination by making these foundational capabilities widely available to the broad research community, governments, and industry; and, build strong partnerships, collaborations and connections across the innovation sector to develop novel products and applications responsibly.

Several other synthetic biology workshops focusing on various areas of capability, laboratory science and social science have been held in Australia since 2012 (Figure 5). These have been hosted by a variety of organisations, demonstrating a broader engagement with synthetic biology through the research and innovation sector. Most recently, in 2017, the Australian Academy of Science together with the Australian Academy of Technology and Engineering and the Chinese Academy of Sciences, hosted the Australia-China Symposium on Synthetic Biology. The upwards trajectory of synthetic biology in Australia is demonstrated by the increase in activities over the last five years (Figure 5).

While involvement and self-association of Australia's scientific community with the synthetic biology field has been slow (compared to countries such as the US and the UK), a much broader cross-section of Australian molecular biologists and biotechnologists have been using synthetic biology techniques since the field arose. Indeed, Australia's publication count in synthetic biology-associated areas has increased at a similar rate to global numbers, whereas an increase in numbers

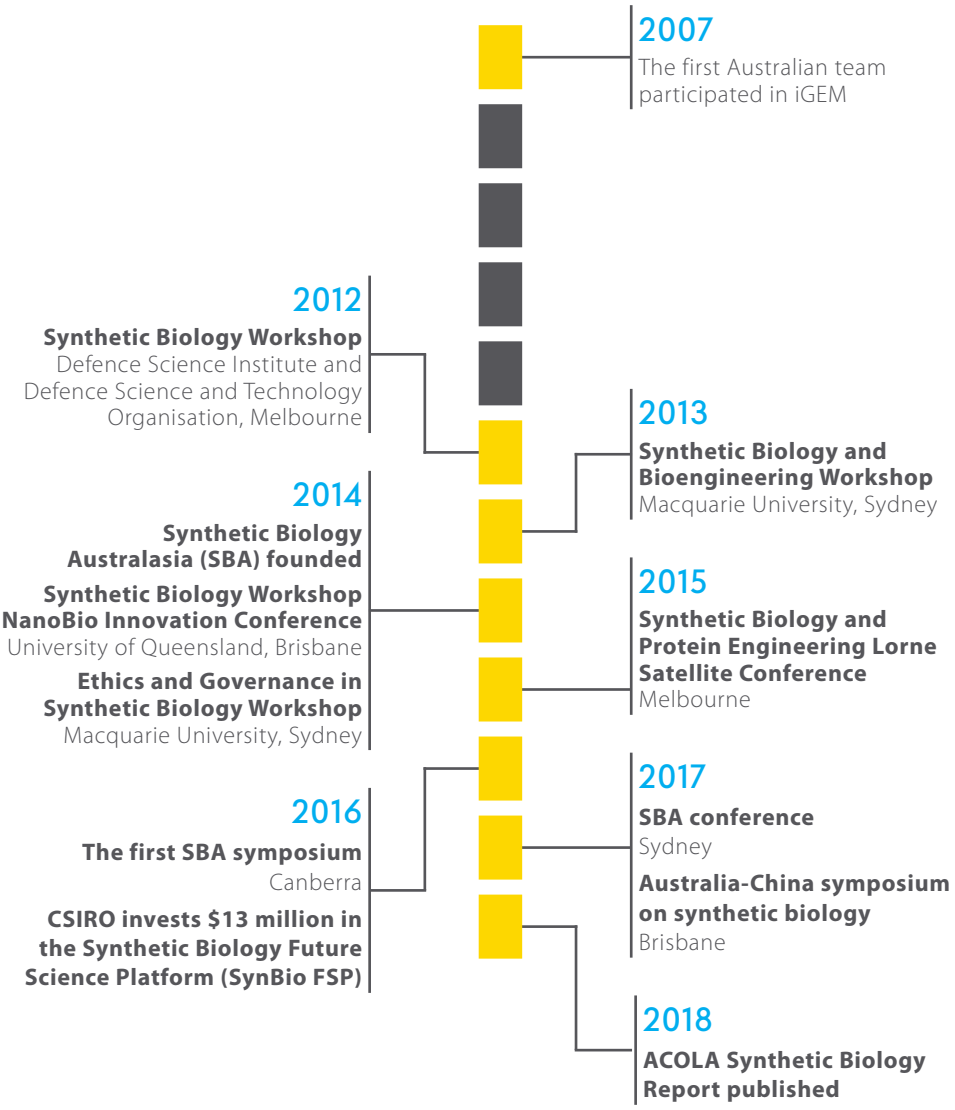


Figure 5: A timeline of the development of synthetic biology in Australia.

of publications using the keyword 'synthetic biology' occurred later in Australia than globally (Figure 6; a list of publication search terms is available at www.acola.org.au/wp/sbio). These considerations indicate that, while Australian's scientific community has used synthetic biology techniques since the earliest days of development, they have not necessarily used the term synthetic biology to apply to their own work.

Australia has a strong research sector ranking tenth in the world for number of publications since 2000 (ISI Web of Science, Appendix C). In line with our strong research capacity, Australia's contribution within the field of synthetic biology is also high, ranking 14th in the world for publications in synthetic biology-associated areas, and 15th for self-identified synthetic biology publications (Appendix C). However, in percentage terms, Australia's research output focussing on synthetic biology-associated areas is the lowest among the top ten countries for total research publications (Appendix C). This suggests that increasing capacity to conduct research in synthetic biology may be of value. As detailed in Box 4, CSIRO invested A$13 million to establish the Synthetic Biology Future Science Platform, which is mandated to help increase capability in synthetic biology across Australia's innovation system through building a collaborative community of practice (CSIRO, 2017). In comparison, as of 2016, the US and the UK have made large strategic investments into synthetic biology research, estimated at over US$500 million (A$637 million) and £300 million (A$529 million) respectively (Si and Zhao, 2016; Synthetic Biology Leadership Council, 2016)

Within Australia, the specialised synthetic biology areas of tool construction, circuit design and development of orthologous componentry, as well as the contributing disciplines of protein engineering, biological modelling, are particularly strong. In addition, applications in biocatalysis, biosensor, and plant and microbial metabolic engineering are well developed (see Sections 3.4.3 and 3.6.2 for examples). Many Australian universities also have capabilities and expertise relevant to synthetic biology, as evidenced by publication details (Figure 7).

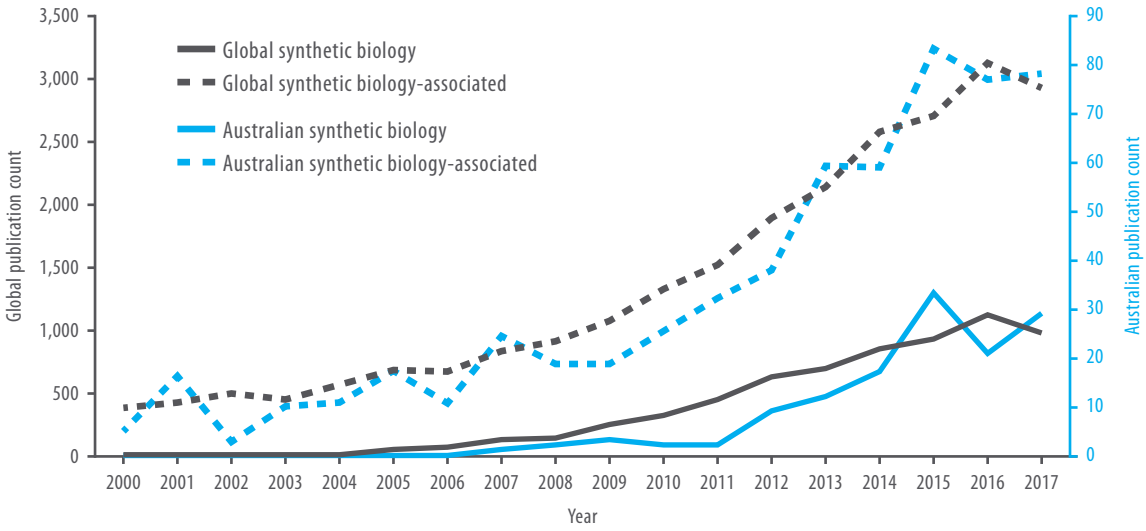


Figure 6: Timescale of synthetic biology publications (2000-2017).

Publications from Australia (light blue) and the world (dark blue) in synthetic biology-associated areas (dotted lines) or self-identified containing the keywords 'synthetic biology' (solid lines) demonstrate an increase post 2005. Data taken from 1 January 2000 to 31 December 2017. Appendix C outlines synthetic biology publications by country.

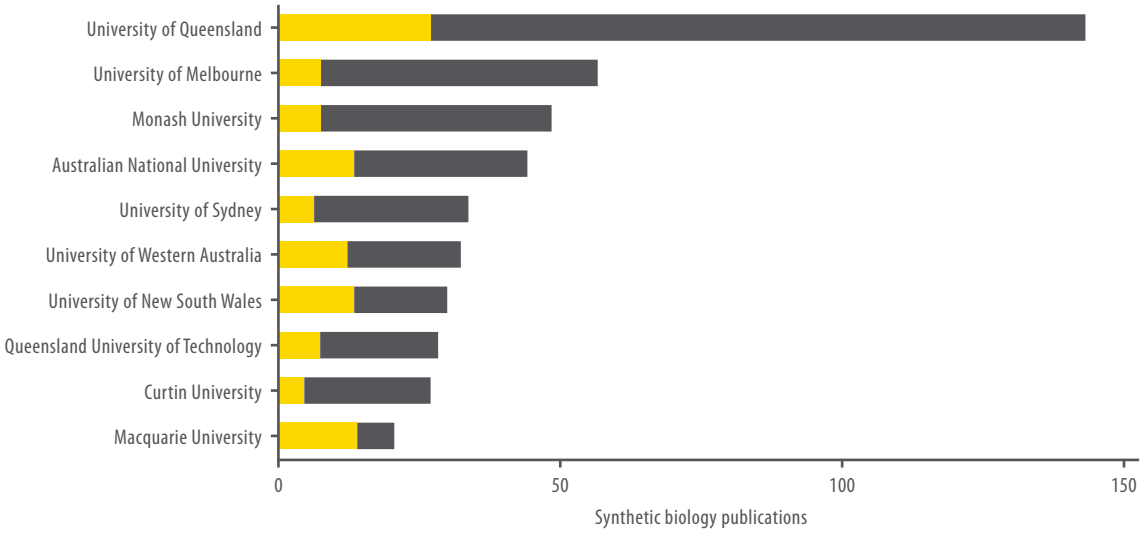


Figure 7: Australian synthetic biology publications by institution.

Australian publications in synthetic biology-associated areas were analysed by institution and the number of publications by the top ten institutions is shown. Yellow sections represent self-identified synthetic biology publications containing topic keyword 'synthetic biology'. Individual publications can be associated with multiple organisations. Data is from ISI Web of Science 12 November 2017.

With recent investments and increasing involvement in synthetic biology spread across multiple universities, the synthetic biology field in Australia is poised to expand, supporting Australia's economy by offering potential for advances in industry, agriculture, the environment and health.

2.3 Requirements to strengthen the synthetic biology sector in Australia

Appropriate skills, infrastructure, research translation and industry engagement will be required to maximise the social, economic, environmental and health benefits that synthetic biology can generate. To assess present and potential future gaps in Australia's capabilities, input was requested from stakeholders and researchers via a survey distributed to Australian universities and research organisations (Appendix D). Results from the survey complement international research on the requirements for a strong synthetic biology sector in Australia (as discussed in the following sections).

2.3.1 Skills and education

2.3.1.1 Key skill areas

Development of synthetic biology research and industry will be underpinned by strong education programs in high school, and at undergraduate and postgraduate levels in university, in the disciplines of maths, science, IT and engineering. From a global perspective, Australia's education system ranks highly. In the 2015 Programme for International Students Assessment, which assessed knowledge and skills of 15-year-old students in 35 OECD countries and 37 partner countries, Australia scored above the OECD average, and ranked higher than

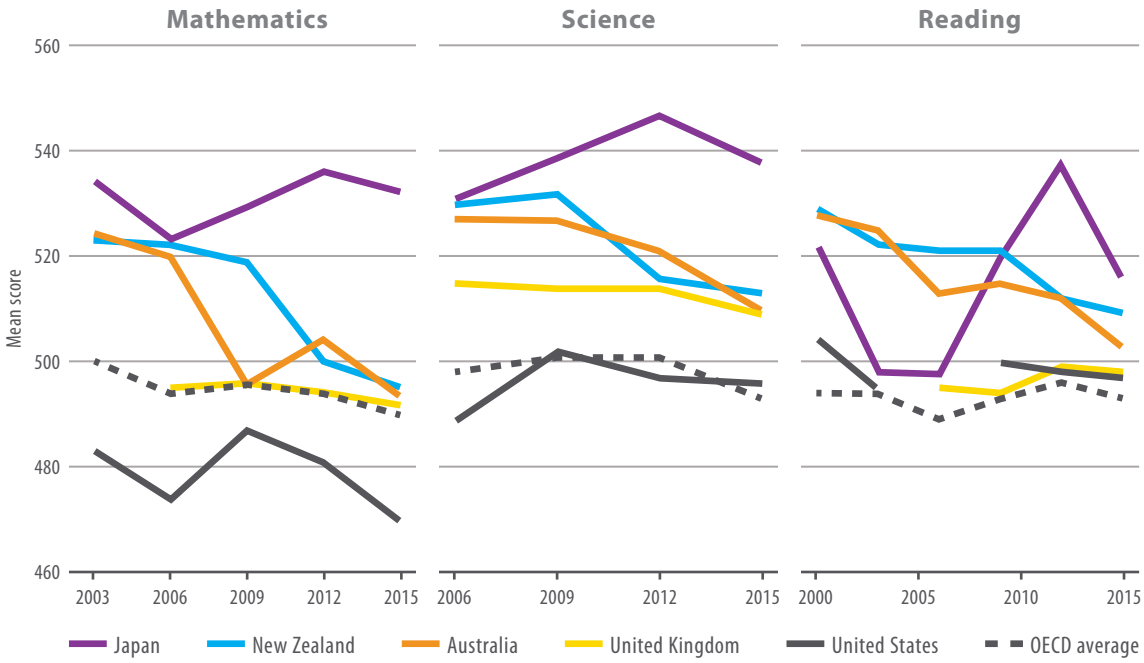


Figure 8: Australia's performance in mathematics, science and reading.

Source: OECD.

the UK and the US, in all three tested areas – science, reading and mathematics (OECD, 2016). Furthermore, Australian students have a strong belief in the importance of science education. In addition to ranking above average in students' scientific ability, Australia was one of only seven countries that scored above the OECD average in beliefs about the value of scientific enquiry and expectation of working in a science-related occupation. However, this positive snapshot must be framed within the context of declining performance (Figure 8). Australia's performance in mathematics and science has dropped 30 and 17 points respectively since first assessed in 2003 and 2006 (OECD, 2003, 2006, 2016). However, OECD average scores have also dropped by ten and seven points, respectively. Thus, while Australia may have a highly educated pool from which to draw synthetic biologists, falling performance in science and mathematics education at school level risks impairing Australia's future capacity for scientific research and innovation in diverse fields, including synthetic biology.

Australia has strong undergraduate courses in fields relevant to synthetic biology. The Times Higher Education World University Rankings 2018, which assesses research-intensive universities against criteria for teaching, research, knowledge transfer and international outlook, lists four Australian Universities in the top 100 for computer science, five for engineering and technology, seven for life sciences and five for physical sciences (Times Higher Education, 2017). This places Australia behind only the US, the UK and Germany in these fields, and Australia compares favourably on the basis of population size (Figure 9).

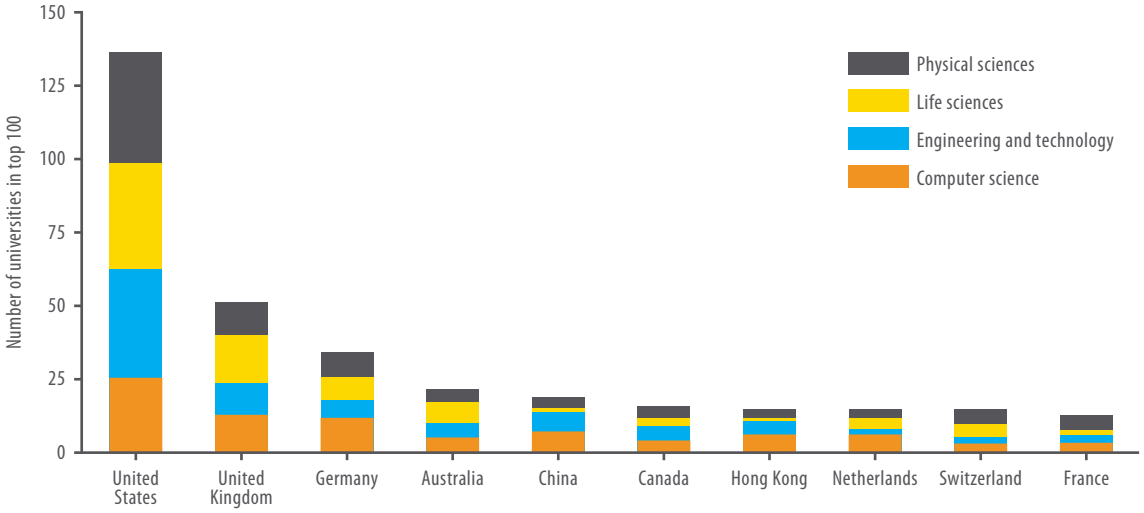


Figure 9: Top-ranking universities in fields important for synthetic biology by country.

Number of universities in the top one hundred according to Times Higher Education Rankings 2018 in fields relevant to synthetic biology. Australia's university system is strong in physical sciences, life sciences, engineering and technology, and computer sciences. The number of Australian universities in the top 100 in these fields compares favourably on the basis of population size with other science and research-intensive countries such as the US, the UK and Germany.

In addition to a strong STEM foundation, survey respondents identified specialist training requirements to support a synthetic biology industry including, molecular biology, biochemistry, computational modelling and simulation, systems biology, bioinformatics and analytical chemistry. Among these specialisations, computational skills were reported as a gap both within Australia, and internationally (Appendix D). This includes modelling and simulation, as well as programming and bioinformatics expertise to process and analyse large datasets. Expertise will also be needed in engineering, robotics, software engineering, artificial intelligence and machine learning to support the global move towards high throughput combinatorial synthetic organism construction (Section 2.3.3). The shortage in computational and programming skills is not unique to synthetic biology. There is an increasing need for computational experts in many fields, and education in these specialised skillsets will need to be promoted and supported at all levels (Merali, 2010; Levine, 2014; BBSRC and MRC, 2015).

2.3.1.2 Interdisciplinary education

Synthetic biology is a highly interdisciplinary field, drawing on diverse STEM disciplines that include engineering, biology, biochemistry and computer science, as well as HASS fields such as science communication, social science, law and ethics (Calvert and Martin, 2009; Linshiz et al., 2012). Globally, the last 40 years has seen an increase in multi-disciplinary training programs (Jacob, 2015). Interdisciplinary training provides a method to equip future synthetic biologists with both breadth of knowledge, and the skills needed to effectively communicate across disciplines and work as part of multi-disciplinary teams.

Survey respondents reported a need for cross-faculty interdisciplinary university training to appropriately equip students with the skills required to contribute effectively to the field and to potentially enhance Australia's capacity for synthetic biology in the longer term. In response to the ACOLA survey, researchers in the field noted a shortage of students with the breadth of skills and knowledge required to undertake synthetic biology

projects, an observation indicating that education programs (primarily undergraduate courses) do not provide adequate coverage of the disciplines required for synthetic biology. In this respect, the segregation of engineering from biological sciences may pose a barrier to cross-discipline education, even for students who wish to pursue both fields. Specially designed joint-degree programs, and the promotion and facilitation of cross-faculty education, were suggested as ways to provide pathways for improving interdisciplinary synthetic biology training at the undergraduate level (Appendix D). This would allow students to access the theoretical and practical engineering philosophies from engineering faculties as well as the technical expertise and fundamental science found in science faculties; in addition, access to HASS specialties is required to provide a well-balanced training program in synthetic biology.

In addition to integrated training in relevant fields, synthetic biology education programs should establish the skills required to communicate ideas across disciplines, engage in interdisciplinary collaborations and embrace an interdisciplinary approach. Such interdisciplinary education is critical not only for synthetic biology research, but also for many other applied sciences due to the convergence of disciplines across the physical and biological sciences.

The inclusion of ethical, legal and social aspects (ELSA) into tertiary curricula should not only ensure that this field develops in a socially responsible manner but will also provide opportunities to inform and train graduate students in other synthetic biology career choices such as public policy, law and ethics, as well as contributing more broadly to community outreach and engagement activities. In alignment with the global synthetic biology community, widespread engagement with the public should be a core activity in which the rationale for, and the potential benefits and risks of, synthetic biology research must be clearly communicated to respond to community concerns about the technologies being used and the applications being proposed.

2.3.1.3 Synthetic biology-specific training

Internationally, several universities offer tailored PhD and master's degrees, undergraduate majors or specific courses in synthetic biology. For example, at the undergraduate level in the UK, Imperial College London runs a course in synthetic biology. In the US, the University of California Davis, the University of California Berkley, and Massachusetts Institute of Technology offer synthetic biology specialisations within their undergraduate biological or biomedical engineering programs. There are also many international universities that offer synthetic biology master's degrees including Imperial College London, University College London, the University of Edinburgh, Newcastle University, University College Cork, and the University of Copenhagen. The Centre for Research Interdisciplinarity in Paris offers an Interdisciplinary Approaches in Life Sciences (AIV) Masters program with a stream in systems and synthetic biology. At the doctoral level, the universities of Oxford, Bristol and Warwick have a collaborative Synthetic Biology Centre for Doctoral Training (SynBioCDT) funded through the EPSRC and BBSRC, which offers a four-year synthetic biology PhD programme. Short synthetic biology training courses are also offered by a variety of different institutions, including Imperial College London and Essex University in the UK, the Chinese Academy of Sciences, the European Molecular Biology Organisation, and Synbiobeta and Cold Spring Harbour Laboratory in the US. Numerous online courses from reputable sources are also

available (including iBiology and synberc). These examples could provide suitable frameworks for Australian institutions to follow should they wish to pursue specific degrees and programs.

In Australia, there is limited synthetic biology training being offered at both undergraduate and graduate level, however universities are looking to expand in this area. Of the 39 Australian universities contacted as part of this study with a request to provide information on teaching in the area of synthetic biology, 22 universities responded of which 13 (59 percent) reported teaching some aspects of synthetic biology in existing subjects at undergraduate or masters level.[1] Of these, only Macquarie University has subjects dedicated specifically to synthetic biology. Several universities (32 percent) plan to increase teaching of synthetic biology. However, no Australian university provides dedicated degrees or discrete programs in synthetic biology. The development of dedicated degree courses may benefit Australia by improving synthetic biology research and commercialisation potential, attracting talented scientists from abroad and by keeping Australian institutions at world standard, whilst maintaining education as a key export for Australia.

In addition to targeted degree programs, undergraduate training also occurs through the synthetic biology competitions iGEM, Biomolecular Design (BIOMOD), and the BioMaker Challenge (see Appendix B for further details). The iGEM competition challenges teams to use genetic engineering to solve real-world problems. The competition emphasises laboratory research, public outreach, safety and security, and the social and environmental impact of the teams' research. Several Australian universities have participated in iGEM since 2008.[2] BIOMOD is a biomolecular design competition in which the University of New South Wales has participated since 2014, with more recent participation by the University of Sydney (BIOMOD, 2017). Despite the participation of few teams, Australia has had good success in both iGEM and BIOMOD competitions.

2.3.2 Industry translation

2.3.2.1 Translation and commercialisation

The primary value of synthetic biology is as an applied science, with the aim of tackling real-world problems, and the potential to generate benefits to industry, energy and agriculture production, the environment, human health and the economy. However, realising this potential requires the translation of research outcomes to commercially viable products and services.

The Australian Government recognises, and is working to address, systemic hurdles that limit the successful commercialisation of research innovation. These hurdles include lower entrepreneurship than other leading research-intensive countries (StartupAUS, 2016), early-stage venture capital investments well below the OECD median (Australian Government, 2015b; Office of the Chief Economist, 2016), and limited collaboration between business and academia (Innovation and Science Australia, 2016). Processes to improve the environment within which

1 James Cook University, La Trobe University, Macquarie University, RMIT University, Swinburne University of Technology, the University of Adelaide, the University of Newcastle, the University of Queensland, the University of Sydney, the University of Western Australia, University of Tasmania, University of Technology Sydney, University of Sunshine Coast

2 Macquarie University, the University of Sydney, the University of Melbourne, the University of New South Wales, the University of Queensland, Monash University, RMIT University and Australian National University

Australian innovation can flourish are being implemented through the *National Innovation and Science Agenda (NISA)* that was launched in 2015 (Australian Government, 2015b). Mechanisms for this improvement include tax incentives for investment in innovation, funding for commercialisation of new discoveries, modifying university funding arrangements to prioritise industry engagement, and initiatives to attract and retain international talent. NISA is supported by an independent advisory body, Innovation and Science Australia, which has set out specific recommendations for enhancing innovation in its report to the Australian Government, *Australia 2030: Prosperity through Innovation* (Innovation and Science Australia, 2017). These initiatives will be imperative to creating impact through diverse technologies, including those of synthetic biology.

Translation and commercialisation of Australian synthetic biology products is also dependent on the development of a relevant industry within Australia. Indeed, Australia's relative paucity of establish biotechnology companies limits opportunities for the acquisition of locally developed biotechnology intellectual property (IP). Looking overseas, US-based companies have started to make substantial co-investments in synthetic biology on the basis that continued advances in the field will have the potential to revolutionise the development of new products through biologically-based manufacturing (Shipp et al., 2012). Further, an industry analysis by Agilent Technologies in the US, forecast that market growth for biologically-based manufacturing will exceed the growth of products in other market categories (National Academy of Engineering and National Research Council, 2013).

Australia offers advantages including biomass production in extensive cropping industries, trusted intellectual property (IP) protection policies, a strong research environment and proximity to the Asian market. Leveraging these advantages will be required for an economically vibrant synthetic biology sector. The US biotechnology company Amyris, in partnership with the Government of Queensland, has announced plans to construct a Queensland biorefinery to use their synthetic biology-engineered yeast to convert sugar cane into the fragrance and fuel ingredient farnesene. Such moves of biotechnology companies into Australia are promising; however, further development of the Australian synthetic biology industry will be required both to support research translation, and to ensure that Australia is an active participant and benefits economically from our synthetic biology innovations.

2.3.3 Infrastructure

Synthetic biology research relies on diverse techniques and access to a range of services and equipment. Development and maintenance of this infrastructure will be important for the continued development of synthetic biology in Australia. The infrastructure requirements discussed in this section are in the context of the DBTL cycle. For many applications of synthetic biology, much of this cycle can be integrated into an automated DNA assembly and testing facility, known as a synthetic biology foundry (other names include genome foundry and biofoundry). Indeed, establishment of a synthetic biology foundry would support an internationally competitive Australian research environment. However, the mechanism used to establish a synthetic biology foundry will need careful consideration. Synthetic biology foundries are discussed in greater detail in Section 2.3.3.8.

2.3.3.1 Design and Re-Design: modelling and computing infrastructure

Many approaches are used by synthetic biologists to design their engineering solutions. Designs may be developed by hand or using specialised software packages, with many inputs going into this design phase. One key input is the use of biological model systems, which are needed due to the complexity of biological systems. For any given problem, there is typically numerous possible solutions – only a few of which will contribute to the final design choice. However, as identifying feasible solutions can be difficult, modelling approaches can help refine options to a more manageable number for testing. Models can be used to examine biology at all different levels, from single molecule interactions, to individual proteins, and whole cell metabolism (metabolic modelling). In addition, modelling typically requires handling and analysis of large data sets from biological systems analysis (bioinformatics) before useful solutions are identified. Models and systems biology (Box 1) greatly facilitate both the design and redesign phases of the iterative DBTL process.

There are many bespoke software packages designed to support all levels of the design process. However, there is a need for high-performance computing facilities to support critical areas of research including simulation, modelling and bioinformatics analysis (Appendix D). Australia has high performance computing facilities; however, they require ongoing maintenance and upgrades to remain current and continue to support world-class research. Australia's two high-performance computing facilities are ranked at 70 (National Computational Infrastructure) and 111 (Pawsey Supercomputing Centre) in the world in 2017 (Top500, 2017). Digital Data and eResearch Platforms is a focus area in the 2016 National Research Infrastructure Roadmap (Australian Government, 2017a), released in May 2017, which recommended urgent upgrading of the National High-Performance Computing facilities, with further upgrades at regular intervals. Following on from this, in December 2017, A$70 million in funding was announced by the Australian Government for the National Computational Infrastructure in 2018 and 2019.

2.3.3.2 Build: making biological parts

As synthetic biology parts are typically DNA-encoded, access to affordable synthetic DNA is a fundamental requirement for synthetic biology research. Efficient and cost-effective suppliers, primarily in Asia, export readily to Australia and it is unlikely that synthesis in Australia could be cost-competitive. Synthetic DNA remains prohibitively expensive for most laboratories to conduct large-scale applications (e.g. whole genome synthesis), however it is anticipated that DNA synthesis costs will continue to decline over the coming years, making some projects more affordable to a broader range of laboratories.

Although DNA synthesis is outsourced very effectively in Australia and local production is likely to be far more expensive, a local synthesis facility may offer several advantages that should be considered. Locally produced synthetic DNA would provide higher capability to protect sequence information, mitigate against commercial espionage and dual use concerns (Section 4.6), and may provide fast access to materials to support an Australian synthetic biology industry. Furthermore, if Australia ratifies the Nagoya Protocol (Box 5), maintaining a local connection between the generation and storage of sequence information and the synthesis of that DNA sequence may improve our capacity to control access to Australia's rich genetic resources, as well as ensure they are used with the informed consent of indigenous and local communities with appropriate benefit-sharing agreements.

Box 5: Nagoya Protocol

The Nagoya Protocol on *Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity* is a global agreement dedicated to the implementation of the third goal of the Convention, "fair and equitable sharing of benefits arising from the utilization of genetic resources", by providing a basis for greater legal certainty and transparency for both providers and users of such resources. Australia is a member of the Convention of Biological Diversity and signed the Nagoya Protocol in 2012 but has not yet ratified it.

2.3.3.3 Build: storing and sharing biological parts

The ability to store and share biological parts – particularly standard biological parts – can reduce costs and save time, thus making secure storage a key enabler of synthetic biology research. Several biological repositories serve this purpose, including Addgene (an international non-profit plasmid repository) and the iGEM Registry of Standard Biological Parts (an international synthetic biology-focussed repository that uses the BioBrick standard). As discussed in Section 1.3.1, standardisation increases the efficiency with which standardised parts can be shared and reused for diverse applications. Many aspects of synthetic biology benefit from standardisation including nomenclature and the annotation of features for ease of communication, standardised assembly strategies that accelerate the build process, and methods to characterise biological parts enabling comparison between parts developed in different laboratories (Box 2).

There are many different synthetic biology standards in use and no globally accepted standards have emerged. Currently, international repositories of biological parts effectively support Australian research. The value of an Australian-based repository would be realised chiefly in the context of a centralised facility offering automated assembly of the stored DNA components in diverse constructs, enhancing part-sharing capability and conferring a concomitant cost reduction. Moreover, protection of Australian genetic resources would come from maintaining Australian DNA componentry on-shore when needed. There has been discussion within the Australian synthetic biology community of both standardisation approaches and parts repositories, including open sharing and IP protection aspects. Such a repository would ideally be co-located with a synthetic biology foundry and would require a sustainable model for establishment.

2.3.3.4 Build: assembly of modules, systems and engineered organisms

Most synthetic biology projects are undertaken using custom-designed DNA assembly strategies and low-throughput integration of DNA into target organisms. Synthetic biology capacity is increased significantly by automated and standardised DNA assembly platforms combined with automated transformation of target organisms, allowing higher-throughput assembly of engineered components and systems. These assembly and transformation systems have become essential for the conduct of internationally competitive research in this field. Economies of scale may arise if the specialised infrastructure being used for DNA storage and assembly, organism modification and high-throughput testing are housed within a centralised facility. These facilities are known as synthetic biology foundries (also known as genome foundries or biofoundries) and are discussed in greater detail in Section 2.3.3.8. Whilst Australia does not have a synthetic biology foundry, access

to a local foundry is considered by some respondents to the ACOLA survey to be a key enabler for synthetic biology to progress in Australia (Appendix D).

2.3.3.5 Test: high throughput screening platforms

The assessment of engineered parts or organisms requires different analytical infrastructure dependent on approach and application. For example, protein engineering may require structure determination and functional testing; synthetic biology in plants typically requires the screening of large numbers of specimens; metabolic engineering routinely involves the analysis of large numbers of small molecules, proteins and genes expressed in the engineered organisms (known as omics, Section 2.3.3.6). Regardless of applications, the throughput of the test phase directly influences the timescale of the DBTL cycle. High throughput screening allows large numbers of engineered organisms or parts to be evaluated in a short timeframe. Technologies for increasing throughput are advancing steadily, and Australia is poised to take advantage of these technological advances.

The 2016 National Research Infrastructure Roadmap, which assessed infrastructure requirements for supporting Australia's research base, lists expansion of synchrotron beamline capabilities as a priority area, highlighting the potential benefits of new beamlines that support high-throughput protein structure analysis (Australian Government, 2017a). In plant engineering, the National Collaborative Research Infrastructure Strategy (NCRIS) funded Australian Plant Phenomics Facility provides sophisticated capability for high-throughput phenotyping (Australian Government, 2017a). High throughput growth of microbial cultures for metabolic engineering applications of synthetic biology can be limiting, as it requires multiple parallel bioreactors.

2.3.3.6 Test: omics analysis

Testing the products of synthetic biology often requires analysis of the organism's genome (set of genes), transcriptome (which genes are turned on), proteome (proteins produced) and metabolome (small molecules generated) (Figure 10A). These analyses, denoted omics, rely heavily on bioinformatics expertise. Omics analyses provides a snapshot of cellular behaviour, which can be used to rationally improve engineering. Omics analytical facilities are a crucial requirement of synthetic biology research within which the initial test phase for many applications are conducted (Appendix D). Bioplatforms Australia (BPA), with investment funding through NCRIS, coordinates a nationwide network of omics facilities that are accessible through research collaborations or fee-for-service agreements (Figure 10B). These centralised facilities have enabled affordable access by researchers to a range of specialised analytical equipment, datasets and training. The importance of improving accessibility to omics analytical facilities was highlighted by survey respondents.

Bioplatforms Australia nodes comprise genomics facilities at the Australian Genome Research Facility (Brisbane, Sydney, Melbourne, Adelaide and Perth), Biomolecular Resource Facility, ANU (Canberra), Ramaciotti Centre, UNSW (Sydney) and Garvan Institute of Medical Research (Sydney). Proteomics facilities are at the University of South Australia Proteomics Centre (Adelaide), Australian Proteome Analysis Facility (Sydney), Monash Antibody Technology and Biomedical Proteomics Facilities (Melbourne), and Proteomics International (Perth). Metabolomics facilities are at the Australian Institute for Bioengineering and

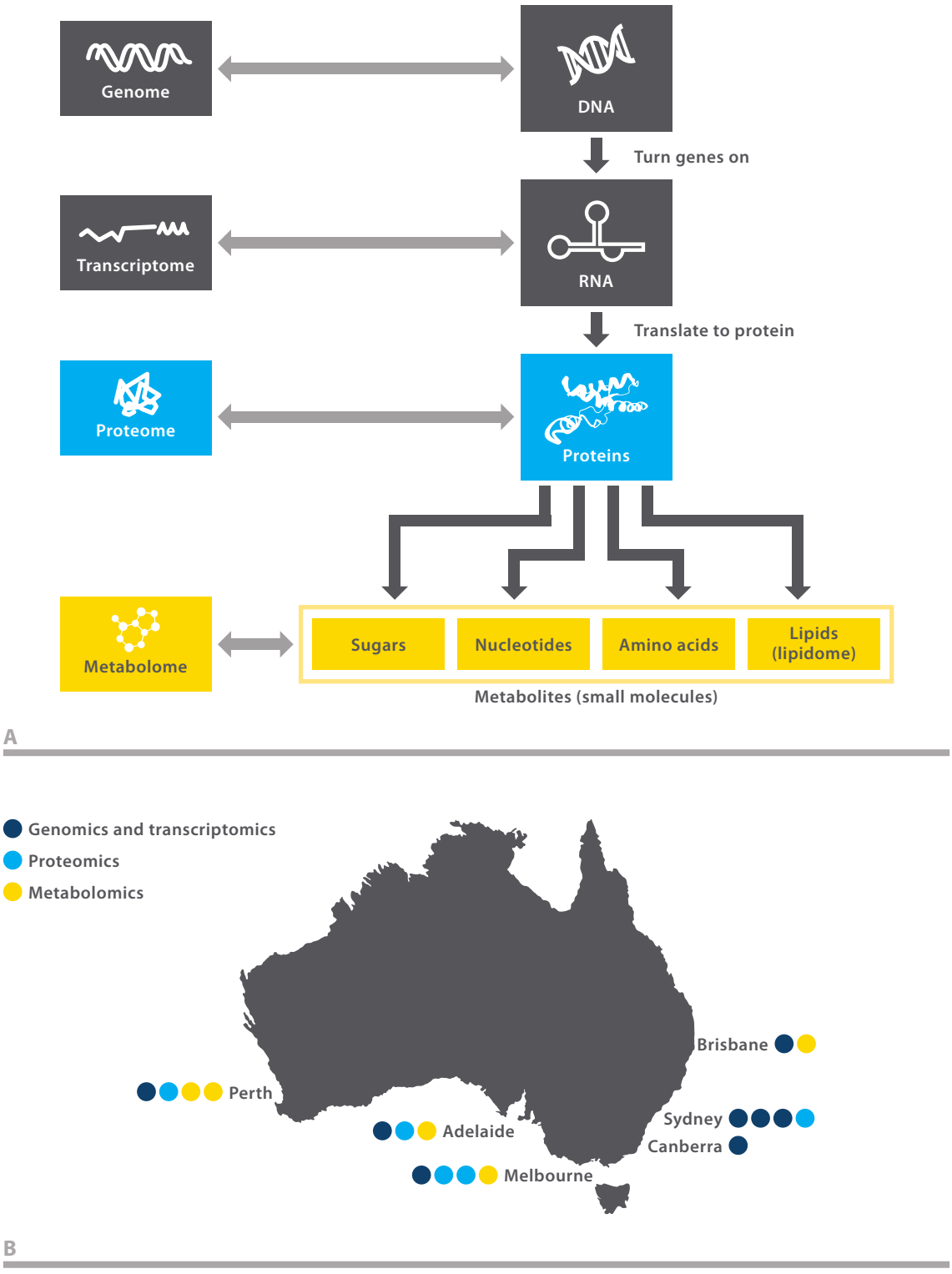


Figure 10: Omics overview. (A) Relationship between the different omics categories.

Omics technologies harness different molecular entities to gain insight into cellular behaviour. An understanding of which genes are turned on (transcriptomics), which proteins are present (proteomics) and the concentrations of different metabolites – including potential high-value target products – (metabolomics), provides further insight into how cells function and provides guidance as to how bio-engineering can be optimised. Adapted from: Koriem, 2017. (B) Location of Bioplatforms Australia's nodes (www.bioplatforms.com/facilities).

Nanotechnology (Brisbane), Australian Wine Research Institute (Adelaide), Murdoch University (Perth), University of Melbourne (Melbourne), and University of Western Australia (Perth). In addition, bioinformatics facilities are at the Centre for Comparative Genomics, Murdoch University (Perth), EMBL-Australia Bioinformatics Resource at Melbourne Bioinformatics, University of Melbourne (Melbourne) and NSW Systems Biology Initiative (Sydney).

The 2016 National Research Infrastructure Roadmap addresses omics research requirements under the Complex Biology focus area and identifies that synthetic biology is dependent on access to high level omics and related bioinformatics capabilities. The 2016 Roadmap also recognises the importance of investing in equipment maintenance and regular upgrades to keep pace with new technology development (Australian Government, 2017a).

2.3.3.7 Scale-up facilities

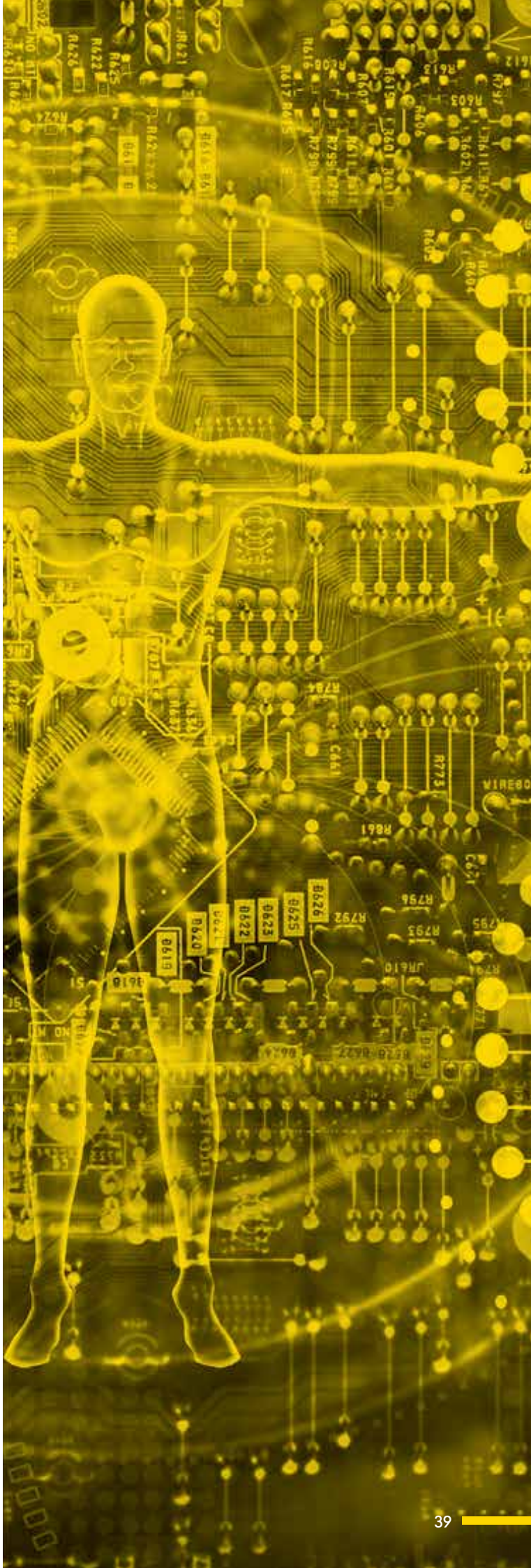
Translation from laboratory scale to production scale is complex and requires the infrastructure and resources to develop, test and refine the scale-up process. This is one of many accessory fields required to commercialise the products of synthetic biology. There are limited facilities for scale-up in Australia. Existing facilities include the National Biologics Facility, with two nodes located in Melbourne (CSIRO Molecular Health Technologies) and Brisbane (the University of Queensland), as well as the Mackay Renewable Biocommodities Pilot Plant, managed by Queensland University of Technology (Queensland University of Technology, 2017). These facilities are accessible to researchers at Australian universities and the corporate sector through NCRIS.

2.3.3.8 Synthetic biology foundry

Automation was highlighted by several survey respondents as a critical enabling capability for synthetic biology research (Appendix D). Automation that supports the DBTL cycle and increases throughput could dramatically enhance synthetic biology output. Synthetic biology foundries (also known as genome foundries or biofoundries) exploit recent advances in synthetic biology in combination with automation, analytics and data integration to construct high-throughput automated bioengineering pipelines for the design, building and testing of complex biological constructs in microbial hosts (Figure 11). They include a repository of parts, robotics for assembling modules, tools for integrating them into cells and performing quality control, facilities for high-throughput cell culture as well as limited integrated analytical facilities. Genome foundries have already accelerated the development of commercial synthetic biology projects for international biotechnology companies, including Amyris, Ginkgo, and Zymergen. In these examples, commercial level production of bulk chemicals and high-value pharmaceuticals was achieved in less than a year and at relatively low cost. Manufacturing these compounds by conventional processes would routinely take five years, over 100 person-years and US$25 million (Nielsen & Keasling, 2016). The increasing use of synthetic biology foundries will enable more economically attractive bio-based production strategies to be developed.

As discussed in Section 2.3.3.3, standardisation of parts is a key component to enable genomes to function effectively in a high-throughput context. Australia has an opportunity to develop an international best practice in standardisation by learning from global experience.

There are also opportunities to learn from other countries' experiences in building synthetic biology foundries. For example, several foundries are under-used due to the high costs of accessing the facility or the incapacity to modify the robotic set-up for varied applications. In addition, the approach to establishing a synthetic biology foundry in Australia would need careful consideration as large automation projects are complex, can be very costly and consume more time than expected. A subsidised access model, similar to the Australian Synchrotron and other NCRIS facilities, may be required in the first instance, at least until sufficient industry use becomes established in Australia. It would be prudent to explore close collaborations with established synthetic biology foundries, particularly operational commercial foundries. Leading synthetic biology companies (e.g. Amyris, Ginkgo, and Zymergen, all of which are in the US) have invested heavily to develop their foundries, in the process building unique technology and experience as well as very large libraries of tested parts, while also greatly reducing the cost through optimisation. A partnership could be one pathway to leverage this experience in the Australian context.



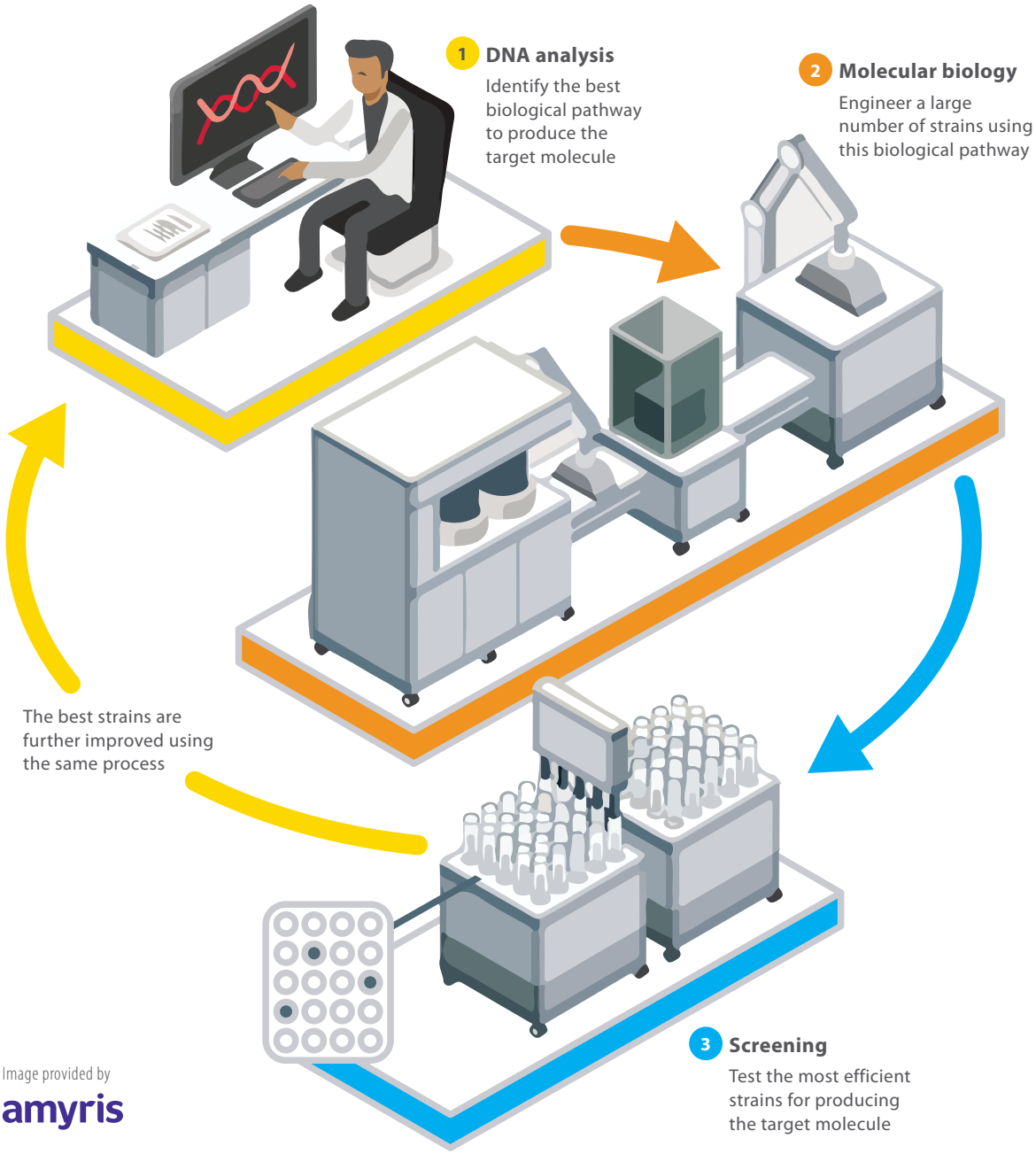


Figure 11: Synthetic Biology Foundry workflow.

Synthetic biology foundries use a semi-automated, flexible workflow. Designs are converted into DNA workflows and robots are used for each step with manual transfer of plates between stations. Robotic fluid handling is a critical part of this process. Fragment sizing and next generation sequencing (NGS) are used for vector and strain quality control. Strains are characterised by high throughput fermentation processes (shown) and analytical chemistry (chromatography and mass spectrometry primarily, downstream of the processes). Data is compiled for subsequent data mining and redesign.

2.4 Conclusion

Internationally, synthetic biology is an area of research priority. The US and UK, in particular, have made large strategic investments in synthetic biology and produce numerous publications. Compared to other research-intensive countries, Australia's focus on synthetic biology is low. However, the Australian Government funds research infrastructure that could contribute to synthetic biology development through NCRIS and Australia has several areas of strength central to synthetic biology, including circuit design, development of orthologous componentry, protein engineering, biosensing and metabolic engineering. Additionally, Australia's small synthetic biology research community is expanding, supported by activities of Synthetic Biology Australasia and the CSIRO Synthetic Biology Future Science Platform.

Developing a strong synthetic biology sector in Australia will require a vibrant research community, strong education and training programs, additional and accessible research infrastructure, and commercialisation opportunities. Recent Australian investments in synthetic biology are expected to develop and support synthetic biology research in Australia. Educating the next generation of synthetic biologists will require Australia to maintain strong mathematics and science education at all levels, enhanced by synthetic biology-specific training programs and strong interdisciplinary training.

Transforming synthetic biology research into societal, economic, environmental and medical benefits will require effective research translation. Successful translation is a weakness in Australia but is appropriately recognised as a priority in the National Innovation and Science Agenda. Australia's biomass production, extensive cropping industries, trusted IP protection policies, recognised research excellence and proximity to the Asian market are unique advantages that could attract synthetic biology industries. The potential for strategic collaboration in the Asia-Pacific region is also high, with heavy investment into synthetic biology in Asia (particularly in China and Singapore) and an active community in New Zealand.

Australia has the research excellence required for world-class synthetic biology, and the country would benefit greatly from enhanced capability in this area. However, many challenges exist, and without further investment, Australia risks falling short of the capacity to effectively apply synthetic biology. Supporting synthetic biology education, infrastructure, research translation and industry engagement would not only provide advances in manufacturing, agriculture, environmental protection and health, but will also be necessary to continue to be globally competitive in these areas. These opportunities are discussed in detail in Chapter 3.

CHAPTER 3
OPPORTUNITIES FOR AUSTRALIA IN SYNTHETIC BIOLOGY

3.1 Introduction

Given Australia's relevant research strengths and the availability of agricultural resources to provide feedstock for industrial processes, synthetic biology has the potential to deliver benefits across industry, agriculture, the environment and health and medicine. Synthetic biology will enable entirely new products and services and will improve efficiency and productivity of current bioproduction methods.

For Australia to gain these benefits, investment by both government and the private sector will be necessary. Other national analyses of synthetic biology, including those cited in this report, show that leading OECD countries have recognised the importance of the technology. These countries have developed national strategies, supported by government investment, to gain competitive advantage from the application of synthetic biology.

This report identifies four broad areas in which synthetic biology is most likely to deliver in the Australian context: industry and energy, agriculture and food, environment and biocontrol, and health. Applications in these areas are currently at varying stages of maturity both internationally and within Australia. This chapter describes the current state of technological advancements in these fields, Australia's efforts in this context, and identifies the economic benefits and prospects in those areas.

3.2 Market scope and opportunities

The market for products and services based on synthetic biology is large and increasing rapidly. Published estimates vary widely depending on definitions used and information sources. The US is the clear leader in exploiting this technology, with revenues estimated to be approximately US$350 million per annum. Given the relatively recent nature of this technology, figures of this magnitude demonstrate the importance of the field.

The expected growth of markets for products and services based on synthetic biology is even more significant. The McKinsey Global Institute (MGI) predicts the economic impact in the biofuels, chemicals, agriculture and health care, sectors alone to be in the range US$700 billion to US$1.6 trillion by 2025 (McKinsey Global Institute, 2013). MGI expects that health-related applications will account for the largest component of these benefits through faster disease detection, precise diagnoses, new drugs, and tailored disease treatments. Australia has a strong health and medical research history. This suggests that there are opportunities for Australia to gain both health and economic benefits from investment in synthetic biology. Health-related applications of synthetic biology will create employment and provide export opportunities.

Synthetic biology can have an impact on many sectors of the economy. While the current focus is on industry, agriculture, the environment, health and medicine, the technology also affects transportation (e.g. biodiesel and bio-jet fuel) and has the potential to impact on scientific services. There is also impact on the production of specialty (or fine) chemicals, vaccines and pharmaceuticals.

There are significant opportunities for Australian firms in all sectors to take advantage of synthetic biology to develop and improve products. Firms that fail to grasp the opportunities presented by synthetic biology may find that they are no longer globally competitive.

3.3 Industry and energy

3.3.1 Introduction

Synthetic biology has applications in industrialised biological processes (bioprocesses) for the production of useful compounds, including pharmaceuticals, food additives, fine and bulk chemicals, fuels and fuel additives. This is known as *industrial biotechnology* (sometimes referred to as white biotechnology). Due to their relative simplicity and the ease of adaptation to industrialise bioprocesses, microbes have been the technological development platform for industrial biotechnology. Plant and animal systems, both cell culture-based and whole organism, have also been developed. These processes use renewable feedstocks (typically from agricultural biomass, though there are an increasing number of direct photosynthetic processes being developed) and offer an alternative to unsustainable petrochemical-based processes, as well as many novel industrial products (pharmaceuticals, bulk and fine biochemicals, fuels, etc.). There are commonly also environmental benefits to bioprocesses relative to petrochemical equivalents.

Australia is a country with a relatively small, sophisticated population that has successfully employed scientific innovation to gain global market prominence as an exporter of high-quality commodities. Applying synthetic biology to develop new, sustainable, advanced manufacturing activities based on our rich supply of agricultural resources will provide new and emerging opportunities for the nation as we head towards 2030.

3.3.2 A brief history of industrial biotechnology

The Industrial Revolution required a shift to fuels with higher energy density (i.e. from wood to coal) for power generation, transport and iron production (Figure 12). The chemical industry grew as a result of lower cost steel and energy which enabled large-scale production of acids, alkalis, cement, and chemical fertilisers.

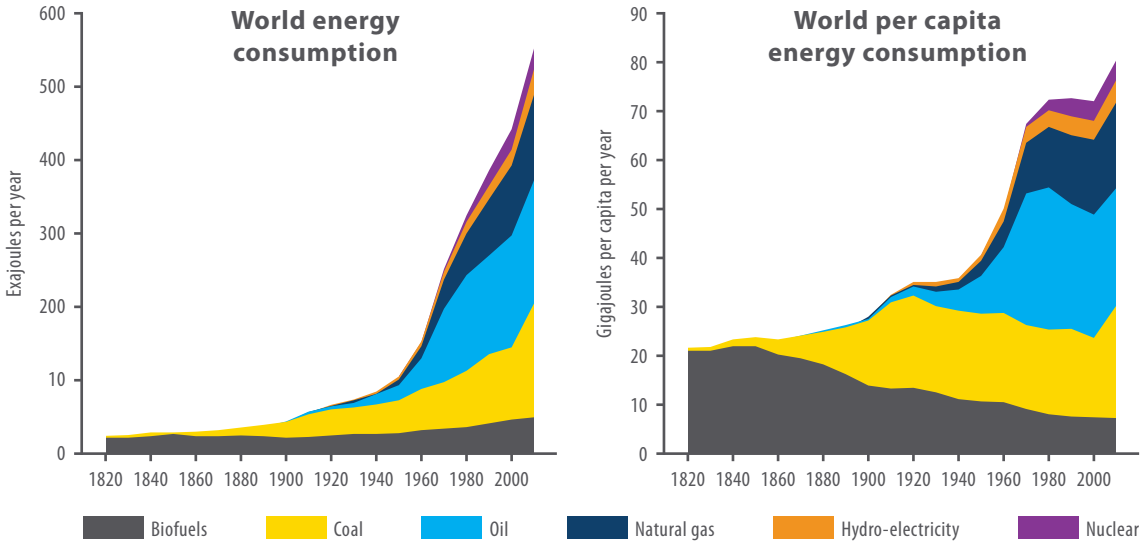


Figure 12: World energy consumption by source and world per capita energy consumption by source since 1820.

Adapted from: Tverberg, 2012.

The organochemical industry started in the mid-19th century with the use of aniline in coal-tar to produce artificial dyes. Production expanded dramatically with the expansion of the petrochemical industry and refineries producing low cost feedstock streams. Large-scale commercial production of plastics only began after the Second World War, but production now exceeds 400 Mt per annum (Geyer, Jambeck and Law, 2017). The largest amount of plastic is used in packaging and equals the amount of paper and cardboard used. Synthetic fibres are the second largest use and account for almost two-thirds of all fibre production.

Fossil fuels are typically used for industrial processes due to cost and availability. However, renewable resources could be used as an alternative: almost everything we produce from fossil fuels can be produced from biomass (Finnegan, 2015). There are also inherent advantages of bioprocesses compared to many petrochemical processes. The catalysts (cells) are inexpensive, self-replicate, operate at standard temperatures and pressures, encode long reaction pathways with minimal yield loss, and can be used in inexpensive bioreactors.

The balance between ethanol and ethylene production illustrates the interchangeability between fossil fuel and biomass as the starting point to produce chemicals at commodity scale. With cheap oil and ethylene, industrial ethanol was produced largely by chemical means (direct hydration of ethylene). The oil crisis increased the cost of crude oil and some production reverted to microbial fermentation from sugars. Ethanol production via fermentation of sugars using Baker's yeast displays the ideal features of an industrial biotechnology process. At the end of the fermentation, the yield is greater than 90 percent of the theoretical value (i.e. there is minimal wastage of the feedstock) and there is a relatively high concentration of ethanol in the product solution. The high yield and product concentration mean that the capital and running costs to build and operate the ethanol production plant per litre of ethanol produced are kept low; the feed sugar is generally the largest cost. Microbial production of several products share these features of high yield, productivity and final product concentration, including lactic acid, citric acid, and glutamic acid. Such bio-products can compete effectively on a cost basis with petrochemical-derived products.

The other broad family of classical industrial biotechnology products are natural products such as penicillin and other antibiotics, which cannot be produced readily by synthetic organic chemistry. With no competition from alternative production methods, commercial production has to be carried out in a bioprocess that often generates a low yield of product at a low concentration, all factors which contribute to increasing the production costs. Synthetic biology approaches can improve the strain of microorganism producing the product. These approaches have developed highly productive processes despite the complexity of the molecule being produced (Adrio and Demain, 2006).

The development of recombinant DNA technology in the 1970s created a new family of products, namely recombinant proteins used as enzymes, biopharmaceuticals and vaccines. These protein products are produced by inserting the DNA that codes for the protein of interest into a host bacterial, yeast or mammalian cell, which then produces the protein. These powerful techniques have been used in the production of biopharmaceuticals, referred to as biologics. The field has rapidly developed from human insulin (first approved by the US Food and Drug Administration in 1982) to biologics, which include the anti-cancer monoclonal antibodies, now the most

rapidly growing class of human therapeutics. The Global market for biologics was estimated to be US$201 billion in 2017 with forecasts anticipating growth to approximately US$400 billion by 2025 (ReportLinker, 2018).

DNA technology was immediately followed by protein engineering, thus starting the process of replacing natural occurring proteins with engineered proteins displaying enhanced features. Expanding the scope of engineering from individual proteins to pathways and whole organisms is known as metabolic engineering, a field that emerged in the early 1990s (Section 3.3.3). These technological developments underpin the rapid advances in industrial biotechnology over the past decade.

When synthetic biology emerged in the 2000s, it introduced the standardisation and manufacturing principles necessary to optimise bioprocessing and fundamentally changed the scope, scale and speed to develop a novel cell factory. In parallel, as cheaper and faster DNA synthesis and sequencing evolved, our capability to engineer genetic sequences in high throughput and at scale increased and a far greater range of genetic sequences became available. For example, it is now possible to obtain DNA sequences from all the microorganisms present in complex mixtures found in the ocean, mining sites, or the gut, providing a diversity of genetic resources and genetic sequences to exploit. Moreover, novel enzymes and pathways that do not exist in nature can now be constructed. These advances have allowed the construction of organisms containing novel pathways making compounds never before seen in nature (e.g. 1,4-butanediol; Figure 14).

Over the last two decades, computer-aided design and computer-aided manufacturing were used to automate the manual tasks of metabolic engineering: converting a hypothesis into a detailed design, constructing and validating the strain, and finally testing strain performance (following the DBTL cycle). More recently, artificial intelligence has been used to search through literature and databases and automatically generate novel designs based on the information collected, while machine learning is increasingly used to extract information from the designs and test data. Over the past decade, metabolic

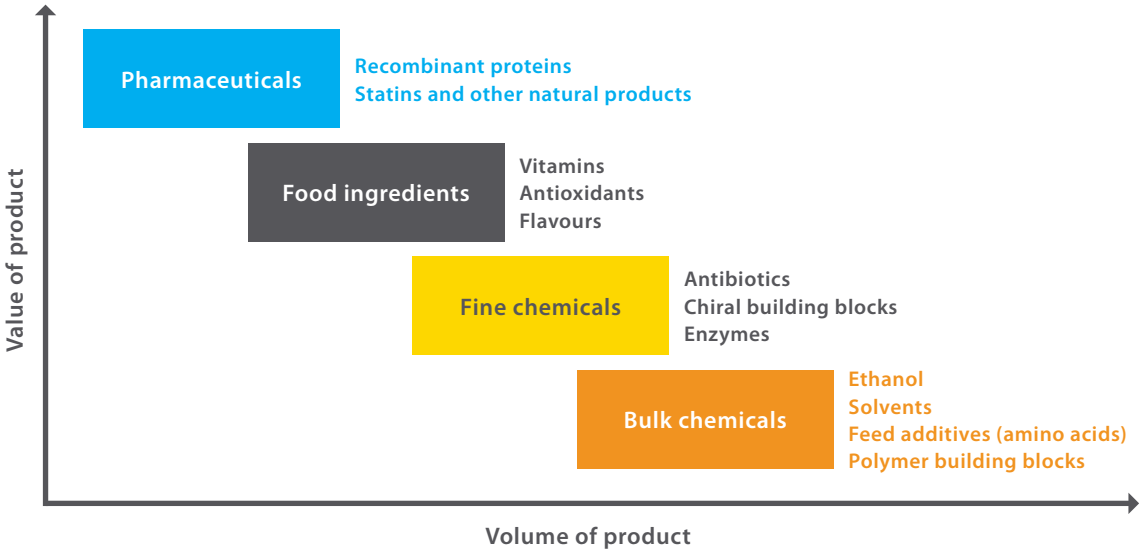


Figure 13: Synthetic biology applications.

Adapted from: Nielsen, 2010.

engineering has moved from an artisanal approach (the highly skilled master builder manually constructing strains) to a BioIndustry 4.0 approach driven by automation, artificial intelligence and big data integration.

The explosion of product diversity afforded by these advanced biological engineering approaches can potentially benefit many different application areas. The nature and scale of these benefits will vary by application and volume of production (Figure 13). The relationship between product value, achievable product volume and market size are the major determinants of the economic viability of a given bioprocess. The application of the iterative DBTL cycle to strain improvement ideally provides increments in product titre with each iteration of engineering. For a high value product where a relatively low volume is required to service the market, economic viability can be reached relatively easily and quickly. However, for low value bulk products where a very large volume is required (such as biofuels and industrial chemicals), the challenge is significantly greater.

3.3.3 Microbial cell factories

The use of microorganisms to carry out bioconversions goes back thousands of years starting with fermentation of sugars to make beer, wine and bread. In 1857, Louis Pasteur discovered that it was a small microorganism, yeast, that was responsible for the production of alcohol, carbon dioxide and energy from these sugars, and the field of microbiology was launched. Subsequently, it was realised that microbial systems had the potential to carry out complex reactions and multi-step pathways with exquisite specificity; they are now used for waste treatment, in bio-mining, and in the production of high value compounds, vaccines and antibiotics, to name just a few applications.

Molecular biology provided a limited capability to engineer cellular biofactories, with the aim of increasing rates, yields and concentrations of specific products. It soon became apparent that a far more extensive approach would be required to achieve economic viability for many target-engineered processes. Metabolic engineering, using advanced synthetic biology and systems biology, has revolutionised our ability to increase product complexity and yield from microbial cell factories.

Synthetic biology provides the molecular tools for the build phase of metabolic engineering (Section 3.3.3.1) and is used in combination with systems biology and other approaches in DBTL processes (Section 2.3.3).

3.3.3.1 Microbial metabolic engineering

During the 1990s the concept of rational cell design for bio-production emerged. This grew into a field that is now known as metabolic engineering and was developed primarily using microbial model systems. Metabolic engineering was defined in 1991 as "*the improvement of cellular activities by manipulation of enzymatic, transport, and regulatory functions of the cell with the use of recombinant DNA technology*" (Bailey, 1991). Through this process, genetic and regulatory processes across the cell's metabolic network are optimised to maximise production of a desired biochemical.

Early metabolic engineering projects focused on removing the metabolic limitations of producing cell to make improve production of natural compounds such as amino acids, vitamins and secondary metabolites (Sahm, Lothar and De Graaf, 2000; Adrio and Demain, 2006). This involved making more of the existing enzymes within the cell, introducing superior enzymes from other species, or using enzymes that had been deregulated to make them more active (Ikeda and Katsumata, 1999;

Box 6: Applications – 1,3-Propanediol

The chemical 1,3-propanediol (PDO) is a building block for the manufacture of polymers, cosmetics, lubricants and medicines (Przystałowska et al., 2015). PDO is produced naturally by many microbial species growing anaerobically on glycerol. However, it is produced at low rates and in low concentrations. DuPont, and Tate & Lyle manufacture the bio-based product (Bio-PDO™) through a joint venture. The process uses corn syrup and a genetically modified strain of *E. coli*. The manufacturing plant in Tennessee is located close to major areas of production of corn, which is the feedstock for this process.

Moving the PDO pathway and efficiently connecting it to glucose metabolism in *E. coli* required 26 deliberate genetic modifications and also resulted in many accidental mutations and rearrangements. The first-generation production strain produced PDO at a productivity of 3.5 g/L/h, a final product concentration of 135 g/L, and a yield of 81 percent of theoretical sufficiently high to reduce production costs to a commercially viable level. The bio-based manufacturing process uses 40 percent less energy than conventional petroleum-based processes (Muska and Alles, 2005), and reduces greenhouse gas emissions by 20 percent.

Given the state and structure of Australia's chemical sector, small domestic market and the established position of major companies in overseas markets, domestic bio-based production of PDO and other small low-value chemicals appears unlikely. However, agriculture-derived sugar feedstock would be available at a competitive price.

Ikeda, 2006). Through metabolic engineering, fermentation became the preferred production method for many specialty chemicals, notably several amino acids.

> *"We are studying microbes as 'programmable' manufacturing factories to make chemicals, monomers and polymers from different nutrient feedstocks. Current feedstocks for these materials are petrochemicals from oil. We are programming microbes to make very sophisticated polymer building blocks and molecules out of simple, renewable feedstocks, like glucose and methane".*
>
> **Chad Holliday, Chairman & CEO – DuPont, Boston Chief Executive Club, Sept 1999.**

Just as the private sector was the initial developer of the recombinant DNA technology that led to biologics as a new major class of human therapeutics, the private sector has led in developing the applications for microbial metabolic engineering. DuPont was an early adopter of metabolic engineering, delivering one of the first bio-products that was cost-competitive with the petrochemical synthesis route to make 1,3-propanediol (PDO) in E. coli (Box 6).

Metabolic engineering has also been applied to engineer microbes that use cheaper or more available feedstocks. In Australia, sucrose from sugarcane is more readily available than corn-derived glucose, and sucrose also offers environmental advantages as a feedstock. However, most *E. coli* strains used in industrial processes cannot grow on sucrose. In an Australian example, a transferrable device for enabling sucrose utilisation was developed for *E. coli* (Bruschi et al., 2012). In a later application of engineered sucrose utilisation, sucrose was shown to be a preferred feedstock for production of a bio-degradable

plastic alternative (Arifin et al., 2011). Similar engineering efforts have optimised yeast for a range of alternative feedstocks (Yaguchi, Spagnuolo and Blenner, 2018).

Metabolic engineering can also provide a solution to the production of complex plant metabolites that are normally extracted from difficult to breed and propagate plants. An early success story was the biosynthesis of amorphadiene, a precursor of the antimalarial drug, artemisinin, in *E. coli* (Martin et al., 2003) by the biotechnology company Amyris. This project involved development and implementation of over 40 different synthetic biology parts in a tour-de-force of microbial engineering. However, fluctuations in the market due to variability in supply of the natural product compromised its commercial viability (Box 7).

An exciting development in metabolic engineering is the development of microbial cell factories for products not found in nature. Genomatica, a pioneering company in the field, has developed a unique *in silico* biology platform that assembles genome scale metabolic models using computer modelling tools. In 2007, Genomatica used its platform to produce 1,4-butanediol (BDO), an intermediate chemical used in the manufacture of plastics, polyurethanes and elastic fibres, with a 1.3 Mt (US$4 billion) market. The pathway was designed using a combination of enzymes from several different organisms (Yim et al., 2011). The final biosynthetic pathway, shown in Figure 14, highlights the *in silico* components of the design. This engineering approach to BDO synthesis resulted in a commercially viable bioprocess that began large-scale production in 2012 – only five years after the project initiated. Although all of the enzymes required for BDO synthesis existed in nature, in other situations it will be necessary to use protein engineering to alter substrate specificity of similar enzymes to develop non-natural product pathways.

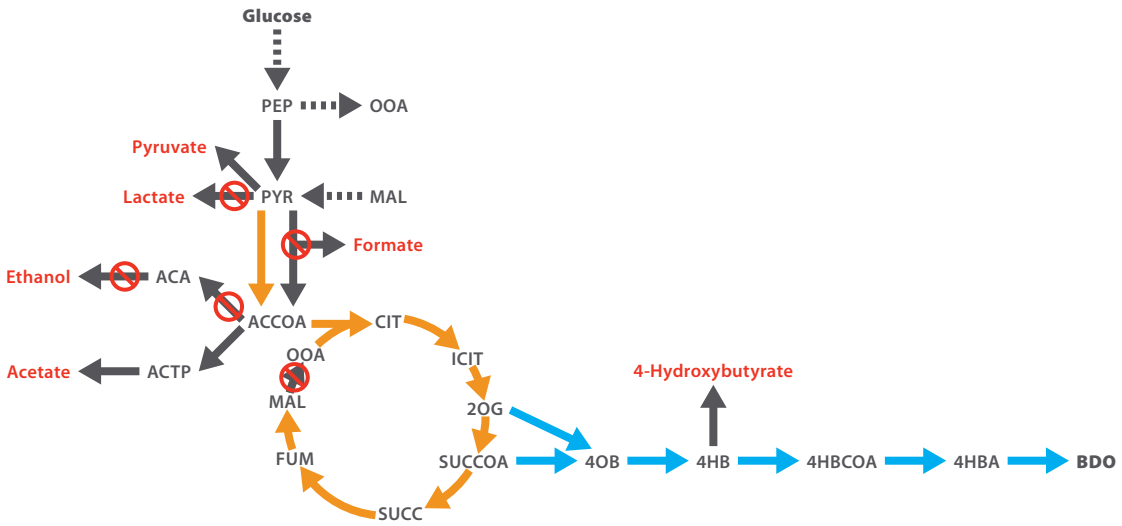


Figure 14: In silico design of the BDO strain.

Adapted from: L. K. Nielsen, 2011. The non-natural BDO pathway (blue) was selected from 10,000 potential biological-like pathways on the basis of yield, thermodynamics and pre-existing enzymes. A final concentration more than 140 g/L and a yield in excess of 90 percent made this a commercially viable process.

Box 7: Applications – Artemisinin

Each year, almost 300 million people suffer from acute malaria. Forty percent of the world's population lives in areas with malaria risk. Over one million people die from malaria annually, mostly children under five years of age, with 90 percent of malaria cases occurring in Africa, south of the Sahara. Malaria has been estimated to cost Africa more than US$12 billion every year in lost GDP, even though it could be controlled for a fraction of that sum (UNICEF, 2004). Commercialisation of the biology-based synthesis of the anti-malaria drug precursor artemisinin demonstrates the potential of synthetic biology for the development and production of pharmaceutical agents (Paddon and Keasling, 2014).

Artemisinin can be extracted from the Chinese wormwood, *Artemisia annua*, but this source is unreliable due to weather and harvest variability. Similarly, the chemical synthesis has not yet been achieved at a scale suitable for economical use as an active pharmaceutical ingredient. The Artemisinin Project sought to provide a more reliable supply of the precursor through metabolic engineering of microorganisms to produce artemisinic acid. The organism selected was *Saccharomyces cerevisiae* (bakers' yeast). Production of plant metabolites in microbes can be challenging due to involvement of difficult-to-express proteins, such as the cytochrome P450 enzymes, requiring extensive optimisation. Final conversion to artemisinin is accomplished through several organic chemistry steps. The project was supported by a grant from the Bill and Melinda Gates Foundation to a partnership between the University of California Berkeley, Amyris Inc and a non-profit pharmaceutical company now known as PATH Drug Solutions. The project had to achieve a result that was priced comparably with the natural product. In 2008, Amyris made its artemisinic acid-producing yeast strains available to Sanofi, via OneWorld Health, on a royalty-free basis. Sanofi established a production facility at Garessio in Italy and in 2014 produced around 60 tonnes of semi-synthetic artemisinin. The target price was US$350-400 per kilogram (at US$350 per kilogram, 60 tonnes of production would be worth US$21 million). In August 2014, Sanofi announced the release of the first batch of semi-synthetic artemisinin, with 1.7 million doses of a fixed-dose artemisinin-based combination therapy to be shipped to African countries (Palmer, 2014).

Apparently, Sanofi produced no semi-synthetic artemisinin in 2015 because a glut of the natural product reduced prices. Not only has the price dropped below Sanofi's target range, but demand has stopped rising. In addition, there have been some indications of parasite resistance to the treatment. Sanofi was reported to be selling its Garessio plant in July 2014 to Huvepharma, a Bulgarian company, which planned to lower costs and make sales to other artemisinin-based combination therapy manufacturers (Peplow, 2016).

The benefits from the use of this anti-malarial are significant. The Artemisinin project shows that while it may take time to get synthetic biology processes to perform competitively, there are opportunities to develop products, particularly where chemical synthesis is expensive, or not possible. There are also opportunities for smaller companies seeking to enter the market. However, there are also vulnerabilities associated with extreme price sensitivity and variability in market supply and demand.

Introducing new pathways into microbes creates competition for resources between the native metabolism and the desired product. This competition often causes a trade-off between microbial growth and product formation, both of which are critical for efficient biofactories. Synthetic biology offers sophisticated solutions to regulate this competition for optimal performance. Pioneering Australian work in this space used protein degradation to minimise the effects of competing enzymes (Peng et al., 2017, 2018). In another example, Australian researchers constructed a genetic circuit in yeast that sensed population density and turned on product formation only after yeast reach high density, creating an automatic switch from microbial growth to product formation (Williams, Nielsen and Vickers, 2013). This circuit was applied to improve the production of p-hydroxybenzoic acid, a specialty chemical used in electronics, cosmetic and pharmaceuticals, worth approximately US$150 million per annum (Williams et al., 2015).

3.3.4 Automated strain engineering

Historically, major productivity leaps occur when automation is introduced to an industrial process. The successful example of BDO synthesis outlined above, demonstrated that it is possible to engineer microbial cell factories for commercial performance at scale. However, while it is relatively easy to demonstrate proof-of-principle (mg/L to g/L titres of a given product), it took 5-10 years, over 100-person-years and more than US$50 million to reach commercial performance (Nielsen & Keasling, 2016). On top of this, it took 3-5 years and US$100 million to confirm the large-scale performance of process and product, and construct and commission a production plant. Automation and parallelisation were required to accelerate the design-build-test-learn engineering cycle for metabolic engineering. Automation requires standardisation of parts; thus, synthetic biology parts principles were critical to enable new automated strain engineering platforms, which represented the first synthetic biology or genome foundries (Section 2.3.3.8).

Using these automated approaches and a platform or chassis cell, which has a minimal level of critical engineering steps already integrated (Vickers, Blank and Krömer, 2010), commercial production of high value and mid-range chemicals is now possible in less than a year. Amyris used a chassis cell developed originally for the Artemisinin project (Box 7) and reengineered it to produce an alternative aviation biofuel molecule, farnesene (Box 8). This product is currently not cost-competitive with petrochemical-derived aviation fuel given the low price of crude oil. However, the farnesene molecule can be used for many other higher-value applications, and these products have been successfully taken to market. There is some exploration of farnesene opportunities underway in Australia (Box 8).

Automation and high-throughput strain construction relies on equally high-throughput methods to screen strains for their desired activities. Researchers in Australia used synthetic biology circuitry to create biosensors that report on the amount of product accumulated for high-throughput screening applications (Williams et al., 2017). Technologies such as this will be particularly important to support automated stain engineering capabilities when they arrive in Australia.

Box 8: Synthetic biology applications – A sustainable bio-jet fuel and high-value chemicals

Renewable energy is a target for synthetic biology impact. In the EU, the Renewable Energy Directive has set a 10 percent target for use of renewable energy in transport. In the US, the Commercial Aviation Alternative Fuels Initiative and the Midwest Aviation Sustainable Biofuels Initiatives have been formed to promote biofuels in the aviation sector (Global Market Insights, 2016).

ASTM International, the leading global authority for aviation fuel standards, approved the first synthetic biology aviation fuel product in June 2014. It was developed by the California based bioscience company Amyris and the French fuel company Total. A yeast was engineered using synthetic biology to produce a renewable fuel component called farnesene from sugar; aviation fuel made with this farnesene reduces greenhouse gas emissions by more than 50 percent when compared to conventional Jet A/A1 fuel (GreenAir, 2014).

The price of farnesene is around US$2.50 per litre (Lane, 2017). While not currently cost-competitive as an aviation fuel, farnesene can also be used to make other higher value products, including cosmetics ingredients, plastics, fibres, and lubricants. For example, farnesene-based Vitamin E oils are currently being marketed and sales expansion into China is anticipated to generate sales of more than US$50 million over the next 12-18 months (Global Market Insights, 2016). The many uses for farnesene make it a valuable synthetic biology product. The farnesene market was estimated at 8,510 tonnes in 2015 (Global Market Insights, 2016). The cosmetics industry alone used almost 4,000 tonnes in 2016, and a compound annual growth rate of 26 percent is predicted during 2017-21 (Technavio Research, 2017). The global farnesene market is forecast to reach US$485 million by 2023 (Global Market Insights, 2016).

Another product that is being produced using very similar synthetic biology processes is squalene. Squalene is a key ingredient in skin moisturisers as an emollient and hydrating agent and can be used in vaccines to increase efficacy. Currently endangered deep-sea sharks are killed for the squalene extracted from shark liver. The European Union has imposed a ban on deep-sea shark fishing and some leading cosmetic companies have self-imposed a ban on using shark-derived squalene (Wiley-Blackwell, 2010). Bulk squalene can sell in the range of US$40-500/kg and the use of the synthetic biology to produce it from sugar provides a low-cost production method that is both sustainable and environmentally acceptable.

Australia's dependence on imported fuels, as well as potential economic, social and environmental benefits from bio-based production of fuels and other biochemicals, makes this a target area of research.

A research collaboration between the University of Queensland and Amyris examined development of a similar process to make another important bio-jet fuel component, limonene, which wold further increase the green credentials of the fuel. Limonene also has many other commercial applications.

An agreement between Amyris and the Queensland Government will bring a factory for production of farnesene and related products to Queensland. The factory aims to produce 23,000 tonnes a year using sugarcane, as well as off-cuts from other agricultural activities (Queensland Government, 2017), with first production expected in 2020. It is anticipated that the plant will generate A$60-80 million in annual revenue. This would potentially give a 2-3 year pay back for investors (Lane, 2017) and generate environmental benefits via reduced greenhouse gas emissions and reduced air and water pollution (Benjamin et al., 2016; Synthetic Biology Project, 2018).

3.3.5 BioIndustry 4.0

Automated strain engineering originally focused on automation of the manual tasks of strain engineering (DNA design, synthesis, assembly and delivery) and comprehensive integration of the data generated during the process. A synthetic biology foundry facility can be used to pursue many projects simultaneously, particularly considering parallel advances in adaptive robotics and the Internet of Things technologies. Recent start-ups, Gingko Bioworks (a spin off from an iGEM competition team) and Zymergen were able to raise US$429 million and US$174 million respectively to service this new market opportunity, following and further developing the path that Amyris pioneered. These companies service other companies by developing novel proteins, strains and processes. Although their end-products are physical, one can think of them as digital biology companies producing and testing many DNA designs, then using the knowledge iteratively to produce better designs.

In less than a decade, strain engineering is moving from a pre-industrial approach of a Master Builder (often with postdoctoral training) hand crafting strains towards an Industry 4.0 approach including adaptive automation guided by artificial intelligence. This new BioIndustry 4.0 fundamentally changes the dynamics of industrial biotechnology and indeed bio-material sciences. Instead of selecting a few candidate molecules for development, hundreds of molecules can be developed and simultaneously tested for producibility and potential applications. An example is the US Department of Defence's *1000 Molecules Challenge* where artificial intelligence is used to undertake repetitive and routine tasks, allowing human scientists to focus on problem solving and design improvement activities (Box 9).

Box 9: 1000 Molecules Challenge

In 2015, the Defence Advanced Research Projects Agency, under the US Department of Defence, launched the Living Foundries program. The first stage – Advanced Tools and Capabilities for Generalizable Platforms (ATCG) – focused on improving tools, while the ongoing second stage – 1000 Molecules – is being conducted in conjunction with Amyris, Zymergen and the MIT-Broad BioFoundry. The second stage seeks to demonstrate advances in automation, genome editing and machine learning to accelerate prototyping. Proof-of-concept strains are being developed for 1,000 distinct molecules and material precursors spanning a wide range of defence-relevant applications including industrial chemicals, pharmaceuticals, coatings, and adhesives. The scale and complexity of the project requires artificial intelligence to be used to design and analyse data from the strains in order to accelerate and standardise the routine aspects of the creative process, leaving human scientists to supervise the design process and focus on more fundamental problems.

3.3.6 Plant and animal biofactories

Whilst many desirable products can be made in microbial systems (Section 3.3.3), plants and animals offer advantages over microbes including more complex biochemistry that sometimes cannot be performed in microbes (Houdebine, 2009) and the ability to segregate the expression of desirable products, such as vitamins in edible parts.

Due to their relative simplicity and applicability to industrial bioprocesses, the development of microbial production systems has been far more extensive than in higher organisms. Moreover, the difficulty

and cost of the various engineering steps (complexity of synthetic biology components, transferral of DNA into host cells, recovery of complex multicellular cultures and structures, etc.) significantly increases the engineering challenge in more complex cells and organisms. Nevertheless, advanced synthetic biology tools have been developed for these organisms, providing increased opportunities to use crops and livestock as biofactories to produce high-value chemicals and proteins. Examples include engineering of biosynthetic pathways from rare medicinal plants into more easily grown crops, and the production of protein therapeutics or vaccines. Engineering of high omega-3 long chain polyunsaturated fatty acids in canola (Box 6) is an example of value-added food products that used a synthetic biology-based metabolic engineering approach applied for development of plant biofactories.

Two major protein production systems have been established based on transgenic animals, which synthetic biology can improve. Firstly, transgenic farm animals (goats, rabbits, sheep, pigs, cattle) can be used to produce specific proteins in their milk (Houdebine, 2009; Kling and First, 2009; Cruz, 2015). Secondly, chicken eggs can be used as bioreactors for large-scale production of a range of pharmaceutical proteins (Sheridan, 2016) including vaccines, therapeutics, diagnostics and other medical products. For example, influenza vaccines have largely been produced in chicken eggs since the introduction of the vaccines more than 70 years ago. Although chicken eggs are now used to manufacture many vaccines, the level of vaccine antigens produced in each egg is low. Australian researchers are exploring the potential of synthetic biology to increase the efficiency of vaccine manufacture from eggs by improving antigen expression levels (Doran et al., 2016).

Plants can also be used as factories for the production of medically relevant proteins and other therapeutics. These include vaccine antigens and proteinaceous nanoparticles for drug delivery (Penney et al., 2011; Wang et al., 2014; Catrice and Sainsbury, 2015; Brillault et al., 2017). Engineering plant-based systems for vaccine production is considerably faster than establishing chicken egg-based production systems (Penney et al., 2011; Leuzinger et al., 2013), which is useful when developing vaccines against rapidly evolving viruses. Synthetic biology can also be applied to enhance production of plant-derived active ingredients. Sun Pharmaceutical Industries Australia has been active in engineering the opium poppy to improve production of target opioids, and have conducted field trials in Tasmania's opium poppy growing regions (patent GB2546285, 2016).

Molecular farming (or pharming) describes the production of pharmaceuticals in engineered organisms. Pharming has potential for low-cost production of extremely high-value products (Sack et al., 2015; Lomonossoff and D'Aoust, 2016; Nandi et al., 2016). Nevertheless, there are potential challenges with the production of bioactive products on a large scale and the purification of products may be complex. Rigorous biosafety controls would be required, and the risks associated with mixing crops or livestock destined for food with those destined for production of drugs are obvious. Hence, it is likely that pharming will continue to be carried out on a small scale in controlled facilities.

3.3.7 Industrial biocatalysis

An important application of synthetic biology in industrial biotechnology is biocatalysis: the use of enzymes to catalyse chemical reactions. Compared to chemical catalysis methods, enzymes can reduce energy costs and waste production. Australia has developed capabilities for biocatalysis in environmental applications (see Landguard

example in Section 3.5.2), as well as for chemical and pharmaceutical production (patent WO2014197941A1, 2014; patent WO2016065425-A1, 2015). In many cases, directed evolution using random mutagenesis (which does not fall under synthetic biology) is used to optimise or modify enzyme activity for industrial biocatalysis. However, synthetic biology offers powerful, and often complementary, approaches for improving activity. For example, Australian researchers developed a modular approach to linking multiple enzymes to facilitate recycling of cofactors, which are required for the activity of some enzymes (patent WO2017011870 A1, 2016). By eliminating the need to repeatedly add new cofactors, this approach has potential to reduce costs in diverse biocatalytic processes.

3.3.8 Perspective

Fossil fuels are geological deposits of biomass exposed to heat and pressure over millions of years. The primary reason fossil fuels are used for energy and chemical production is their low cost and availability. With advances in synthetic biology over the past two decades, it can be argued that biomass provides a suitable alternative to fossil fuels. Microbes can be programmed as manufacturing factories, chassis strains are being developed for many product families, and continued improvements in automated strain engineering, including design, ensures that commercial strain development will become cheaper. Over the next decade, efficient catalysts could be developed for thousands of compounds.

Box 10: Fuel production

As discussed in Section 3.3.2, production scale is an important factor in bioprocessing. Typical plants using readily fermentable substrates achieve optimal economy at 20-50 kilotonne per annum (ktpa), beyond which, further scale-up becomes scale-out (e.g. building more fermenters). Typically, the plants are flexible and can produce several products through the year. For example, the Amyris plant in Brazil may produce farnesene most of the time but can still be used for production of low volume but higher value fragrances and vitamins. Flexible production capacity at modest scale (and cost) is attractive to the chemical industry and the scale is considered ideal for the production of many life science chemicals and some oxo-chemicals (which are used in chemical and manufacturing processes of paints, plasticisers, coatings, adhesives and lubricant additives). Efficient bio-based production will be viable for many organic chemicals worth more than $5-10/kg, which represent a significant fraction of the market value, but a small fraction of market volume.

Large-scale fuel ethanol plants produce in the order of 1 megatonne per annum (Mtpa) of ethanol, which is similar in scale to plants producing large volume olefins such as ethylene and propylene. However, olefin production via bioprocesses is at best marginally viable given that it requires 3 kg of sugar to produce 1 kg of olefin and oil-derived ethylene is priced at $1/kg. Replacing the world olefin production (currently at 250 Mtpa) would require 750 Mtpa of biomass, equivalent to the annual wheat production or 20 percent of world cereal, corn and sugar production!

The disparity is even more marked with liquid fuels. Oil is refined into fuel in refineries operating at 25-50 Mtpa, with minimal loss, and at a few percent refinery margin. Ethanol can be produced from simple sugars with minimal loss of energy content, but at a 25-35 percent cost margin. Replacing the world oil production (around 4,000 Mtpa) with an energy equivalent amount of biomass would require 10,000 Mtpa biomass or 2.5 times the world cereal, corn and sugar production.

A decade ago it was commonly assumed that support of biofuels and biofuel development would help establish a bioindustry that would then be able to diversify into other products. This model expanded throughout the petrochemical industry due to strategic concerns over oil cost and control of oil reserves. However, these drivers for expansion ignored the scale limitation and different operational approaches in the bioindustry and it is now recognised that driving the bioeconomy through fuel production is neither feasible nor optimal (Box 10).

Alternative feedstocks and greater efficiencies will be required if synthetic biology is to meet a significant part of liquid fuel and olefin production without significantly affecting food production. Lignocellulosic fuels (created from plant dry matter) have been pursued since the first oil crisis 40 years ago but remain significantly more expensive than first generation fuels. Lignocellulosic fuels remain an important research field for synthetic biology, focussing particularly on plant engineering for bioenergy crops and new enzymes for biomass processing, and has been the target of investment by the US Department of Energy for the last ten years. The main issue to be solved is the low yield of usable compounds (sugars and oil) that can be extracted from the biomass. Synthetic biology offers ways to increase the sugar or oil content of the biomass and improve its extractability (Shih, Liang and Loqué, 2016).

Carbon monoxide, carbon dioxide and methane (C1 gases) are other feedstocks of increasing relevance. Gas fermentation has been pursued for many decades, particularly for the production of single cell protein from oil well methane and ethanol from syngas. Calysta and Cargill are building a 20 ktpa commercial plant in Memphis, TN and have plans to increase production to 200 ktpa by 2020 using abundant coal seam gas in the area (Cargill, 2017). LanzaTech has demonstrated efficient ethanol production from steel flue gas (gas exiting to the atmosphere from a steel mill) in several pilot projects and are constructing two commercial scale facilities at steel mills: in Belgium (63 ktpa with ArcelorMittal; and China (48 ktpa with Shougang).

While there are many sources of waste gasses – biogas in agriculture, landfill gas, as well as flaring in oil, gas and mining industries – few sources are of a size where commercial utilisation is feasible today (Clomburg, Crumbley and Gonzalez, 2017). Gasification of solid municipal and agricultural waste is a possible means to achieve commercial scale production but is currently not cost-effective.

In the near term, opportunities exist for using synthetic biology to engineer microorganisms that generate acetyl coenzyme A (acetogens) to produce higher value products, such as organic acids and alcohols, from natural gas. The chemical industry already uses large quantities of natural gas (conventional and coal seam) in the process generating syngas mixtures that are difficult to balance optimally for the product mix across a plant. Syngas is a mixture of carbon monoxide and hydrogen, which is toxic to most living systems. Acetogens are less sensitive than regular catalysts to the gas composition and thus could be used to balance demands. LanzaTech has partnered widely with university and government laboratories, including Australian partners, to establish systems and synthetic biology capabilities for acetogens. Lanzatech has so far demonstrated production of 20 chemicals, including isopropanol, at pilot scale.

In the longer term, there is the prospect of using synthetic biology to develop artificial photosynthesis to bypass the need for land, water, and nutrients to build the high-energy bonds needed to synthesise biofuels and

chemicals. For these processes to become feasible, hydrogen must be made from the electrolysis of water with renewable electricity produced in solar photo-voltaic cells. Currently, hydrogen is heavily used in the production of ammonia (and fertilisers) and in petrochemical processing.

In the hybrid photosynthetic systems under development, renewable hydrogen would be fed to specialised microbes developed by synthetic biology in a bioprocess designed to capture and convert environmental carbon dioxide. While the conversion of carbon dioxide to fuel is relatively expensive using inorganic processes, carbon dioxide fixation occurs in many microorganisms. Scale-up problems associated with such bioprocesses could be overcome by using hydrogen, and recent Australian research (Valgepea et al., 2018) has shown that acetogens efficiently convert hydrogen and carbon monoxide or carbon dioxide into acetate and ethanol, where acetate can be upgraded to oil using oil producing yeast.

3.3.9 Economic benefits of synthetic biology in industrial biotechnology

Australia has a number of well-established industries in food, health and energy which are underpinned by industrial biotechnology processes using microorganisms or cells and which could be affected by developments in synthetic biology.

Synthetic biology has the potential to play an increasing role in well-established Australian food-related sectors that employ fermentation processes (such as brewing, wine, cheese and yoghurt production). The contribution of the field could be in production of the feedstocks (Section 3.4) or in the development of improved functionality of the micro-organisms used in the fermentation processes.

The global market for fermented food and beverages was estimated in 2016 to be A$1.9 trillion and growing at an annual rate of approximately 5 percent (BIS Research, 2017; Credence Research, 2017).

Synthetic biology will also impact the production of protein based human and veterinary pharmaceutical (biologics) and vaccines through development of improved products and production processes (Section 3.6). In Australia there are several companies producing vaccines and biologics for human and veterinary use, including CSL, Zoetis, Virbac, Patheon and a number of smaller SMEs who could benefit from synthetic biology. The Australian pharmaceutical sector generates annual revenues of $1.7 billion, and it has been estimated that alliances between local and international companies working in the field and Australian research groups to develop and market applications of synthetic biology could increase this by 10 percent – A$170 million per annum (ACIL Allen, personal communication 2018).

In the case of biofuels, the economic competitiveness depends on the price of oil. When the latter moves above US$100 per barrel, biodiesel and biojet production in Australia should become a viable proposition. Currently, there is major production of fermentation ethanol for use in fuel and in 2016 Australian production was 220 mega litres (Cochran, 2017). The ethanol fermentation process is highly efficient and the opportunity to improve the production yeasts used in the process through synthetic biology is very limited – however as mentioned in Section 3.3.8, there is considerable potential for synthetic biology to engineer plants and produce specialised bioenergy crops that can be used as feedstocks for ethanol production. Such applications of synthetic biology

have the potential to reduce the ethanol price and result in an expansion of the market. A 2014 study estimated that ethanol production directly and indirectly contributed A$402 million to the Australian economy in 2012-13, comprising A$193 million in labour income and A$209 million in gross operating surplus (Deloitte Access Economics, 2014). That year, the industry contributed to the employment of an estimated 3,000 full-time equivalent staff.

The indirect value added (A$351 million) was significantly higher than the direct value added (A$51 million), reflecting the fact that the industry generates a large amount of demand for intermediate inputs produced by other industries, particularly feedstock such as wheat starch, molasses and sorghum, and freight transport. Feedstock constitutes a significant component of total production costs (Deloitte Access Economics, 2014)., as is the case for all low value bulk products, where the feedstock price is the primary driver of bioprocess cost

The opportunity exists in Australia for the development of a new advanced manufacturing sector based on bioprocesses developed using synthetic biology to produce higher value specialised molecules from Australian agricultural feedstocks. An agreement reached between Amyris and the Queensland Government in June 2017 to establish a farnesene production facility, shows that it may be possible to develop new speciality chemical production facilities in Australia (Lane, 2017). Higher-value products, chemicals that are required only in smaller quantities, and processes that can use price-competitive Australian feedstocks such as sugar, wheat or sugarcane waste, should all be candidates for Australian business. Such facilities would produce of the order of 20-50,000 tonnes per annum of products priced in the $5-10/kg range and would have sales of the order of A$100-500 million per annum. Sugar is Australia's second-largest export crop and has a total annual revenue of almost A$2 billion. Around 85 percent is exported overseas at commodity market prices (currently ~35 cents/kg). If the bulk of the export tonnage was converted into $5-10/kg products, up to $4 billion in products could be generated from the current annual sugar crop providing significant value addition to the sugar industry. This could double through development of Northern Australia. Establishing such a manufacturing sector would have a considerable market pull on all aspects of the development of industrial synthetic biology in Australia.

3.3.10 Prospects for synthetic biology in Australian industry and energy sectors

Considerable opportunities exist for Australia to capitalise on developments in synthetic biology to establish new advanced manufacturing capacity.

There are opportunities for establishing new SMEs specialising in aspects of synthetic biology, and for more established companies using the technology to diversify their range of products and to protect their market position. The growth in number of synthetic biology companies in Australia could be analogous to the expansion of the biotechnology industry, now worth approximately A$1 billion per annum (AusBiotech, 2017).

Australia's supply of raw materials as feedstock provides opportunities for the country to become a commercial leader in industrial synthetic biology. The most cost-effective feedstocks for synthetic biology energy and industry processes are sugar and starch. Sugar (sucrose, from sugarcane) is arguably the preferred substrate as it is far

less affected by the food versus other uses debate. Australia is a major sugar producer and exporter, generating over A$2 billion per annum in export earnings (Australian Government, 2017d). The sugar industry is an agro-industry and has many synergies with the type of bioprocessing plants envisaged for synthetic biology products at the 50-100 ktpa production scale. The potential also exists for a major expansion in sugar cane production in northern Australia. Other future market factors may also influence the international sugar market. The association of sugar with obesity has driven introduction of sugar taxes in 28 countries. More recently, synthetic biology is now producing high quality zero calorie sugar replacements such as the Evolva rebaudioside product derived from Stevia, which is currently being brought to market in a Coca-Cola product. Market forces such as these may damage Australia's current export market, creating a push towards alternative value-added products from sugar.

Lignocellulosic feedstocks, while desirable from a biomass feedstock perspective, still represent a significant challenge for technical and economic reasons. However, as these challenges are addressed with technological developments, Australia has the potential to provide a wide variety of different lignocellulosic feedstocks.

There are two developments that would play a major role in stimulating the commercial uptake of synthetic biology-based industrial biotechnology in Australia:

Firstly, the sector would receive a major boost if it were possible to attract national or international investment to establish a facility in Australia alongside existing feedstock opportunities, such as sugar mills. The Australian sugar industry has for many years sought new products that would complement their export of raw sugar. Such alternate products, other than ethanol for fuel use, have not eventuated in large part due to the combined risk for any company simultaneously pursuing a new way of manufacturing and a new product portfolio. Federal and state government initiatives have successfully driven establishment of new industrial biotechnology facilities previously, such as the Patheon GMP biologics facility in Brisbane, now part of Thermo Fisher Scientific. The facility opened in 2013; it has been experiencing strong double digit annual growth and now employs over 160 people.

Secondly, while Australia has good national research infrastructure in the omics, high performance computing, and a number of other relevant sectors, it lacks the type of facilities that would be encompassed in a synthetic biology foundry (Section 2.3.3.8). Establishing a synthetic biology foundry would underpin the research and development interface between public and private sector researchers and support Australia to be truly on the world stage when it comes to translating high-quality research to commercial reality.

3.4 Agriculture and food production

3.4.1 Introduction

Based on United Nations estimates, a doubling in global food production must occur by 2050 in response to the demand of an increasing world population (Alexandratos and Bruinsma, 2012). However, there is limited potential arable land available to expand into and doing so has environmental consequences. At the same time, arable land used for agriculture is being lost due to erosion, encroaching salinity and climate change. To meet food security needs, agriculture will need to become more efficient in a smaller footprint. Changing climate conditions will also affect future agricultural output.

Synthetic biology has the potential to deliver more productive and sustainable farming and farming practices that reduce environmental damage

Australia's agriculture sector is diverse and is a major pillar of the country's economy. The gross value of agricultural commodities produced in Australia in 2016-2017 was estimated at A$63.7 billion (2.6 percent of total GDP) (ABARES, 2017a). Australia has a production advantage in broadacre agriculture (non-irrigated crops, cattle and sheep). In 2015-16 Australia's Agricultural Census highlighted Australia's most valuable crop types as wheat, fruit, nuts, grapes and vegetables (Australian Bureau of Statistics, 2017c). In livestock, cattle and calves provided the most value, followed by sheep and lambs and poultry. Looking at livestock products, milk was the most valuable, followed by wool and eggs. The agricultural sector provides approximately 275,000 jobs in Australia, while another 200,000 people are employed in food product manufacturing (Australian Bureau of Statistics, 2017b). Approximately 85 percent of fresh agricultural produce sold in Australian supermarkets is produced in Australia (ABARES 2017b).

Approximately three-quarters of the value derived from Australia's agricultural commodities came from the export market in 2016-2017, bringing A$48.7 billion to the economy (ABARES, 2017a). The major export commodities in 2017 were beef and veal, wheat, wool, wine, barley, sugar, canola, chickpeas, lamb, and cotton. Australian agricultural produce is predominantly exported to China, South-East Asia and Japan (ABARES, 2017b). Population growth together with income growth and changing dietary preferences in Australia's major export markets in China and South-East Asia have further increased demand for our high-quality agricultural produce. In particular, there is an increasing market demand for animal protein, horticultural crops and value-added fresh food. Australia has a strong agricultural sector and our proximity to the expanding Asian markets will support increased demand for Australian produce.

With the significant economic benefits of Australia's agricultural sector, it will be important to maintain and improve Australia's output in this sector. Nearly half of Australia's land surface area is used for agriculture (Australian Bureau of Statistics, 2017a) and this figure is higher in some states. Increasing on-farm productivity within existing farming districts will become even more important. However, the dry climate and extreme weather events will continue to pose special challenges to agricultural productivity in Australia. Synthetic biology has the potential to deliver more productive and sustainable farming and farming practices that reduce environmental damage (Alfred et al., 2014; Fesenko and Edwards, 2014; Ricroch and Hénard-Damave, 2016). This section of the report examines the historical context of synthetic biology in agriculture and explores opportunities for Australia.

3.4.2 A brief history of agricultural biotechnology

Typically, synthetic biology products will be genetically modified (GM) organisms, or derived from them. It is therefore useful to examine the history of GM in agriculture in Australia. Since the 1990s, agricultural companies globally have sold GM crop seeds that confer insect or herbicide resistance to crops that are grown extensively in agricultural production systems. While this genetic technology pre-dates the conception of synthetic biology, it involves the transfer of genes for engineering specific plant traits.

In Australian agriculture, commercial growth of GM crops has been limited to just two of the major crop plant species, namely, cotton (270,000 ha) and canola (444,000 ha) (Brookes, 2016). The genetic modifications that have been introduced are relatively simple involving the addition of one or two genes from bacteria, conferring either herbicide tolerance or insect resistance. Almost all Australian cotton and an increasing proportion of Australian canola (now about 20 percent) carry GM resistance to the herbicides glyphosate or glufosinate (Brookes and Barfoot, 2017). The main advantage of these GM herbicide-tolerance traits is more effective weed control in crop rotation systems (Brookes and Barfoot, 2017). In cotton, herbicide tolerance is commonly combined with GM resistance to the insect pest, bollworm. The insects are exposed to an insecticidal chemical when they consume the plant, reducing the need to spray crops with pesticides.

Other single gene GM traits are being investigated for potential commercial release in the near future, of which tolerance or resistance to diseases caused by bacteria, fungi and viruses predominate. Crop diseases account for yield losses of 20-40 percent (Godfray et al., 2010; Savary et al., 2012) and thus developing resistant plant varieties will be important in increasing crop yields. Australian crops in which this technology is being tested include bananas (Dale et al., 2017), wheat, potatoes and clover (for more examples see Table 2).

Existing GM crops have proven highly advantageous for farmers and for the environment. For example, it has been estimated that over the past decade Australian farms have gained over A$1 billion in additional income through the use of GM cotton, largely through reductions in pesticide and herbicide use and thus reduced production costs (Brookes, 2016). There are also significant environmental benefits from these reductions.

3.4.3 Synthetic biology in the plant context: Engineering more complex traits

Synthetic biology allows more complex traits to be engineered into organisms than have previously been achieved by gene technology approaches, thus providing many opportunities for major impacts on agriculture and food production. In crops, improvements to complex traits such as water and nutrient use efficiency, pest and disease resistance, photosynthetic efficiency, increased yield and nutritional enhancements are all being actively researched. Optimising these complex traits will require the combination and modification of multiple genes and is becoming increasingly tractable with the development of new synthetic biology tools.

Nearer to market are synthetic biology applications aimed at the manufacture of high-value products. Engineering a metabolic pathway that produces a specific high-value product is a considerable jump in complexity from earlier single-gene constructs. A good example is the production of essential long-chain omega-3 fatty acids such as eicosapentaenoic acid and docosahexaenoic acid (DHA) in oilseed crops such as canola (Box 11). The multi-part transgenic pathways used to modify the oil profile in these plants uses synthetic biology (Petrie et al., 2012). GM canola bearing these traits has recently been approved for commercial release in Australia by OGTR, and has been approved for both animal and human consumption by FSANZ (FSANZ, 2018a; OGTR, 2018).

Box 11: Synthetic biology applications – Omega-3 long chain polyunsaturated fatty acids

Omega-3 long chain polyunsaturated fatty acids (LCPUFAs) occur mainly in certain marine species. They are widely considered to provide health benefits, including a reduction in cardiovascular disease. The National Health and Medical Research Council (NHMRC) provides suggested dietary target (SDT) intakes for the prevention of chronic disease (NHMRC, 2006). The SDT for omega-3 LCPUFA is 430 mg/day for women and 610 mg/day for men, but a number of studies have shown that Australians are not meeting this recommended intake (Meyer, 2016).

Although LCPUFA supplements reduce major cardiovascular events by a few percent at best (Aung et al., 2018), the prevalence of cardiovascular disease means that even small effects could have substantial public health benefits.

Transgenic plants provide an alternative source of LCPUFAs for the human diet and also for the diet of many farmed species of fish that are not able to synthesise LCPUFAs (Napier et al., 2015). The industry providing feed for fish farming is reported to consume more than 750,000 tonnes of fish oils annually (Hixson, 2014). These come from ocean species such as sardines, the supplies of which are limited.

Australian researchers have reported good yields for one LCPUFA in *Arabidopsis thaliana*, exceeding the 12 percent level generally found in bulk fish oil. They estimated that one hectare of oil seed crop containing an LCPUFA at this level would provide as much as would be obtained from 10,000 fish (Petrie et al., 2012).

Plant-based LCPUFAs from camelina and possibly canola could provide both a direct source of LCPUFAs for humans and an indirect source, through incorporation in the diet of farmed fish.

It has been estimated that 20,000 hectares of camelina could produce 150,000 tonnes of oil as a direct replacement for fish oils in aquafeed, which would replace 15 percent of the global oceanic harvest of these oils. By comparison, Australia's canola production in 2017 was expected to be 250,000 tonnes. This was below normal production due to drought conditions in NSW (Australian Oilseeds Federation, 2017). Worldwide, aquafeed production exceeded 1 billion tonnes in 2017, with the industry valued at A$430 billion (AquaFeed, 2018).

Increasing the dietary intake of LCPUFAS is expected to reduce cardiovascular disease (CVD), which affects about 16 percent of the Australian population (Australian Bureau of Statistics, 2012). Nearly 44,000 deaths in Australia in 2011-12 were attributed to CVD. The Heart Foundation estimates that CVDs are responsible for the death of one Australian every 12 minutes. An analysis of the relative risk reduction of a CVD event, assuming the recommended daily intake of LCPUFAs, found that the economic gains in 2015 from the total possible avoidance would be A$559 million (Shanahan and de Lorimier, 2014).

This example illustrates the potential human health benefits from the metabolic engineering of plants and the opportunities for Australia to gain environmental and economic benefits from the substitution of plant-based LCPUFAs in aquafeed.

This is just one of the many applications that are being investigated in Australia and elsewhere. Further examples are outlined in Table 2.

Table 2: Agricultural applications of gene technology.

Yield stability		
Target species	Target trait	Transgene origin
wheat, barley	aluminium tolerance	other cereals
wheat, barley	cold/frost tolerance	other cereals
potato	disease resistance	other plants
banana	disease resistance	nematode
wheat, barley	drought tolerance	other cereals
canola, sugarcane, cotton	herbicide tolerance	bacteria
cotton	insect resistance	bacteria
wheat	nitrogen use efficiency	grasses
wheat, barley	salt and drought tolerance	yeast, other plants
white clover	virus resistance	virus
wheat	water use efficiency	grasses
wheat, barley	yield enhancement	other cereals

New or improved product		
Target species	Target trait	Transgene origin
sorghum	enhanced digestibility	synthetic
wheat	enhanced dietary fibre	other cereals
oil seeds	enhanced oil content	algae, yeast
wheat	enhanced oil content	other plants, fungi

Examples of potential applications that are being trialled in Australia. Most of these have been developed predominantly using classical gene technology rather than synthetic biology, but illustrate the diversity of traits being targeted and the diversity of organisms from which transgenes are sourced (a transgene is a gene or genetic material that has been transferred naturally, or by genetic engineering techniques, from one organism to another).'

3.4.4 Livestock engineering

In animal-based agriculture, synthetic biology has potential applications that could significantly improve the welfare of livestock (Box 12) as well as increase productivity and sustainability of farming and aquaculture systems. DNA was first introduced into animal genomes more than 35 years ago, before similar techniques were available for plants (Gordon et al., 1980; Herrera-Estrella et al., 1983). Genetically engineered crops have become an established part of the agricultural system in many countries, but the first genetically engineered animal line, the faster growing AquAdvantage salmon, only gained preliminary regulatory approval in the US in December 2015 after a 12-year application process involving lengthy environmental impact and food safety assessments (Ledford, 2015b).

Near-term applications of genetic engineering in livestock are more likely to involve genome editing than synthetic biology. Pigs resilient to the porcine reproductive and respiratory syndrome virus (Whitworth et al., 2016) and African swine fever (Lillico et al., 2016) have already been produced using genome editing. Similar approaches could be used to engineer resilience to other livestock diseases by analysing genetic, epigenetic and transcriptomic variations within species or related species to determine factors associated with susceptibility or resistance to diseases such as avian influenza virus.

In Australia, no applications for the commercial release of a GM animal have been made yet. However, current research efforts in the poultry industry provides examples of the ways synthetic biology may increase productivity while also addressing ethical issues (Box 12).

3.4.5 Value added food products

Many of the GM traits being targeted are aimed at improving yields. However, some target nutritional improvement, including enhancements in digestibility, dietary fibre, and oil quality (Table 2). Other targets addressed internationally include reducing or removing allergenicity factors in foods (e.g. allergenic proteins in milk, eggs, and peanuts), reduction of toxic or unhealthy compounds, consumer traits such as reduced browning, and increased muscle mass in animals. Fortification of staple foods is another important area of development. Historically, perhaps the best example of enhanced food value is that of Golden Rice. In this example, a vitamin A precursor (which provides a yellow colour) and increased iron content were engineered into rice to combat vitamin A deficiency and anaemia in developing countries. Similar traits are being introduced into other staple food crops by scientists at Queensland University of Technology. Synthetic biology provides the potential to progress this work more rapidly and introduce more complex multi-gene traits (such as the example discussed in Box 11).

Organisms used to process food products are also an important target. Particularly relevant are the fermentation and bread-making industries. Internationally, a variety of traits have been targeted for beer improvement through engineering of yeast, including improvement of foam (head) stability, introduction of the health-promoting compound resveratrol from wine, improved flavour and aroma, improved shelf life, and various other attributes. Many other properties could be introduced into beer, bread, wine and other fermented products by using synthetic biology to modify the fermenting organism.

Box 12: Synthetic biology applications – Poultry

Male poultry birds are not commercially viable for meat production. Consequently, six billion one-day-old male chicks are culled globally per annum; this is costly and raises ethical issues. Using genetic engineering, researchers have introduced specific marker genes on the male sex-determining chromosome such that male chicks will carry the marker gene and females will not. For example, the marker gene could produce a fluorescent protein detectable with a laser through the shell of a freshly laid egg (Doran et al., 2016). Synthetic biology is being used to develop genetic componentry aimed at achieving cost-effective sex selection methods at various stages of the egg fertilisation and development process, potentially making male eggs available for a wide variety of applications, including the production of a range of therapeutically useful biologics such as vaccines and nutritionally-enhanced egg products. This would represent a significant cost saving to the industry, diverting the male eggs to alternative biological production uses early in the incubation process and avoiding the termination of live male chicks after hatching.

3.4.6 Food ingredients

Synthetic biology also provides avenues to engineer microbes for the commercial production of food additives and ingredients, including flavouring compounds, sweeteners, vitamins and food processing enzymes. Steviol glycoside is a sweetening compound from the plant *Stevia rebaudiana* (sweetleaf) which is about 250 times sweeter than sucrose (table sugar) and calorie-free. Engineering production of steviol glycoside was a major synthetic biology achievement by the company Evolva (patent EP2742142B1, 2016). Importantly, the major component of the plant-based mix of steviol glycoside compounds include one which delivers an undesirable liquorice-like flavour; other sweet non-bitter steviol glycosides are only a minor component. Evolva were able to remove this compound from the mix of products in engineered yeast, thereby delivering a superior product in an intensified fermentation-based production system. In 2017, a long-term commercialisation agreement for the product, EverSweet™, was launched between Evolva and Cargill; commercial production started in May 2018 (Evolva, 2017a, 2017b). This product may provide a viable market replacement for sugar, with potential impacts on the sugar industry.

Alternative animal products are a significant target for the synthetic biology industry for sustainability and ethical reasons. The Californian company Impossible Foods also employed simple synthetic biology to engineer yeast cells for production of leghaemoglobin, a protein from plants very similar to animal haemoglobin, an iron-containing protein which transports oxygen in blood. Leghaemoglobin confers a red meat flavour, aroma and cooking characteristics to their meat-free burger product (Fraser et al., 2015; Shankar and Hoyt, 2016). Similarly, biotech start-ups in the United States are producing animal proteins in genetically engineered microbes to replicate the molecular composition of animal products such as milk or egg whites (Anchel, 2016; Pandya et al., 2016).

3.4.7 Pest control

Insect and vertebrate pests cause significant damage to Australian agriculture. Invertebrate pests are estimated to cause over A$350 million damage to Australian grain crops annually; fruit fly damage to fruit and vegetable crops is estimated at A$159 million per year alone (Murray, Clarke and Ronning, 2013; Plant Biosecurity Cooperative Research Centre, 2017). Vertebrate pests are estimated to cause over A$600 million in annual losses to Australian agriculture (Gong et al., 2009).

Current control methods for most pests primarily rely on the application of pesticides, which has economic and environmental consequences. For some insect pests (e.g. fruit flies), an alternative approach employs laboratory-raised male fruit flies that are radiation-sterilised and released into the environment, mating with females to produce non-viable eggs; however, this is also a costly and labour-intensive process.

Synthetic biology offers the potential of alternative control mechanisms via several different technologies targeting the weed plant or the pest. To date, pest resistance in plants has been achieved by inserting single genes encoding proteins that are toxic to the target pests. Synthetic biology approaches could be used to engineer entire defence pathways into plants, or to redesign plant immunity factors (R-genes: resistance genes) to recognise factors secreted from the target pests. Strategies targeting pest insects include improvements on the sterile insect technique through the engineering of post-zygotic mating incompatibilities. Gene drives

can also be engineered to enable the rapid propagation of genes that either reduce or eliminate a target pest population (discussed in more detail in Section 3.5.3).

3.4.8 Synthetic biology research capabilities in Australian agriculture

Australia has traditionally had a strong agricultural research and development capability. CSIRO and several Australian universities are particularly strong in plant, animal and agricultural sciences and have interest and expertise in synthetic biology. The University of Queensland, University of Western Australia and Australian National University are all in the top 20 in the world for Plant and Animal Sciences; the University of Queensland and University of Western Australia are in the top 25 for Agricultural Sciences according to the 2018 US News Best Global University Rankings (US News, 2017).

Two Australian Research Council (ARC) Centres of Excellence (CoE) specialising in plant science and with strong synthetic biology programs have been funded since 2014, with an expectation to run until 2020. The ARC CoE in Translational Photosynthesis is focusing on engineering improvements to photosynthetic efficiency and is involved in Bill and Melinda Gates Foundation-funded synthetic biology projects to transfer the efficient carbon dioxide concentrating mechanisms found in algae and some tropical grasses into crops such as rice. The ARC CoE in Plant Energy Biology is working on improving plant yields by reducing energy costs involved in growth and nutrient acquisition in challenging environments and has research programs in wheat and other crops. Thus, Australia has a strong research base in synthetic biology relevant to agricultural applications.

The conversion of research findings into real-world applications is considered a weak point in Australia. Increased commercial involvement in synthetic biology could take multiple forms. Multinational seed companies are looking to import their overseas-developed technology into the Australian market. Bayer Crop Science, Monsanto (who recently merged with Bayer), Dow AgroSciences and Syngenta have all field-tested GM plant varieties in Australia. Multinational companies have also invested in, and collaborated with, Australian researchers to develop home-grown solutions for export. For example, DuPont Pioneer part-funded the Australian Centre for Plant Functional Genomics in Adelaide for a decade. In addition, smaller Australian biotechnology and seed companies are developing innovative solutions based on synthetic biology, notably Hexima (developing resistance in crops to fungal pathogens and insect pests, development of plant-derived proteins and peptides as human therapeutics) and NuSeed (omega-3 oilseeds).

CSIRO has played a major role in the past in bringing research to the development phase. The recent creation of the CSIRO Synthetic Biology Future Science Platform (Box 4), which hosts several projects in the agriculture space, will accelerate CSIRO-university partnerships in synthetic biology and aims to bring academics into closer contact with researchers whose focus is more on applications. Given the research strengths in this area in Australia, there is considerable potential to expand industry partnerships and to build a thriving synthetic biology-based biotechnology industry.

3.4.9 Economic impacts of synthetic biology on agriculture

In agriculture, the economic benefits from the application of synthetic biology can be realised in both plants and animals. For plants, this includes providing resistance to pests

and diseases, increasing yields, removing allergens and developing value-added foods. New varieties that are a source of speciality chemicals, pharmaceuticals and biofuels are also likely to provide economic benefit. For animals, synthetic biology can be used to make products that reduce or even eliminate some diseases, improve the quality or quantity of product and provide pharmacological products for human and animal treatments.

The gross value of agricultural commodities produced in Australia in 2016-2017 was estimated at A$63.7 billion (ABARES, 2017a) and is growing at approximately one percent per annum by value of production. Synthetic biology has potential to improve the economics of Australian agriculture through both producer-oriented and consumer-oriented benefits. Production costs may be reduced by increasing yield potential, by improving resilience to disease or drought, or by decreasing expenditure on costs such as water, fertilisers, herbicides or pesticides. Synthetic biology may also increase profitability by enabling the production of higher quality, premium products that fetch higher prices, or by generating new-to-market products. Many of these approaches will also deliver environmental and social benefits.

Previous experience with GM crops provides a precedent for understanding the scale of gains possible through crop modification. Genetically modified crops have provided economic advantage over non-GM crops by improving the economics of production through increased yields and reduced use of pesticides (Biden, Smyth and Hudson, 2018). A recent study quantified the environmental and economic opportunity cost of delayed adoption of GM canola due to state moratoria, and estimated a net loss of A$485.6 million to Australian canola farmers, as well as significant environmental burden, attributable to this delay (Biden, Smyth and Hudson, 2018).

A major area in which synthetic biology has capacity to reduce production costs is by improving resilience to pests and diseases. The cost of the top ten invertebrate pests in grain crops in Australia was assessed in a report commissioned by the Grains Research and Development Corporation (Murray, Clarke and Ronning, 2013). If the application of synthetic biology to these crops resulted in just a 10 percent reduction in the damage done by these pests, the benefit would be A$36 million annually. Similar economic gains may be possible in animal agriculture, where the cost of parasite, pest and viral diseases of Australian cattle and sheep reach into the billions of dollars annually (Lane et al., 2015).

In addition to production benefits, synthetic biology opens up the possibility of consumer-oriented improvements with higher quality or entirely new products that can be sold at a premium. Developing varieties of oil seeds with enhanced omega-3 long chain fatty acids, as discussed earlier in this report (Box 11), would create new markets potentially worth more than US$100 million annually.

Australian agriculture may face significant potential losses if the country does not engage in using synthetic biology to improve the properties of its major exports, while our competitors do. At most immediate risk are industries based on natural products extracted from plants that have not been optimised for agricultural production. For example, Tasmanian-grown poppies produce about half of the starting materials that end up in the A$12 billion per annum global opiates painkiller market. There is a clear threat that the relevant molecules may soon be produced at lower cost by fermentation with microbes engineered by synthetic biology (Galanie et al., 2015).

In the medium-term, there is also a risk to bulk commodity products such as wheat or

sugar through use of synthetic biology by competitors to improve the quality of their products or to produce novel, competing products. The profitability of Australian agriculture is to a large extent dependent on our capacity to access premium markets, a capability that was listed as one of the five key priorities in the Australian Government's Agricultural Competitiveness White Paper (Australian Government, 2015a). Wheat, our largest grain crop and our largest crop export, worth A$4.8 billion in exports annually (Australian Government, 2017e) is a good example. Different grades of wheat attract different prices, with a high protein wheat with good baking characteristics, Australian Prime Hard, attracting a premium of up to 10 percent over Australian Standard White wheat.[3] Such premiums are at risk if synthetic biology is used by competing countries to ensure that their exports meet the same or higher quality thresholds. Also at risk is the Australian sugar industry, currently worth almost A$2 billion in exports to Australia (Australian Government, 2017c). Molecules that can be used in place of sugar as sweeteners can be produced by microorganisms constructed by synthetic biology (patent EP2742142B1, 2016) and may be preferred if the idea of a sugar tax spreads globally. Importantly, synthetic biology also provides an avenue to diversify the sugarcane industry towards chemical and biofuel production (Section 3.3.9) making it robust to changes in global sugar demand.

Using synthetic biology to develop more sensitive and reliable tests for use in monitoring programs for bovine tuberculosis (BTB) would enable earlier and more accurate detection of outbreaks of the disease. No numbers are available for the Australian context as a successful eradication program eliminated BTB in 1987. However, overseas experience illustrates the high cost of control measures and compensation payments if vigilance is not maintained and which could be reduced with the deployment of improved testing methods. In the US these have amount to approximately $1 million per outbreak and the costs to the UK were estimated at $184 million in 2014 (discussed in Section 3.6.2 and Box 16).

These examples illustrate just some of the impacts of synthetic biology on agriculture. Their application would result in increased employment, production and exports.

3.4.10 Prospects for synthetic biology in Australian agriculture

Synthetic biology allows for increased sophistication of genetic engineering applications in food and agriculture. Genome editing technology facilitates the engineering of complex traits involving multiple genes and synthetic regulatory circuits. This allows synthetic biologists to envisage more ambitious projects implicating the stacking of multiple molecular parts under stricter control. Examples of potential projects of this type include re-engineering photosynthesis (Long, Marshall-Colon, & Zhu, 2015) or transferring nitrogen-fixing pathways from bacteria to plants (Allen et al., 2017; Vicente & Dean, 2017). If successful, such projects could have significant positive impacts on crop yield and the sustainability of modern agriculture, but these are not likely to be realised within the next decade, given the long development and testing time needed for radically new crop varieties. Other agricultural applications

3 Based on an average of daily cash prices for wheat types from several regions in Australia. Prices accessed from www.graincorp.com.au on 19 April 2018.

of synthetic biology include the development and production of biochemicals that have agricultural applications in microbial, plant or animal cell factories.

3.5 Environment and biocontrol

3.5.1 Introduction

Synthetic biology presents a range of new opportunities to protect and remediate the environment. Application areas include invasive species control, biosensing and bioremediation of environmental contaminants, and engineering resilience into endangered species and ecosystems.

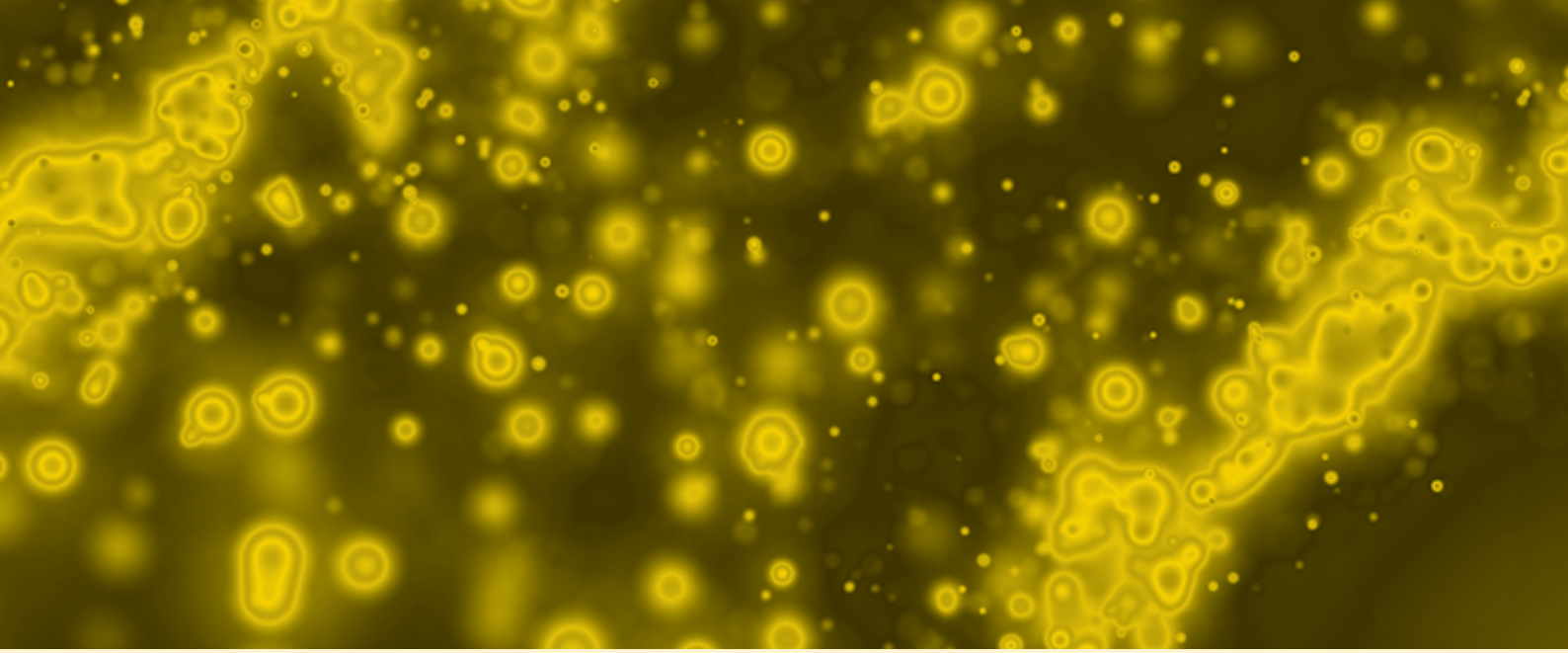
3.5.2 Biosensing and bioremediation

Human activities including agriculture, mining and other industrial processes, can release toxic chemicals into the environment, threatening both ecosystems and human health. Two important aspects of managing contamination are monitoring and remediation. Genetically engineered systems – both whole cells (typically bacteria) and individual proteins (molecular machines) – have been developed for both environmental biosensing and bioremediation applications. Synthetic biology offers new tools and approaches to extend this genetic engineering for higher efficiency, new compound targets, and more sophisticated functionality (Box 13). Australia's strength in biosensor and protein engineering, combined with our dependence on agriculture and mining industries, provide the expertise and incentive to be a world leader in cell-free biosensing and bioremediation technologies.

Heavy metal and chemical contaminants in both soil and aquatic systems can be detected using bacterial biosensors. The simplest bacterial biosensors use an environmentally-responsive promoter (a DNA regulatory element that turns a gene on or off) to control a reporter gene that creates a detectable signal, such as the gene coding for a luciferase protein that produces light. Whole-cell biosensors have the advantage over alternative analytic chemistry methods of detecting only the bioavailable portion of contaminants, which is a critical requirement for evaluating toxicity. As such, bacterial biosensors have been used to assess the bioavailability of arsenic, iron, mercury and diverse organic pollutants in a range of environments including lakes, soil, ocean and polar snow caps (Trang et al., 2005; Boyanapalli et al., 2007; Tecon, der Meer and Roelof, 2008; Larose et al., 2011).

Challenges to formulating cells for long-term survival at ambient conditions, as well as the need for portable measurement devices, limit the deployment of biosensors for on-site field-testing (Michelini et al., 2013). Recent years have seen the development of portable chip-based or single-use vial hardware for deploying whole-cell biosensors in the field. However, the refrigeration or freezing required for chip storage remains a challenge (Siegfried et al., 2012; Truffer et al., 2014; Tsai et al., 2015; Yagur-Kroll et al., 2015; Roggo and van der Meer, 2017). Enzyme-based biosensors provide an alternative to cell-based systems, with better capacity for long-term storage.

In addition to detecting environmental contaminants, genetically engineered microbes and enzymes can be used for bioremediation. Bacteria are naturally able to degrade or detoxify diverse environmental contaminants including pesticides, solvents, explosives and heavy metals, and naturally-sourced bacteria have been used for environmental remediation since 1975 (Raymond, Jamison and Hudson, 1975). Synthetic biology offers potential to



Box 13: Synthetic biology applications – Biosensors

Biosensors have a wide range of applications, such as drug discovery, diagnosis, medicine, food safety and processing, environmental monitoring, defence, and security. Recent advances in biological techniques and instrumentation involving fluorescence tags and nanomaterials have increased the sensitivity of biosensors. The medical biosensor market is dominated by US companies, together with a few from Germany, Switzerland, Japan, the UK and Singapore (MarketsandMarkets, 2017a).

Point-of-care applications held the largest share of the biosensor market in 2016. This includes glucose monitoring, cardiac markers, infectious diseases, coagulation monitoring, pregnancy and fertility testing, blood gas and electrolytes assessment, tumour or cancers markers, urinalysis testing and cholesterol tests. Cardiac markers are the most dynamic point-of-care applications owing to the increasing number of people suffering from cardiovascular diseases and rising demand for instant diagnosis of these diseases.

Glucose monitoring held the largest size of biosensors in 2016 and is expected to hold the largest share of the biosensors market for point-of-care applications by 2022 (MarketsandMarkets, 2017a). Blood glucose monitoring plays a crucial role in the management of diabetes. Glucose biosensors provide real-time information on the changes in glucose concentration. The glucose biosensor technology helps people maintain normal blood glucose levels. The rising prevalence of diabetes worldwide and technological advancements in self-monitoring of blood glucose are the key factors boosting the demand for glucose monitoring biosensors.

In Australia, UBI has partnered with global healthcare company Siemens Healthcare Diagnostics to develop the Xprecia Stride blood coagulation analyser. Launched in December 2014, the analyser helps patients taking the anticoagulant drug warfarin manage their medication.

Recent developments in cell-free synthetic biology overcome the difficulties of using living organisms in biosensors. However, cell-free systems are generally more expensive than *in vivo* production of proteins, although there are some examples where the cost have been reduced significantly (Smith, Wilding, Hunt, Bennett, & Bundy, 2014).

The world medical biosensor market was valued at around US$16 billion in 2016 and is likely to reach US$27 billion by 2022 (MarketsandMarkets, 2017a). Australia could secure niche opportunities in this market. Biosensors are increasingly finding applications in agriculture and the environment.

improve the remediation efficiency, to add or modify functionality, or improve bacterial fitness. For example, it may be possible to engineer dual functionality for remediation of sites with mixed contamination, such as sites contaminated with heavy metals and also radioactive or organic pollutants (Brim et al., 2000; Lee, Wood and Chen, 2006; Wu et al., 2006).

Despite the high potential of genetically modified bioremediating microbes, the stringent requirements of the regulatory system to obtain approval for the release of genetically modified organisms (GMOs) into the environment may deter their commercial development. An alternative approach may be to apply synthetic biology in engineered cell-free systems to progress beyond individual proteins to complex biological networks that function *in vitro* (Box 14).

Application of enzymes that convert contaminants into less toxic chemicals is an established method for bioremediation, with potential for significant enhancement through protein engineering. An Australian bioremediation product, Landguard, is a new enzyme based technology that accelerates biodegradation of organophosphate pesticide residue in water. The product was commercialised in 2006 by Orica Watercare and CSIRO, but the business was closed in 2008 due to slow market uptake (Orica, 2006, 2008).

Protein engineering plays an important role in developing enzymatic bioremediation by enhancing enzyme activity, or by altering the substrate specificity to degrade new contaminant molecules. Australian researchers have previously developed engineered enzymes for remediation of a range of organophosphate insecticides, synthetic pyrethroid insecticides, and the herbicide atrazine (Scott et al., 2010, 2011).

In addition to degrading toxic chemicals, enzyme engineering may provide a method to combat plastic pollution. It has been estimated that if current trends continue, there will be approximately 12 billion tonnes of plastic waste in landfill or the environment by 2050 (Geyer, Jambeck and Law, 2017). In an exciting development from the UK, researchers rationally engineered improved activity in an enzyme that degrades one of the most abundant plastics, polyethylene terephthalate (PET) (Austin et al., 2018). The enzymatic method breaks down PET to its constituent building blocks, meaning that the plastic could in theory be recycled and re-used forever – unlike current plastic recycling approaches, which result in decreased plastic quality each cycle so that plastic still goes to landfill eventually. Future engineering for even greater activity, as well as better properties for industrial bioprocesses may optimise this enzyme to create higher-value recycling streams, as well as a method to break down PET in the environment. This could close the sustainability loop and significantly improve environmental and economic outcomes.

The majority of bioremediation and biosensing applications discussed above sit somewhere between genetic engineering and true synthetic biology. However, synthetic biology approaches are commonly used to develop economically viable microbial cell factories for enzyme production in the case of engineered enzymes for environmental remediation. Moreover, the sophisticated genetic circuits and higher order systems that are enabled by synthetic biology have great potential to enhance bioremediation. Detoxification pathways may be linked directly to biosensor components, triggering bioremediation only in the presence of the target contaminant. Existing sense and detoxify systems include bacteria engineered to couple heavy metal detection with induced

Box 14: Synthetic biology applications – Bioremediation

Environmental pollution from toxic chemicals has become a major problem around the world. Therefore, there is an increasing interest in developing new, cost-effective, and eco-friendly remediation technologies that are capable of the partial or total recovery of a polluted environment, with particular emphasis on soils.

Bioremediation using microorganisms can be an efficient mechanism for cleaning up certain pollutants. However, there have been concerns about the release of these organisms. On the other hand, enzymes have a great potential to effectively transform and detoxify soil pollutants. Some classes of enzymes, mainly oxidoreductases and hydrolases, are useful in neutralising chemicals (Piotrowska-Długosz, 2017).

The use of enzymes may represent a sound alternative for overcoming most of the disadvantages related to the use of microorganisms. They can be used under extreme conditions that limit microbial activity and are effective at low pollutant concentrations. They are also readily biodegradable, thus minimising concerns about their long-term impact on the environment.

The world market for bioremediation technology and services was valued at US$32.2 billion in 2016 and is predicted to reach US$65.7 billion by 2025 (Transparency Market Research, 2018). Australia can benefit from the use of synthetic biology in the development of bioremediation agents and from the application of these agents on contaminated sites.

expression of surface proteins that adsorb the heavy metals (Ravikumar et al., 2017). Analogous systems could be engineered using gene circuits in cell-free systems to mitigate risks that may be associated with the environmental release of GMOs (Karig, 2017).

A powerful extension would be the incorporation of chemotaxis, that is, movement towards the target compound. Chemotaxis is a naturally occurring bacterial response to their environment, where detection of chemicals by molecular sensors send signals to molecular motors that permit the bacterium to swim. Biological parts that are used naturally for chemotaxis could be harnessed and re-assembled into microbes engineered for bioremediation. In this way, engineered microbes could seek out and destroy contaminants within the environment, resulting in more complete remediation of the contaminated site (Singh and Olson, 2008).

3.5.3 Invasive and pest species control: Gene drives

Invasive species represent one of the largest threats to Australian ecosystems and have long been the target of chemical and biological control strategies. Unfortunately, conventional methods have not been effective against many of the most damaging invasive species in Australia, including black rats, cane toads, rodents and carp (Australian Academy of Science, 2017). One potential solution being investigated is the application of synthetic gene drives.

Gene drives exist naturally as selfish genetic elements that are inherited at a higher frequency than other genes. The availability of CRIPSR-Cas and other programmable, site-directed nuclease (SDN) techniques enable the development of synthetic gene drives to force specific traits through a population, or to modify reproduction to reduce, or even eliminate, the population of target pest (Box 15) (Sinkins and Gould, 2006).

Box 15: Gene Drives

Gene drives are genetic mechanisms that increase the inheritance of a particular gene such that it spreads quickly throughout a population. By spreading a disrupted version of a gene involved in reproduction, gene drives could, for example, reduce a population of an agricultural or environmental pest. Alternatively, gene drives could force the inheritance of a specific trait throughout a target population. Although gene drives occur naturally, engineering these gene drive mechanisms is not straightforward, so other technologies are required to develop custom-made synthetic gene drives for bespoke applications.

CRISPR-enabled gene drives combine the DNA cutting machinery with a repair template that the cell copies in order to fix the cut DNA, causing the drive to be duplicated onto the other chromosome (Figure 15) (Ledford, 2015a). Therefore, while most genes are inherited by only half the offspring, gene drives can theoretically be inherited by all of them.

Recently, two laboratory studies demonstrated proof of principle of the technology by developing CRISPR gene drives into mosquito species that act as vectors for the malaria parasite (Gantz et al., 2015; Hammond et al., 2016). The studies took different approaches, with one driving the transmission of genes that confer resistance to malaria parasites (Gantz et al., 2015), and the other aiming to control the mosquito population by targeting female reproduction (Hammond et al., 2016). These studies showed strong initial inheritance rates (up to 99.5 and 99.6 percent of progeny in the two studies). However, they also identified the development of resistance and poor spread due to early infertility as barriers to effective transmission. Thus, while these studies provide technical proof-of-concept, they remain a long way from field application.

Understanding how gene drives will spread throughout target populations, and how resistance may arise, is critical prior to implementation of any gene drives in wild populations. A 2017 study from the University of Adelaide modelled several CRISPR gene drive approaches to eradicate mice from island environments. The study found that targeting several DNA cut sites simultaneously was essential for overcoming the development of resistance. When targeting three DNA cut sites within a single gene, the model predicted eradication of a population of 50,000 mice in less than five years after introducing only 100 genetically engineered mice (Prowse et al., 2017). On the other hand, the possibility of accidental spread of gene drives and unintended destruction of native population is a critical risk of gene drive use. A recent study using modelling to investigate gene drive invasiveness, reported high risk of unintentional spread, and advocated an extreme cautionary approach with respect to field trials (Noble et al., 2017).

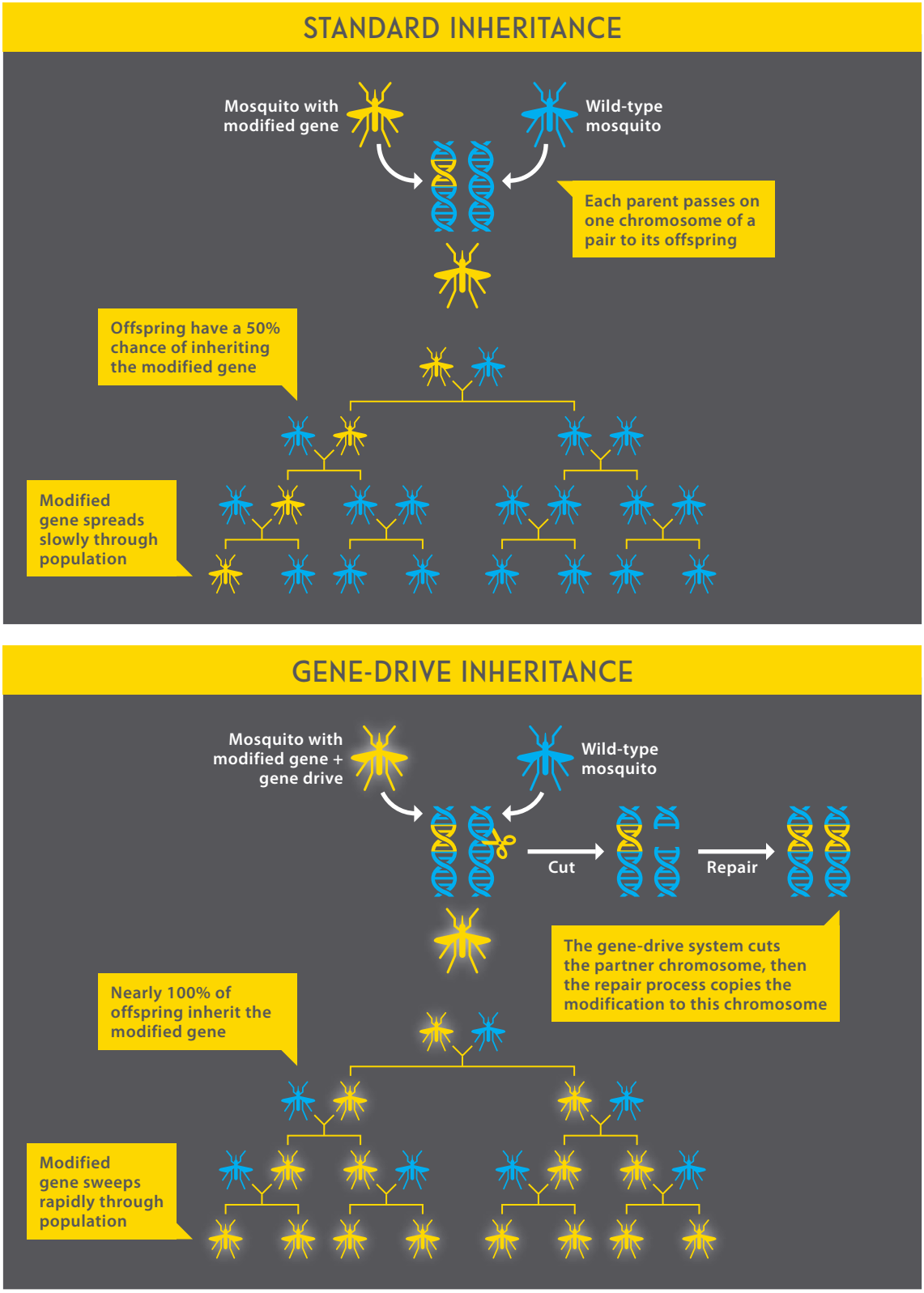


Figure 15: Standard vs. Gene drive inheritance.

Adapted from: Ledford, 2015a.

Australia's strong regulatory framework and geographic isolation makes the country particularly well suited to explore gene drives for pest population control. However, any hazards that may be associated with the deployment of gene drives will need to be comprehensively assessed and any identified risks carefully managed. Potential issues include unintended spread of the trait into genetically-related non-pest species, unforeseen ecosystem disruption due to release of predation or habitat competition as a result of extinction, and accidental spread to the natural habitat of the target species causing destruction of native populations. Molecular strategies, such as parallel development of gene drives to reverse the genetic changes, or designs that cause the gene drive to disappear from the population after a couple of generations, may mitigate risks of uncontrolled spread and provide methods to combat unforeseen negative consequences of deploying gene drive technology.

While gene drive research is currently in its infancy, it is likely that the next decade will see continued exploration of both the technological and socioeconomic aspects of the approach, including methodologies for risk assessment. This should lead to a clearer picture of the risks and potential benefits of gene drive technology. The development of a rigorous risk assessment process for the release of an engineered gene drive would require a significant investment in ecological and evolutionary modelling.

3.5.4 Engineering resilience

Some Australian ecosystems are under threat because a key species is being significantly impacted by environmental change. It may be possible to engineer resilience into some of these species by using synthetic biology tools. Generally, synthetic biology is geared towards creating organisms with altered or novel functions that are designed to be cultured, grown or housed in controlled conditions in a fermenter, laboratory or field. However, there are potential applications in synthetic biology where the ultimate goal is not the direct output of the synthetic organism itself but rather its effect on the wider ecosystem. Ecosystem engineering aims to protect and restore ecosystems, for example, by controlling populations of invasive species or disease-transmitting organisms. Such applications would necessitate the deliberate release of synthetic organisms into the wild and require a comprehensive understanding of the target ecosystem. The regulatory approval process would involve careful risk assessments of environmental health and safety informed by the results of scientific trials conducted under strict containment conditions. As with gene drives (Section 3.5.3), a rigorous risk assessment process would require significant investment in research in ecological and evolutionary modelling.

In marine systems, both coral reefs and kelp forests are undergoing rapid decline due to the effects of rising seawater temperature. In both cases, any natural adaptation response will likely occur too slowly to prevent further substantial losses. One synthetic biology solution could be to introduce metabolic pathways that provide higher thermal tolerance in the target species itself or, in the case of corals, into the holobiont (the coral and its associated symbiotic algae). In Australia, research is already underway to identify the mechanisms by which individual corals are able to survive conditions that have caused bleaching elsewhere in the reef (Levin et al., 2017). It is hoped this work will form the basis for a synthetic biology solution that involves introducing metabolic pathways that provide higher thermal tolerance in the coral itself or into its symbiotic algae.

Disease also poses a substantial threat to some species. Fungal diseases, in particular, are an increasing global threat to some animal and plant systems. While disease resistance can sometimes be achieved with the transfer of a single gene in plant systems, in animals it is more likely that fungal disease resistance will require a more complex array of defence responses. For example, resistance to dieback caused by the plant root pathogen, *Phytophthora cinnamomi*, in the eucalypt forests of southwest Western Australia may be achieved using single R-genes (resistance genes) – although no naturally-occurring resistance has yet been identified. Resistance to *P. cinnamomi* has been achieved in *Arabidopsis thaliana* with RNAi gene silencing targeting the oomycete pathogen. Effective protection of frogs and other amphibians threatened by chytrid fungus (chytridiomycosis) will likely require enhanced anti-fungal defences in the mucous layer of the skin, perhaps generated by both the frog and its skin symbionts.

3.5.5 Economic benefits of environmental synthetic biology

Environmental monitoring and contaminated site remediation are the major applications for which there are likely to be economic benefits from synthetic biology within the next decade. The environmental monitoring market has been forecasted to reach just under US$20 billion per year by 2021 (MarketsandMarkets, 2017b). While the major application of biosensors will likely continue to be in the health sector (Section 3.6), synthetic biology is beginning to provide solutions for environmental monitoring, which, coupled with falling biosensor production costs, is likely to result in a rapid increase in the use of biosensors for environmental applications.

The world market for bioremediation technology and services is more than at $US32.2 billion in 2016 and is estimated to reach $US65.7 billion by 2025 (Transparency Market Research, 2018). New synthetic biology products will likely form a share of this market over the coming years, and Australia's strong research capabilities in bioengineering for waste remediation should enable Australian firms to benefit.

Australia also stands to benefit economically from any improvements in site remediation capability enabled by synthetic biology. Australia has a large burden of contaminated land, estimated at over 160,000 sites (Plant, Wilmot and Ege, 2014). The application of these products and services in Australia will generate significant benefits and make it possible to remediate previously intractable sites. For example, the cost of large-scale treatment of areas polluted with per-fluoroalkyl and poly-fluoroalkyl substances (PFAS) is very high. These flame-retardant substances are a major problem in the ground around certain Australian airports. There are few practicable remediation options available in Australia (CRC CARE, 2017). The successful application of synthetic biology could result in significant environmental benefits and potentially large savings compared to other more conventional remediation technologies.

Other potential areas where synthetic biology may benefit Australia's economy in the longer term include management of invasive species and engineering ecosystem resilience. Invasive species are a significant economic burden on Australia's economy, causing livestock and crop production losses, as well as incurring costs associated with managing populations. The cost of invasive species in Australia was estimated to reach $720 million per year (McLeod, 2004). Through gene drive-mediated population management, synthetic biology has potential to overcome some

of these costs. However, these economic benefits are unlikely to be achieved in the short term and are contingent on significant investments to advance research ecological and evolutionary modelling to accurately assess and mitigate risks. Engineering resilience into keystone species has potential to protect native ecosystems. In addition to providing environmental benefits, ecosystem resilience has major implications in the tourism industry. For example, the Great Barrier Reef – the target ecosystem of a CSIRO coral engineering project – is worth A$56 billion to the Australian economy each year (O'Mahony et al., 2017).

3.5.6 Prospects for environmental synthetic biology in Australia

Constraints to progressing this sector technological and include lack of availability of baseline information on our natural ecosystems, a need for enhanced population modelling capacity as well as public acceptance and regulatory hurdles. Conservationists have also highlighted the importance of improving mutual understanding between environmental scientists and synthetic biology engineers when considering the use of this technology to protect the natural world (Conniff, 2017).

Australia has strong research capability in the relevant technologies for biosensor development and waste remediation and is likely to continue to be globally competitive in these areas. Australia is also in a good position, both geographically and environmentally, to investigate potential value from gene drives and engineered environmental resilience. As these latter applications would involve release of genetically modified organisms into the environment, a strong regulatory framework will be important to mitigate environmental risks and address societal concerns, while still supporting innovation. Whole of government policy considerations should include benefits that the technology may provide, while addressing the risks of inaction.

The Australian Academy of Science recently considered the potential for gene drives to alter ecosystem function in Australia and observed that the dynamics of these highly interlinked systems are "*controlled by positive and negative feedback cycles that respond to external forces in ways that are often difficult to predict*" (Australian Academy of Science, 2017, p. 7). For these reasons the Academy recommended extensive studies of gene drives under stringent containment conditions prior to any consideration of their release, and continuation of the requirement for release decisions to be made on a case-by-case basis following a comprehensive environmental risk assessment that includes ecological and evolutionary modelling.

Effective deployment of either gene drives or engineered organisms for bioremediation or enhanced resilience will require greater capacity in population modelling, and a better understanding of evolutionary theory and ecosystem biology. Population modelling is a key requirement to predicting the effects of widespread release of engineered organisms and will be critical to the effective and safe implementation of synthetic biology strategies. Survey respondents identified modelling as a gap area within Australia, and indeed, worldwide. Strengthening existing training in this area will be an important step in ensuring Australia is equipped with the appropriate skills and expertise to evaluate potential environmental applications of synthetic biology. Furthermore, as a world-wide gap, upskilling in this area provides Australia with the opportunity to be a global leader.

There is much potential for synthetic biology to enhance environmental management in Australia. However, implementation of strategies deploying genetically modified organisms for environmental remediation is likely to be beyond the ten-year mark and will require appropriate regulation underpinned by capacity building in evolutionary and ecological risk assessment. Nevertheless, significant technological advancements are likely to advance this sector. With gene drives, better models of efficacy and spread, new genetic approaches to control unwanted spread, and confined laboratory studies in several species, targeting a range of different genes, will better place Australia to evaluate the risks and potential benefits of gene drive technology. Further development and greater deployment of enzyme-based sensing and remediation will keep Australia competitive in this area.

3.6 Health and medical applications

3.6.1 Introduction

Synthetic biology has the potential to revolutionise the way in which we generate biological tools to advance the wellbeing of humans, to more proactively manage human and animal health and potentially, to bolster commercial activity in the biomedical field. A recent survey conducted for this project with the assistance of Synthetic Biology Australasia identified Australian medical research institutes and universities that are conducting synthetic biology research projects with potential medical applications. The activities range from basic laboratory research, through translational studies and in some cases, first in-human clinical trials. Applications include diagnostics, therapeutics and theranostics (diagnostic approaches linked directly with therapeutic outcomes). The new field of human cancer immunotherapy is one that appears to have special promise.

3.6.2 Diagnostics and bio-detection: new biosensors and smart micro-devices and nano-devices

Synthetic biology is being used to develop biosensors for use in high-performance diagnostic techniques for various human and veterinary diseases. Such new methods have a number of advantages over existing techniques, including specificity, sensitivity, stability and cost.

Australian laboratories are developing novel biosensors that produce electric signals that can be integrated with portable electronic devices for direct detection of chemicals. To date, this has been demonstrated with naturally occurring enzymes for detection of single targets, such as glucose. Broader biosensors are being developed that can recognise drugs, such as immunosuppressant, or biochemicals associated with disease, such as α-amylase protein (acute pancreatitis) and to measure the activity of proteins involved in blood clotting and stroke (thrombin and Factor Xa). This approach could be expanded to detect modified proteins, nucleic acids, toxins, inorganic molecules or neurotransmitters (Cui et al. 2015), providing a platform technology for diagnostic bio-electronic detection tools. One example of biosensor design involves use of protein-based nanowires produced by bacteria. These nanowires can be designed to specifically recognise chemicals in biological samples. This recognition creates an electrical signal that can be detected directly or used to control nerve cells (Glover et al. 2016).

One of the biggest difficulties in studying normal brain function, or degenerative brain

Box 16: Synthetic biology applications – Bovine tuberculosis

Bovine tuberculosis (BTB) is a major animal health problem worldwide. It is estimated that 50 million cattle are infected with *Mycobacterium bovis*, the causative agent of this disease (Waters et al., 2012). BTB is not just a problem for cattle—it can cause human disease.

The skin test used on cattle to detect BTB lacks specificity, and the antigen on which the assay is based is difficult to produce and unstable when stored. A new test has been developed which uses synthetic biology to fuse an antigen to an enzyme, polyhydroxyalkanoate synthase, that synthesises polyester beads. The enzyme is incorporated into the bead, with the antigen displayed on the outside of the bead (Chen et al., 2014). The new product has three-fold increased specificity and the same sensitivity as the commercial product. The biopolymer beads are now being redesigned as a blood assay and for detection of human TB.

Australia was declared officially free from BTB in December 1997, and the last confirmed case of TB in any species in Australia was detected and destroyed in 2002. Australia is the only major exporter of livestock that has successfully eradicated BTB. Animal Health Australia has a disease surveillance program for BTB to ensure that our agriculture industry remains free from this disease.

In many other countries, the incidence of TB in cattle has been reduced but reservoirs of tuberculosis in wild-living animals have prevented total eradication. Eradication in Australia was facilitated by the fact that Australia does not have wildlife reservoirs for BTB.

In the US, BTB is a sporadically epidemic disease in the cattle industry, with endemic infection having been a problem in Michigan. Although some states have experienced BTB outbreaks from infected wildlife populations, most of the country has eradicated the disease. Infection is usually believed to be due to animal movement from endemically infected areas, primarily Mexico. In 2011, the US was reported to be identifying an average of ten or less infected herds each year (Smith, Tauer, Sanderson, & Gröhn, 2014).

Despite the rarity of herd-level outbreaks, state and federal authorities spend considerable sums to control BTB. Such expenditure may increase. The cost to Nebraska of two outbreaks in 2009 was US$750,000 for state employee overtime, outside help, and purchase of animal restraint equipment (Smith et al., 2014). The federal costs associated with an outbreak in Indiana were approximately US$281,000 (Smith et al., 2014).

In the United Kingdom, one estimate puts the cost of BTB to the country at £100 million (A$184 million) in 2014, for compensation and control measures. The UK Department for Environment, Food & Rural Affairs (DEFRA) has estimated the estimated average cost of a bovine TB breakout on a farm is £34,000. Of this, £20,000 is borne by the Government, mainly as compensation for animals compulsorily slaughtered and the costs of testing, and £14,000 falls to the farmer as a result of the loss of animals, on-farm costs of testing, and business disruption because of movement restrictions. In 2011, TB Free England estimated that the costs of bovine TB control could exceed £1 billion over the next decade, if no action is taken.

diseases such as Alzheimer's, Parkinson's or multiple sclerosis, is the inability to visualise neurotransmitters – chemical messengers that carry information between neurons and other cells – in the brain. Fluorescent biosensors that allow neurotransmitters to be detected in intact cells or in live animals in real time have been developed using synthetic biology (Whitfield et al. 2015). These sensors could lead to significant improvements in models of degenerative brain diseases in humans and livestock.

Bovine tuberculosis (BTB) can cause human disease and is extensively monitored in beef producing countries (Section 3.4.9). The test used to detect BTB is not specific for virulent strains and the reagents are difficult to produce and store. Synthetic biology has been used to produce biopolymer beads that are more stable and specific for virulent BTB strains. In field trials, this new method shows a three-fold improvement in specificity, retains sensitivity and is much more stable than the standard method (Chen et al. 2014) (Box 16). The method is being adapted to detect human TB, a significant health concern in many countries.

3.6.3 DNA origami for preventative, diagnostic and therapeutic applications

DNA can be used as a template to create artificial three-dimensional structures (DNA origami) upon which proteins and other biomolecules can be arranged, and which can be used for a wide variety of applications. As a biomolecule with well-characterised molecular self-assembly properties, DNA origami techniques allow the formation of nanostructures that can be modified to improve their utilities as biosensors or drug carriers (reviewed by Wang et al., 2017). DNA origami structures are being developed by Australian researchers as nanodevices to encapsulate and deliver drugs with enhanced efficiency and with fewer side-effects (Glover & Clark 2016). Other Australian groups are constructing protein machines on DNA scaffolds (Baker et al. 2016). This technology can be used for many different research and clinical applications, including vaccine design, molecular diagnostics, and to engineer arrays of highly stable antibody-like single chain proteins (known as monobodies) that are capable of binding to a range of clinically important target molecules for diagnostic and treatment applications (Box 17). Variants of the technology have been marketed by international pharmaceutical companies under names such as Adnectins which have been developed by Adnexus Therapeutics and Bristol Myers-Squibb, and more recently by Roche (Parent Project Muscular Dystrophy, 2017).

Box 17: Monobodies

Monobodies are synthetic binding proteins, created using fibronectin type III domain (FN3) as a molecular scaffold that can bind to target molecules with high affinity and selectivity. Fibronectin domains occur in a variety of extracellular proteins from animal species, yeast, plants and bacteria (including *E. coli*) and are involved in cell adhesion and migration, maintaining cell morphology, thrombosis and embryonic differentiation. Monobodies provide an alternative to antibodies in the creation of target-binding proteins. They provide advantages over conventional antibodies due to size, simpler structure and ease of manufacture and production.

DNA origami structures can also be used to develop larger biomaterials that can play a central role in regenerative medicine and tissue engineering by serving as tuneable environments that can enable cells to hone-in on sites of tissue damage, then stimulate them to proliferate, differentiate and thus, participate in tissue regeneration or replacement (Glover et al. 2016).

3.6.4 Biopolymer vaccines

There is a considerable unmet demand for safe, broadly protective and cheap vaccines. Biopolymer beads produced in *E. coli* (similar to those described in Section 3.6.2 for the detection of BTB) can also be used to display antigens from pathogens such as *M. tuberculosis*, *S. pneumoniae*, *N. meningitidis* and Hepatitis C (Rehm 2017). Advanced biomanufacturing for these novel vaccines has been developed and extensive animal trials show that these novel particulate vaccines are safe and induce protective immunity (Rehm 2017).

3.6.5 Anti-microbial agents: engineered phages

Phages are viruses that can specifically target, infect and kill bacteria, including multi-drug resistant strains such as *S. aureus*. In this approach, phage-derived enzymes disseminate mucosal biofilms to kill the pathogenic bacteria. Phage therapy has been developed clinically in eastern Europe but is very rare in Western countries. Natural phages may or may not be effective against a given pathogen. Engineering using synthetic biology approaches has been used to improve specificity and effectiveness, improve targeting, or modify other key characteristics. The most effective proteins would be used in synthetic phage to generate a self-replicating, bactericidal nanomachine (Citorik, Mimee & Lu 2014).

3.6.6 Drug delivery: Caveospheres

While over 100 approved peptide anti-microbials are on the market, their use is limited by rapid clearance and proteolytic degradation. To address this challenge, a nanoparticle delivery system called caveospheres uses the expression of mammalian caveolin in bacteria, where it self-assembles into 50 nm particles that can be engineered to contain targeting and anti-microbial peptides (Box 18). Biological function can also be modified by designing caveolin fusion proteins that contain targeting groups, therapeutic agents or trafficking motifs that direct the particles to specific cellular compartments (Glass et al. 2016).

3.6.7 Re-engineered antibodies and cellular therapeutics for cancer

A variety of synthetic biology approaches are being applied in the emerging field of cancer immunotherapy. This field either uses the patient's immune system to attack cancer cells by boosting the native immune response or deploying engineered immune responses, or, in some cases, suppress aspects of immune function. Various novel chimeric molecules engineered with synthetic biology approaches are being developed for application in immunotherapy. Many of these approaches centre on engineering smaller and less complex antibody molecules that avoid problems with large and complex immunoglobulin (Ig) antibodies (Figure 17). This is achieved by taking the antibody component that recognises the antigen (target molecule) and engineering it onto simpler protein scaffolds that provide better functionality in the new therapeutics (e.g. shorter half-life to improve pharmaco-kinetics, improved targeting, tumour-penetrating functions). A key aspect of the

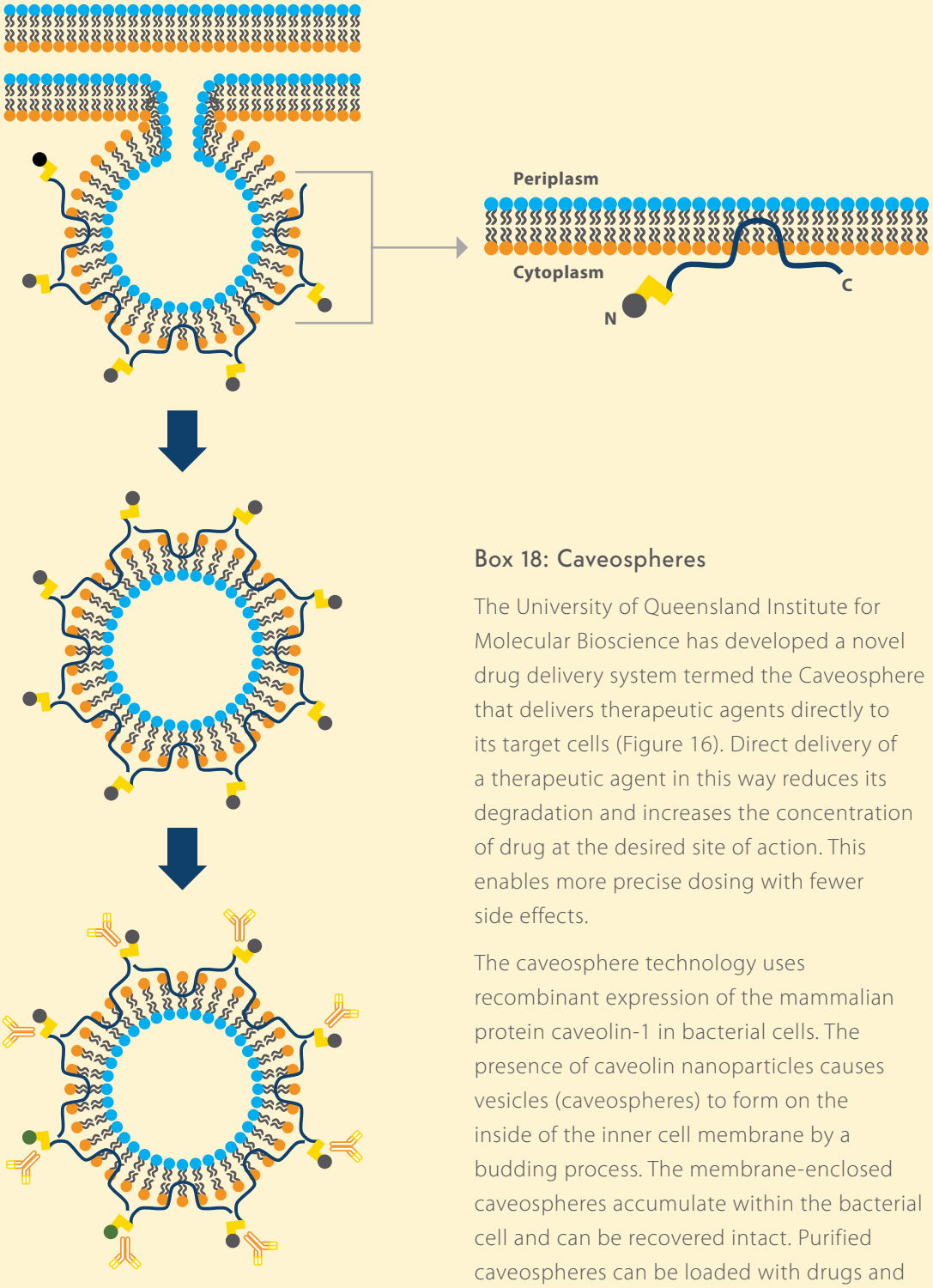


Figure 16: The caveosphere.

Adapted from: Glass et al., 2016.

Box 18: Caveospheres

The University of Queensland Institute for Molecular Bioscience has developed a novel drug delivery system termed the Caveosphere that delivers therapeutic agents directly to its target cells (Figure 16). Direct delivery of a therapeutic agent in this way reduces its degradation and increases the concentration of drug at the desired site of action. This enables more precise dosing with fewer side effects.

The caveosphere technology uses recombinant expression of the mammalian protein caveolin-1 in bacterial cells. The presence of caveolin nanoparticles causes vesicles (caveospheres) to form on the inside of the inner cell membrane by a budding process. The membrane-enclosed caveospheres accumulate within the bacterial cell and can be recovered intact. Purified caveospheres can be loaded with drugs and targeted to specific anatomical sites using specific antibodies or targeting moieties.

re-engineering is to fully adapt the resultant molecule to the host immune system, eliminating immunogenicity. In this way, antibody components isolated from chicken, camel, shark or mouse Ig can be seamlessly integrated into human or veterinary therapeutics.

An important emerging aspect is the development of bi-specific reagents, that is, high affinity bivalent Ig-like molecules that can link quite different molecules on different cell types for therapeutic purposes. Bispecific killer engagers (BiKES) can be used to link immune killer cells to its target (e.g. a cancer cell or virus-infected cell), exploiting a checkpoint blockade mechanism that can be used to rapidly destroy the target cell. Examples of Australian companies using bi-specific reagents for targeting cancer cells include EnGeneIC, which received FDA Orphan Drug Designation for its Targeted EDV Nanocell technology in March 2017 and is commencing Stage II trials for the treatment of glioblastoma brain cancer.

Many novel and potentially useful immunotherapeutics might be developed using a similar chimeric strategy. Modified approaches can be used to other immune cells types which would then permit specific forms of inflammation to be either enhanced (e.g. in cancer) or diminished (in auto-immune diseases such as multiple sclerosis, or where an exaggerated immune response to a pathogen needs to be suppressed). Applications potentially include therapeutics that prevent undesired effects of the new wave of immunotherapies; for example, approximately 10 percent of cancer patients who respond to checkpoint blockade develop off-target immune responses that require controlling.

A further aspect of synthetic biology involves the development of cellular therapeutics. In

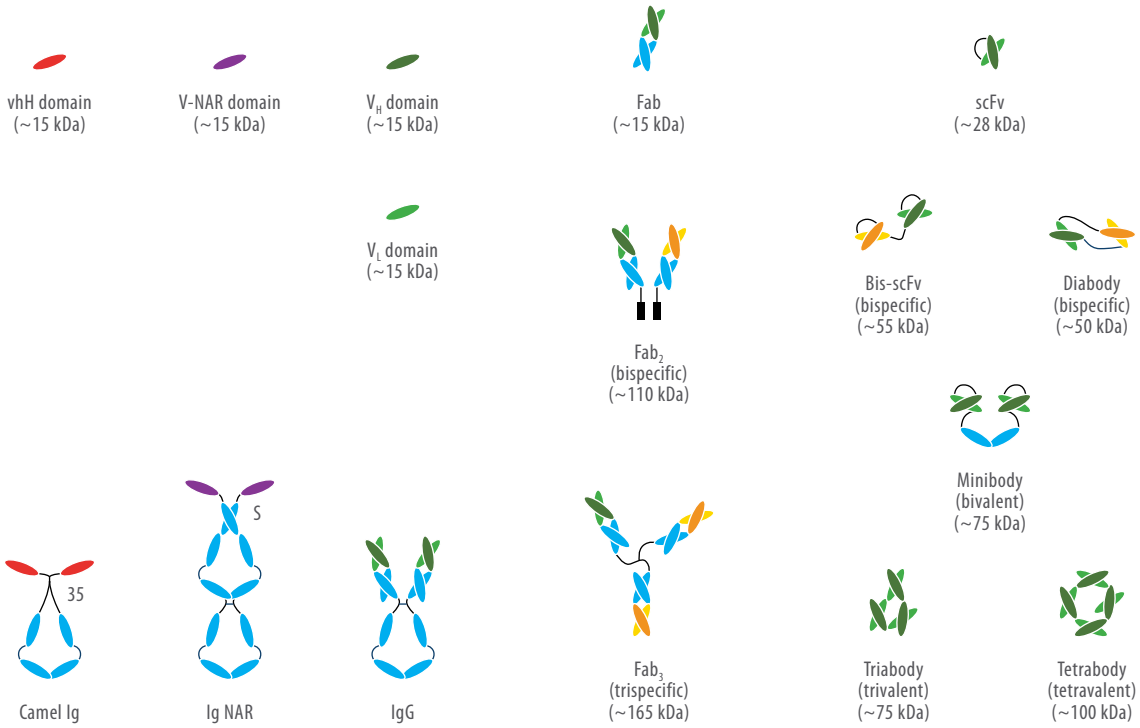


Figure 17: Representation of the various redesigned and re-engineered antibody formats.

The classic IgG molecule (boxed) is shown alongside Camelid and shark Ig-NAR immunoglobulins. Adapted from: Lalatsa and Leite, 2014.

adoptive T cell immunotherapy of human cancer, cytotoxic lymphocytes (immune killer cells) that can detect and kill cancer cells are isolated from a patient's tumour, activated and expanded by culturing them *in vitro* to generate a cellular vaccine, then re-administered to the patient (Box 19). However, the usefulness of this approach is limited by the scarcity of naturally occurring killer cells that detect the cancer and also their ability to persist and replicate in the host.

To overcome these problems, retroviruses can be used to repurpose the plentiful supply of circulating killer cells from their usual task of responding to viruses towards identifying and eliminating cancer cells. This is achieved by over-expressing a chimeric antigen receptor in the killer T cell so that it preferably interacts with cells that present antigens specific to particular cancers. These repurposed killer T cells are referred to as chimeric antigen receptor (CAR) T cells (Box 19). The extracellular part of the synthetic receptor is linked to an activation domain within the cell. When the receptor binds to its specific target antigen, it sends signals for the CAR T cells to become activated and stay active for months, progressively killing cancer cells. Once activated, the CAR T cells can continue to proliferate and persist as long as the target tumour antigen is still present. CAR T cells have proven to be highly effective in the treatment of several refractory cancers such as childhood acute lymphocytic leukaemia (ALL), but in principle can be applied to many other forms of cancer providing an appropriate chimeric receptor can be devised for that particular type of cancer. Several Australian research groups are actively developing CAR T cells and related approaches for adoptive T cell immunotherapy. While proof-of-concept has been achieved in ALL, attention is turning to approaches that will effectively control, or even eliminate, the common solid tumours that cause the greatest mortality and morbidity: those affecting lung, breast, pancreas, as well as disseminated melanoma. Synthetic biology applications of CAR T cells are further explored in Box 20.

Australian companies such as Cartherics are exploring options that enable off-the-shelf CAR T cell products or similar cellular vaccines to be made available. By using inducible pluripotent stem cells (iPCs) as the starting cell population, T cell cultures that proliferate indefinitely *in vitro* can be generated. Simultaneously modifying or eliminating the major histocompatibility complex (MHC) gene products would prevent immune rejection of the cells, providing a product suitable for a broad and genetically-diverse population of recipients.

Box 19: CAR T cells

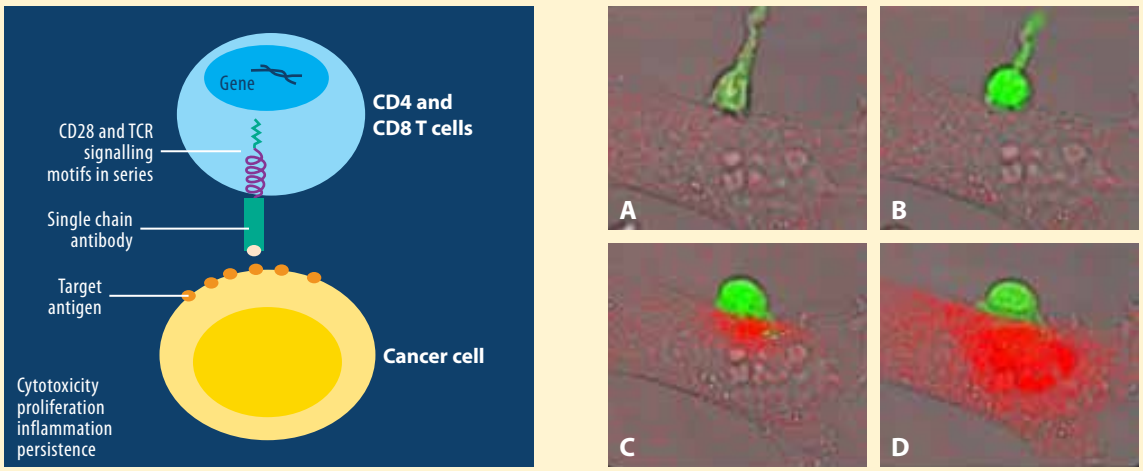


Figure 18: CAR T Cell schematic (left) and immunofluorescence images showing cancer cell death in vitro.

Adapted from images supplied by Professor Joe Trapani.

Panel 1: schematic showing CAR T cell interacting with a cancer (target) cell *in vitro*. The chimeric antigen receptor (CAR) comprises several domains: an extracellular domain which recognises an antigen on the surface of the cancer cell; a transmembrane domain which anchors the receptor molecule to the T cell; and an intracellular domain which sends signals to make the T cell's defence mechanisms active. Upon engaging the target cell, the CAR T cell is stimulated to (I) kill the target (cytotoxicity) (ii) secrete inflammatory cytokines to broaden the host's immune response (inflammation); (iii) proliferate in response to antigen; and (iv) differentiate into long-lived memory T cells that are re-activated if the tumour recurs. Other types of T cells, called helper cells, typically lack cytotoxic capacity of their own but provide essential help for the killer cells by releasing cytokines, growth factors and other biochemicals involved in inflammation and immune reactions.

Panel 2: sequential immunofluorescence images of a human killer T cell engaging a cancer cell target *in vitro*. The killer cell was pre-loaded with a calcium sensitive dye (A) that fluoresces bright green (B) upon receptor engagement and signalling through the cytoplasmic domain. Red fluorescence is generated in the dying cancer cell when a fluorescent dye (propidium iodide) present in the culture medium enters the cell through large pores that form in its plasma membrane and binds to nucleic acids (C), within minutes diffusing throughout the cancer cell (D) to kill it.

Box 20: Synthetic biology applications – CAR T Cells

Synthetic biology is providing the tools for programming immune cells (Lim and June, 2017). The development of Chimeric Antigen Receptor (CAR) T cells as a form of cancer therapy demonstrates the usefulness of engineered immune cells as cancer therapeutics. CAR T cells are a type of white blood cell engineered to recognise certain types of cancers. They have shown a high rate of response in blood cancers, particularly B cell cancers that express the target CD19. This type of treatment has not yet been as successful with solid tumours.

In 2017, the US Food and Drug Administration approved two CAR T cell therapies. One was for the treatment of children with acute lymphocytic leukaemia (ALL) and the other for adults with advanced lymphomas (National Cancer Institute, 2017). By 2026, the market for branded therapies for haematological malignancies is expected to exceed US$20 billion, with CAR T cell therapies accounting for US$1.1 billion (Yip and Webster, 2018). US company Juno Therapeutics Ltd, which focused almost entirely on CAR T cell technologies was recently acquired for US$9 billion by Celgene.

According to the US National Cancer Institute, ALL is most common in children, adolescents, and young adults, or those 15 to 39 years of age. In Australia, about 300 people are diagnosed with the disease annually. The overall survival rate at five years after diagnosis is more than 70 percent. ALL is responsible for 19 percent of all deaths in children aged 1 to 14 years (Cancer Australia, 2018). However, it is a relatively rare disease, accounting for 0.3 percent of all cancers diagnosed (Australian Cancer Research Foundation, 2018).

CAR T cells are also becoming important in the treatment of immune diseases. A French company, TxCell, is seeking to expand the applications of CAR T cells beyond cancer by using a special type of T cells known as regulatory T cells (Treg cells) that can protect their target from being attacked by the immune system.

The engineered CAR Treg cells could fight autoimmune disease caused by excessive immune responses against the patient's own body. The potential applications range from transplant rejection to multiple sclerosis and lupus, for which there are few effective treatment options for advanced cases (Rodríguez Fernández, 2018).

The use of CAR T cells could generate significant benefits to people suffering from autoimmune conditions, which affect 5 percent of Australians and are more common than cancer or heart disease. There are over 100 different autoimmune diseases that affect Australians and lead to significant disability. Allergy and immune diseases have a significant cost to the individual and the community. In 2005, the cost of allergic diseases alone in Australia was estimated to be A$30 billion, comprising A$1.1 billion in direct health system expenditure, A$7.1 billion due to lost productivity and A$21.3 billion due to lost wellbeing (disability and premature death). In per capita terms, this amounts to a total cost of approximately A$7,400 per person with allergies per annum (Access Economics, 2007).

3.6.8 Harnessing cell factories for production

Synthetic biology is also contributing to medical advances through metabolic engineering (Section 3.3.3.1). Medicinal compounds formerly extracted from plant-based material may be more efficiently synthesised following redesign of metabolic pathways (Box 7). The approach may particularly enable the synthesis of small bioactive molecules, or improve their efficacy when combined with screening in model organisms. In some cases, researchers are transferring and repurposing whole gene clusters from organisms whose growth characteristics do not favour industrial applications to those long adapted to fermentation, greatly amplifying the yield of medicinal compounds. Phage λ Red/ET recombination or Transformation Assisted Recombination (TAR) employing the natural recombination proficiency of yeast, are both tools for inserting large amounts of DNA (multi-gene constructs) onto microbe chromosomes. Combining such approaches with new methods that enable the successful growth of soil bacteria in artificial culture chambers has already led to the identification of vital new antimicrobial agents such as teixobactin, with further progress anticipated (Ling et al., 2015).

3.6.8.1 New sunscreen molecules

Cyanobacteria is a largely untapped phylum that produces a multitude of biologically active molecules. However, its production is limited by slow growth, low production and our inability to genetically manipulate the organism. Synthetic biology is being used to express the biosynthesis genes of Cyanobacteria in *E. coli* and generate gene knockouts to characterise the biosynthetic process (Liu et al. 2017). For example, by screening microbial cultures, environmental DNA libraries and accessible databases, gene clusters involved in sunscreen biosynthesis are identified and expressed in the *E. coli* host. The isolated compounds are then structurally characterised and their UV absorption capacity and physico-chemical properties tested to identify those with potential industrial applications (Katoch et al. 2016).

3.6.8.2 Antiviral drugs using biopolymer bead scaffolds

A further strategy is to produce multi-biocatalyst assemblies for multi-step conversion and synthesis reactions on polymer beads similar to those described for the bovine tuberculosis (BTB) diagnostic tool in Section 3.6.2. For example, *E. coli* can be engineered to produce polymer inclusions (using a polyalkanoate synthase polymerisation enzyme from *Ralstonia eutropha*) along with both an aldolase enzyme (from *E. coli*) and an epimerase enzyme (from various Cyanobacteria). The resultant nano-particles and micro-particles can carry out the multi-step synthesis of sialic acid, which has potential anti-viral activity (Rehm, Chen & Rehm 2017).

3.6.8.3 Antibiotics

Many existing antibiotics are too complex for routine chemical synthesis. However, non-ribosomal peptide synthetases (NRPS), a class of biocatalytic enzymes that assemble proteins independently of the ribosome, can remedy the problem for the production of β-lactam antibiotics, daptomycin, teixobactin, ramoplanin and the glycopeptide antibiotics such as vancomycin. The NRPS architecture is based on a series of juxtaposed catalytic domains, each of which performs a specific role during biosynthesis. Domains are assembled into modules, each module corresponding to a single amino acid in the peptide. This modular activity particularly lends NRPS to synthetic biology approaches

for engineering. All the peptide assembly modules and ancillary proteins are expressed via recombinant over-expression, then assembled *in vitro* to reconstitute NRPS antibiotic assembly lines (Haslinger et al. 2015).

An alternative way to enable polyketide antibiotic synthesis comes from the observation that levels of acetyl-CoA, (a key metabolite of glucose metabolism) are 20-30 times higher in the yeast mitochondria than they are in the cytosol (Filipovska & Rackham 2008). This observation suggests that biosynthesis in the mitochondria might provide higher yields. To this end, entire polyketide biosynthetic pathways are being transferred to mitochondria by re-engineering the genes to include mitochondrial-targeting sequences. Following validation of both protein expression and accurate targeting, polyketide production can be assessed.

3.6.9 Current and emerging strengths in the Australian health and medical sector

Although small in scope by international standards, there are several promising areas of activity in Australia. Many of these examples are being developed within specialised and well-resourced research facilities with Good Manufacturing Practice (GMP) rated clean rooms for cellular therapeutics) and with access to leading clinical trials infrastructure. Collection of detailed medical records of subjects enrolled in clinical trials also makes international collaboration feasible, even for technologies developed overseas. Even with the limited scope of current activity at, or close to, commercial or clinical application, existing projects provide opportunities for economic growth and well-being in Australia. Some examples are described in the following sections.

3.6.9.1 Activity in the health sector

Anti-microbial resistance is a major global health problem and any advances made by Australia will have global benefits and provide access to major international markets. In the area of phage based anti-microbials, the highly acclaimed medical teams at the Queen Elizabeth Hospital in Adelaide have already conducted phase 1 (first in human) clinical trials on patients suffering chronic rhinosinusitis. Regulatory approvals for clinical trials using phage-based treatments are difficult to obtain. However, Australia's streamlined approvals process, coupled with the availability of a large animal (sheep) model of the disease, gives Australia a sizeable advantage over other countries for developing and testing new anti-microbial agents.

Another largely untapped advantage for Australia in antibiotics discovery comes from its unique bacteria and fungi that can produce new and potentially useful antimicrobial agents. Given Australia's excellent capabilities in characterising novel pathways for antibiotic biosynthesis, further increasing its capability for sequencing bacterial and fungal genomes from the Australian environment represents a major opportunity. Producing new anti-microbial agents is an area where the products of synthetic biology have significant commercial opportunities; for example, producing cheaper anti-fungal agents for the treatment of immunosuppressed cancer patients (typically costing around A$100,000 per course of treatment) would help meet a large unmet clinical need and save public money, while at the same time opening new commercial opportunities.

Cellular therapeutics based on the immune system and redesigned antibodies underpin an enormous international high-tech industry with applications in cancer, neuro-degeneration, joint diseases (such

as rheumatoid arthritis) and other severe inflammatory diseases. Australia has already made significant contributions in CAR T cell technology and boasts expertise in GMP cell production as well as in navigating the relevant regulatory approval processes both locally and in the US. Australia is well placed to provide GMP-grade therapeutics into the rapidly expanding US consumer market for medicinal products. The development of new targets for cancer immune therapy by improving chimeric antigen receptor design is ongoing in several Australian laboratories, especially in Melbourne and Brisbane. Major new areas of interest include applying CAR T approaches to poor outcome paediatric cancers such as neuroblastoma, other germ cell tumours and brain cancers (an initiative already partly funded through the Federal Zero Childhood Cancer Initiative). Other applications include the treatment of common solid tumours in adults (lung, colorectal, pancreas) which have an enormous unmet clinical need.

One additional area of strength for Australia is in developing synthetic antibodies that have been designed to carry drugs or other chemicals to specifically targeted tissues within the body. Examples include work underway at Austin Health and the Olivia Newton-John Cancer Centre in Melbourne to target drugs active against brain cancers and efforts to target biochemicals that can be metabolised by the tissue and detected by metabolic imaging. Some approaches can have both diagnostic and therapeutic applications, such as the work at the Peter MacCallum Cancer Centre in Melbourne to synthesise radioactively labelled (^{177}Lu) parts of a protein that is only found in the prostaten and use it to simultaneously define the extent of metastatic spread of prostate cancer while also deliver local radiation for therapeutic effect.

3.6.9.2 Opportunities, challenges and constraints

Health and medical products arising from synthetic biology are likely to have a large global market and Australia is well positioned to capture significant benefit. International engagement will become increasingly important as collaborative research in synthetic biology becomes more global. Strengthening existing and developing new collaborative partnerships with local and international research groups alongside involvement in global research-industry networks will contribute to keeping Australia's synthetic biology research programs at the forefront.

The linkage of disciplines across disparate research fields can cause uncertainty about which funding agency is most appropriate to support a given research proposal pertinent to a medical application. In the US, there are at least ten government agencies funding synthetic biology activities due to the lack of a coordinated funding mechanism (Si & Zhao 2016). In Australia, synthetic biology project proposals may not align with the funding guidelines of major agencies, as the multidisciplinary research focus may not meet the criteria of programs closely enough. A welcomed combined approach from the NHMRC and ARC occurred most recently under the Boosting Dementia Research Initiative in 2015.

Combining Australia's established strengths in materials engineering with synthetic biology could have substantial benefits. Learning how to control the ways in which proteins interact with synthetic materials can significantly optimise the activity of the hybrid materials, while reducing the cost of manufacture. There are several small to medium biotechnology companies (e.g. Starpharma, Universal Biosensors) that have an interest in applying synthetic biology to their materials, and

partnership with universities and research institutes should be highly advantageous for companies such as these.

The field of diagnostics and biosensors holds particular potential for industry collaboration in Australia. There are also significant opportunities for Australia to develop the enabling tools for synthetic biology and to develop heterologous microbial sources to produce naturally occurring bio-active metabolites through photosynthesis or by other means.

3.6.10 Economic benefits of health and medical synthetic biology

In health and medicine, the benefits from the application of synthetic biology are likely to be large. They may include treatments to cure some forms of cancer and some autoimmune conditions, pharmaceuticals for the treatment of other diseases, and nutritional products such as the omega-3 long chain fatty acids that may reduce the incidence of cardiovascular disease.

Major benefits are predicted from the development of novel cellular therapeutics for cancer. As one team of researchers has noted:

> *… CAR T-cell therapy represents a potential paradigm shift in the treatment of cancer …The optimization of conditions and technologies for generating safer CAR T-cells has the potential to make CAR T-cell treatment against cancer safer and more effective*
>
> Muhammed et al, 2017

For autoimmune diseases, synthetic biology could potentially halve the A$1.1 billion direct cost in annual health system expenditure (Access Economics, 2007). The economic benefits in Australia from the successful treatment of acute lymphocytic leukaemia, assuming that the lives of the 30 percent of patients who do not respond to conventional treatment are saved, is estimated to be A$378 million annually. The increased consumption of omega-3 long chain fatty acids in Australia could lead to a reduction in cardiovascular disease. If this reduction amounted to just 10 percent of the current costs in Australia, the benefit would be A$56 million per annum.

Some of the new pharmaceuticals being produced with synthetic biology command very high prices, suggesting that there are opportunities for Australian companies to make significant returns. There are also opportunities for Australian medical research facilities to provide services to clinicians treating patients in the Asia Pacific region, where the ability to develop therapeutics based on a patient's own cancer cells or components of their immune system may be limited.

3.6.11 Prospects for synthetic biology in Australia's health and medical sector

The Australian synthetic biology community investigating medical applications is small, but ranked highly amongst leading nations. Australia has strong presence in areas highly relevant to medical innovation, including protein engineering, and boasts a growing community of synthetic biologists with expertise in natural product design and production, gene expression modulation, artificial gene construction and circuit or pathway engineering. Coupling this activity with the enormous existing capacity and excellence in medical research, particularly in fields of unmet need such as cancer, infectious disease and neuro-degeneration, should offer enormous opportunity. Facilitating closer links between the medical research and synthetic biology communities and industry partners will be important in progressing this sector.

Synthetic biology is contributing to low-volume, high-value manufacturing by harnessing the capacities of biological systems for synthesis and assembly. The field promises breakthrough solutions for global health while significantly contributing to economic growth. In ten years, advanced materials developed from synthetic biology are likely to be more common, particularly for drug delivery and diagnostic applications.

To facilitate the emergence onto the market of new healthcare products developed to address unmet clinical need, the Australian Government's Biomedical Translation Fund will assist in the translation and commercialisation of new biomedical discoveries including those arising from synthetic biology.

South-East Asia offers a special opportunity to produce and supply cellular therapeutics to the region's large population, as most countries in our region are unlikely to have the GMP-grade manufacture and technical support skills necessarily for local manufacture and quality assurance.

The regulatory environment will need to anticipate rapid advances in synthetic biology. Producing top class academic outcomes without the regulatory environment to put the findings into health practice may result in opportunities lost to international competitors who have a more agile regulatory regime. In this regard, considerable value may be added, and clinical outcomes realised more efficiently, by linking academic and industry innovations with Australia's international excellence in early phase clinical trials capability. Our highly urbanised population, supported by an accessible, high-quality and centralised health system, provides Australia with opportunities to lead clinical adoption of products arising from synthetic biology, whether they were developed at home or abroad.

CHAPTER 4
SOCIAL, ETHICAL AND LEGAL FRAMEWORKS

4.1 Introduction

Biotechnological innovation takes place in a social context, and society plays, or should play, a key role in both responsible research and the uptake of emerging technologies. Recent controversies over genetically modified (GM) products and human embryonic stem cell (hESC) research illustrate the importance of societal direction of research and innovation, and of appropriate public engagement. Regulators and policy makers will need to consult and inform public understanding, earn public confidence, and develop regulatory processes that are socially legitimate as well as scientifically rigorous in order for innovation to progress.

This chapter provides an overview of social scientific, ethical and legal research on synthetic biology.[4] The literature identifies public concerns relating to synthetic biology, gauges the degree of public understanding, and addresses ways in which social oversight and foresight can be integrated into the research and innovation process. The chapter also provides an overview of the international regulatory landscape (Section 4.5) and addresses issues raised by dual-use technologies and the IP landscape around synthetic biology (Sections 4.6 and 4.7 respectively).

4 Identified through a comprehensive literature search in Web of Science and ProQuest in September 2017.

4.2 Social and ethical issues raised by synthetic biology

The issues of concern raised by synthetic biology are not unique to the field, but are shared with the broader domain of genetic modification and biotechnology. These concerns can be grouped into three categories: the relationship between humans and nature, distributive justice, and synthetic biology's benefit or harm to humanity (following Kaebnick, Gusmano and Murray, 2014).

Synthetic biology raises the question of the appropriate relationship between humans and nature. It has been suggested that it is intrinsically ethically problematic to treat living things in a purely instrumental manner. Kaebnick, Gusmano and Murray (2014, p. 8) comment that synthetic biology is sometimes described in a way that "*sounds like the clearest case imaginable of adjusting nature to accommodate human ends*". However, as these authors recognise, the instrumental use of living beings for human ends is well-established and socially acceptable within ethical boundaries and given appropriate regulation. The capacity of synthetic biology to create novel organisms raises ethical concerns around the moral status of the entity, but many ethicists consider that these concerns are addressed not through a focus on the way an organism is made, but rather on the intrinsic properties of the organism – sentience, the capacity for pain and suffering and intelligence, for example. Here, distinctions between natural and synthetic entities may not be helpful (Douglas, Powell and Savulescu, 2013; Newson, 2015). Similar, and perhaps more salient, ethical concerns surround the domain of the beginnings of human life, the integrity of the human genome, and the potential applications of CRISPR-Cas techniques to human embryos, and to human germ-line editing (Nuffield Council on Bioethics, 2016). Such concerns are an important part of the background against which the Australian community will evaluate the acceptability of research in synthetic biology and proposals to apply that research in innovative products.

Distributive justice concerns include whether the development of these technologies will promote just or unjust distributions of power, wealth and social resources. Will IP regimes associated with synthetic biology innovation favour a small number of monopoly corporations, and will they concentrate control in the global north? Will applications favour wealthy countries over less developed, for example, biofuels contributing to the food crisis through competing land use or synthetic biology products replacing the livelihoods of developing world subsistence farmers? Will the relationship between indigenous peoples and their genetic resources be recognised and respected? Will research and development involve democratic principles of public engagement and will citizens have some say in the direction of research programs? These questions are likely to become of increasing concern as synthetic biology raises its public profile.

Synthetic biology has great potential to both aid and harm humanity. As detailed in Chapter 3, extensive beneficial applications in industry and energy, agriculture and food production, the environment, and medicine and public health may bring about tangible social benefits. However, new synthetic biology production processes may divert natural resources and land use in ways that are detrimental, and many potential applications, particularly those that would involve the release of engineered organisms into the environment, will require extensive risk assessments and cost-benefit analysis taking into account not only technical aspects, but also public and normative values (see for example Smith and Kamradt-Scott, 2014). Furthermore, the potential for synthetic biology techniques to be used in the manufacture of biological weapons, known as the dual-use dilemma, is a realistic and significant concern (Kaebnick, Gusmano and Murray, 2014).

4.3 Current extent of public understanding and engagement

This section reviews available information on public attitudes to the issues raised in Section 4.2. Both quantitative and qualitative research suggest that public awareness about synthetic biology is low. The literature on public attitudes to synthetic biology can be usefully separated into quantitative and qualitative studies, with the former primarily gauging public awareness and initial impressions and the latter attempting to more precisely model what a debate on synthetic biology might look like.

Among quantitative studies, reports from Hart Research Associates (2013a) and Eurobarometer (2010) are highly informative about public awareness and attitude towards synthetic biology in the US and the EU, respectively. The longitudinal data analysed in Hart Research Associates (2013) bring together annual US national representative survey data for the years 2008 to 2013, in which representative samples of adult respondents (N= 804 in 2013) are asked about their knowledge and attitudes towards synthetic biology. They find that awareness has been slowly but steadily increasing, with 9 percent saying they had heard a lot or a significant amount about synthetic biology in 2008, which rose to 23 percent in 2013. Asked to volunteer their open-ended understandings of synthetic biology the most common response was that it is unnatural, man-made, and artificial (31 percent), with 15 percent associating it with recreating life, cloning, or genetic manipulation. Other associations were with prosthetics, synthetic oils and material, medicines and agricultural applications. The risks and benefits of synthetic biology were most commonly considered to be equal

(40 percent), with 18 percent believing benefits will outweigh risks, 15 percent that risks will outweigh the benefits, and the remainder were unsure. When provided with more information about the science, concerns about risks increased. Most common concerns include biological weapons (28 percent), moral concerns (27 percent), human health effects (20 percent) and environmental effects (12 percent). Support is application-dependent, with just over majority support for gene drives in mosquitoes, but majority opposition towards synthetic biology fertilisers or food additives. Within the EU, Eurobarometer (2010), a general survey of attitudes to biotechnology, had a special section devoted to Synthetic Biology. Only 17 percent of respondents indicated they had heard of synthetic biology, and the majority of these were primarily concerned about its risks.

In Australia, there are few specific studies on community attitudes to synthetic biology. However, recent community attitude to biotechnology studies provide indicative knowledge, with some reference to synthetic biology. The Ipsos report on *Community Attitudes towards Emerging Technology Issues* provides some informative knowledge about general attitudes to biotechnology, but nothing specifically on synthetic biology (Ipsos Social Research Institute, 2013). The study is based on 2,000 responses, with weightings to provide a representative national sample with regard to age, gender, employment status, language spoken at home, and location. The study found that more than 80 percent were aware of the term 'biotechnology', more than 90 percent were aware of stem cell research and cloning of animals and just under 90 percent were aware of GM. Awareness of all applications increased significantly compared to 2010. However, respondents had low levels of specific knowledge: only 23 percent believed they "*know enough about [biotechnology] to explain it to a friend*". The sample were in broad agreement that new technologies are more exciting than worrying, and that science brings more benefits than harmful effects. Issues on which there was a more mixed response included the distribution of benefits of scientific progress, the appropriateness of the pace of change, and the dependence on science instead of faith. There was moderate agreement that regulations on GM are sufficiently rigorous and that producers are compliant; more confidence in regulation of medical research; low levels of awareness of the Office of the Gene Technology Regulator (OGTR), and better recognition of the Therapeutic Goods Administration (TGA).

The OGTR-commissioned reports, Community Attitudes to Gene Technology 2015 and 2017 does include specific data on synthetic biology (Office of the Gene Technology Regulator, 2015, 2017). The 2017 study tracked changes in comparison to 2015, with comparable methods and sets of questions. Both studies used a gender-balanced survey with weightings to represent the states, and rural and metropolitan locations (N= 1160 (2015), N=1255 (2017). Focus groups were convened to validate survey findings with qualitative data. The 2017 study found that general attitudes to GMOs were relatively stable compared to the 2015 study, with 13 percent of the population completely opposed to GMOs, and considerable differentiation in support depending on the application: medicine (63 percent), industry (55 percent), environment (54 percent) and food and crops (38 percent). Young respondents (under 31) and men were more in favour of GM foods than those aged 31 to 50 and women. In 2017, a high proportion of respondents were in favour of biotechnology and considered that it would improve our way of life in the future (71 percent), up from 2015

(69 percent). There was significant support for synthetic biology, with 62 percent (59 percent in 2015) stating they thought it would confer social benefit in the future. 57 percent were similarly in favour of gene editing. The survey demonstrated a high level of confidence in the regulatory environment and the quality of information about the risks and benefits of gene technology. The 2017 OGTR reports seems to paint a more encouraging picture of public understanding of the regulatory environment than the 2013 Ipsos study, but given their very different methodologies such a conclusion would be premature.

Additional qualitative studies, which provide further analyses of stakeholder knowledge and attitudes towards synthetic biology, have been undertaken internationally. Studies were predominantly located in the UK (Bhattachary, Calitz and Hunter, 2010); Germany and Austria (Kronberger, Holtz and Wagner, 2012; Starkbaum, Braun and Dabrock, 2015; Steurer, 2016); the Netherlands: (Rerimassie, 2016a, 2016b) and the US (Pauwels, 2013). The last item complements the US quantitative study previously discussed (Hart Research Associates, 2013b) with a qualitative focus group study, confirming many of the findings of the representative survey. No Australian-based qualitative research specifically concerned with synthetic biology was discovered in our review.

Qualitative studies provide insight into values that may inform participant attitudes. For example, a focus group study conducted in Germany and Austria, involving nine groups, 37 women and 32 men, with a range of educational levels and ages (18-76) used specific examples of synthetic biology innovation to gain insight into the deliberative process of non-expert citizens (Starkbaum, Braun and Dabrock, 2015). The examples were (i) anti-malarial pharmaceutical (Artemisinin) from modified yeast; (ii) insecticide from a modified virus; (iii) biofuels from modified algae, and participants were provided with scientific information about each of them. Benefits of (i) were more widely discussed than (ii) or (iii). Risks discussed included environmental hazards, noxious side-effects, inequitable distribution of benefits (i.e. antimalarial drugs) and monopolisation of financial gains. For the non-medical applications, participants questioned the need for synthetic biology to address the problems, discussing alternatives including renewable energy sources and mixed crop cultivation. Most groups agreed that the research had the potential to bring huge economic rewards, and were concerned about how benefits might be distributed, specifically that large corporations would take advantage of the Global South. Participants mainly advocated a gradual approach, sensitive to risk and to questions of distribution.

Overall, this research suggests a low but increasing awareness of synthetic biology in Europe, the UK, the US, and Australia.

4.3.1 Importance of adequate public understanding and engagement

The social science literature stresses the risks associated with not sufficiently attending to social and ethical concerns. The GM debates during the early 2000s, widely perceived to have held back research and applications and to have produced concerted social opposition and consumer disaffection, present cautionary tales regarding the consequences of poor regulation and public consultation.[5] Some researchers conclude that synthetic biology is likely to be anchored to GM in the public

5 (Gutmann, 2011; Ahteensuu, 2012; Gregorowius, Lindemann-Matthies and Huppenbauer, 2012; Kurian and Wright, 2012; Ishii and Araki, 2016; Blancke, Grunewald and De Jaeger, 2017; Capps et al., 2017).

mind, and will take a similar trajectory in public debate if there is not a serious public engagement effort (Kronberger, Holtz and Wagner, 2012).

However, it has been proposed that the emergence of synthetic biology may also present an opportunity to improve on the earlier GM debate and to refine and develop public engagement approaches (Calvert and Martin, 2009; Torgersen, 2009; Torgersen and Schmidt, 2013). Torgersen and Hampel (2012) argue that to date, in the European Union (EU) context at least, synthetic biology lacks some of the trigger events and obvious links to consumer concerns evident in the GM debates. They see the possibility that synthetic biology will be more akin to nanotechnology, to which there has been little public opposition. Furthermore, policy makers in the field have learnt the lessons of the GM debates and are more proactive regarding ethical, legal and social aspects (ELSA), and are aware of the need for greater public consultation (Torgersen and Hampel, 2012). Deplazes-Zemp et al. (2015) regard debate about synthetic biology as an opportunity for fruitful philosophical discussion about divergent conceptions of life and nature, while van Doren and Heyen (2014) view early engagement with synthetic biology as a productive opportunity to engage the public in sharing visions for the future. Marks and Russell (2015) suggest that there may be a special place for Australia in innovative forms of public engagement and technology governance: arguing that, given the small size of the commercial biotechnology sector in Australia, and the preponderance of the university sector, there may be more openness to public shaping of the direction of research.

The research reviewed in Section 4.3 suggests a degree of public openness to biotechnology innovation in Australia that is higher than parts of Europe, and broad interest in the potential applications and implications. The greatest risk to development of the synthetic biology field in Australia would be a public debate that follows the trajectory of the GM debate. Research overseas suggests that public assessment of the risk biotechnologies are substantially influenced by levels of trust in institutions and processes, as well as by perceptions of risk and benefit (Gaskell et al., 1999, 2000; Allum, 2007). Hence policy makers, regulators and social scientists need to proactively engage the community and different interest groups to develop dialogue and build consensus on both benefits and risks and on the regulation of the field (Torgersen, 2009; Gregorowius, Lindemann-Matthies and Huppenbauer, 2012; Mackenzie, 2013; Torgersen and Schmidt, 2013; Bogner and Torgersen, 2015). The survey and focus group literatures discussed suggest very strongly that public evaluation of Synthetic Biology may initially be anchored in GM concerns, along with other controversial biotechnologies like cloning. However, it also suggests that evaluation tends to be case by case, with more supportive attitudes evident where a clear public good benefit can be discerned. A major failing of the GM crops issue was post-facto rationalisation and regulation, and a sense among the public that the benefits were commercial and at the expense of consumers concerned about food safety and environmental impact (Hess et al., 2016). The use of synthetic biology hence needs to involve public participation not in the *implications* of completed research but in the *purpose and public good possibilities* of research as it is being formulated (Calvert and Martin, 2009). To put it another way, synthetic biology as a field will find more pathways to socially acceptable innovation if it develops methods for upstream public collaboration and co-production, rather than post-facto deliberation. This kind of approach must always be open to the possibility that public

collaboration may result in the legitimate rejection of particular forms of research, if they are deemed incompatible with public good.

If public engagement in ethics, values and democratic governance are to be included in the synthetic biology field, the social science literature suggests that the most effective approach will be to embed ethical, legal and social aspects research in synthetic biology research teams and funding programs. This approach is well established in the EU funding mechanism through the Horizon 2020 *Science with and for Society* work program and the Responsible Research and Innovation (RRI) framework (Box 21). Again, this approach learns the lessons of the GM crops debate, ensuring that matters of ethics, values and public governance be intrinsic elements in the innovation process (Calvert and Martin, 2009). In the UK, seven dedicated synthetic biology research centres established as part of the 2012 Synthetic Biology Roadmap include research into ethical, legal and social aspects of their work, with embedded Responsible Research and Innovation framework goals, as do smaller centres and teams throughout the country (Synthetic Biology Leadership Council, 2016).

RRI has been adopted by CSIRO as its preferred approach to the interface between new technologies and societies. An initial investment of A$3.5 million in RRI work forms part of CSIRO's investment in Future Science Platforms, including the Synthetic Biology Future Science Platform.

Box 21: Responsible research and innovation (RRI)

RRI is an approach to the application of new technologies now in wide use in the European and UK research landscape. It constitutes a major platform of European Commission policy and has been adopted by research funding councils in the UK and Europe. RRI involves the consideration of the social, legal, cultural and ethical risks and benefits of innovation, as well as technical risks and benefits. It is based on the presumption that scientific knowledge and technical progress are co-produced with social agents and institutions. The *Rome Declaration on Responsible Research and Innovation in Europe* (2014) defines RRI as "*the on-going process of aligning research and innovation to the values, needs and expectations of society. ... RRI requires that all stakeholders including civil society are responsive to each other and take shared responsibility for the processes and outcomes of research and innovation*". The Declaration advocates the need for a diversity of viewpoints and interests in the framing of research agendas and questions, as well as the regulation of new technologies, and the necessity to aim scientific research towards the public good. Like earlier approaches to managing the interface between science and society, RRI stresses the need for democratic oversight and governance, but it has a distinctive emphasis on upstream engagement. That is, on social engagement and steerage at the earliest stages of research and development, rather than the downstream engagement that focuses on the regulation of already developed products and processes (Guston et al., 2014). Owen and colleagues (2012) note that RRI requires deliberation "*not only on the uncertain products of science and innovation – products which in the fullness of time we have been asked in the past as a society to accept or reject in the face of norms and values – but on the very purposes of science and innovation itself, before the innovation journey has begun*" (p. 754). In this regard, RRI aspires to a greater degree of social foresight and embedding than earlier approaches to social engagement.

4.4 Current regulatory regimes

The majority of existing regulation applicable to the assessment and management of risks presented by gene technology and GMOs will also be relevant to synthetic biology. As earlier chapters have established, the division between synthetic biology and earlier genetic technologies is fluid, as are the challenges they pose to regulators. However, synthetic biology is likely to raise additional challenges. Examples might include newer gene editing technologies that cannot be detected after the fact because they need not introduce any foreign DNA into the modified organism's genome, or difficulty in finding suitable comparators to predict likely behaviour for organisms that have no equivalent in the natural world. As discussed in earlier chapters, if synthetic biology constructs are intended to be used outside contained facilities, for example in bioremediation or targeting pest species with a gene-drive, evolutionary and ecological modelling will be a key aspect of identifying and assessing potential risks. At present, the fields of evolutionary biology and ecology are not adequately integrated with biotechnology risk assessment (Antonovics, 2016). It is also widely recognised that the modularisation of biological systems will reduce technical proficiency and infrastructure requirements, enabling users outside of researchers in academic institutions and industry to access and apply some synthetic biology techniques ('biohacking').

Several countries, including Australia, are actively reviewing whether and how they will deal with emerging gene technologies that are likely to have application in synthetic biology (such as the CRISPR-Cas editing systems), their modifications may range from making small, precise changes that are indistinguishable from natural variability through to rapid genetic change in whole populations via gene drives (Section 4.5.2).

The following sub-sections compare existing regulatory frameworks on several distinct axes: process-based versus product-based; promotional versus permissive versus precautionary versus preventive; narrow versus broad assessment; and consumer right-to-know. They highlight key issues and choices that will confront regulatory regimes designed specifically for synthetic biology.

4.4.1 Process-based vs product-based

A fundamental distinction between regulatory systems concerns whether oversight is triggered by the techniques (process) used to create a product or by the characteristics of the resulting product. For example, the EU and many other countries including Australia have process-based systems, based on a classification of the techniques used to create products. Canada has a product-based regulatory system, where all novel products are subject to regulation regardless of the techniques used to introduce changes. The US has a hybrid system where the use of gene technology is regulated via a coordinated framework that includes legislation that controls the use of products, such a pest control agents, foods and therapeutics.

Product-based regulation has the *prima facie* advantage that the underlying intention of legislation will not be compromised by subsequent technological developments. However, process-based regulation can address this issue by refining the definitions of the technologies that trigger regulation. By incorporating provisions for appropriate exemptions based on accumulated experience with techniques and a history of safe use both systems are able to avoid over-regulation.

4.4.2 Promotional vs permissive vs precautionary

Regulatory regimes differ as to whether their primary intention is to ameliorate risk or to encourage the uptake of new technologies. Where both aims are present, as is usually the case, the balance between them can be affected by several aspects of the regime: risk can be assessed as acceptable or not without reference to benefits, or it can be assessed as proportional or not to the benefit of the new technology. The requirement to generate data for risk assessment can be imposed on the users seeking approval of the new technology, or it can be borne by government and either adequately resourced or under-resourced.

A 'precautionary' regulatory regime emphasises the need to avoid harm, even when uncertainty exists about whether harm will eventuate. Several interpretations of the precautionary principle or precautionary approach, exist in the academic literature and in the legislation of different jurisdictions. One version of precaution that gains recognition in Australia's gene technology legislation is that action to prevent major harms, particularly to the environment, should not be delayed because of scientific uncertainty. However, in the stronger form which has figured in earlier public debates about biotechnology precaution requires that actions which *might* cause major harm must demonstrate that they *will not* cause such harms. This places a high bar in the way of the introduction of new technology. Because of this, the endorsement of such a strong interpretation carries the risk that the precautionary principle will be applied selectively, in high-profile cases, rather than as part of a transparent and consistent approach to regulation. In practice, jurisdictions that have endorsed the precautionary principle have adopted an interpretation more compatible with conventional approaches to risk assessment (Thompson, 2011, pp. 92-100). Such approaches combine the idea that uncertainty should not be an excuse for inaction with the recognition that benefits as well as risks should be considered when evaluating new technologies.

4.4.3 Narrow vs broad assessment

The considerations to be assessed when deciding the regulatory treatment of a new technology may be restricted to human health and biosafety, or may include a range of other issues. In Europe for example, as of 2015, whilst the European Commission may regulate cultivation of a GMO based on its scientific risk assessment, individual member states may choose to ban cultivation in some or all or their territory for a range of reasons not limited to the safety of the GMO. A similar situation exists in Australia where the Gene Technology Regulator is required to evaluate risks to the safety of people and the environment in making regulatory decisions, but the cultivation of genetically modified crops is prohibited in some states by legislation that is based on market considerations. In some jurisdictions, such as New Zealand, cultural issues, including those specific to indigenous populations, must be considered as part of the assessment process. Some international regulatory regimes have attempted to add considerations of benefit sharing and distributive justice to the process by which new technologies are assessed.

4.4.4 Consumer right-to-know

Regulators must balance the right-to-know of consumers and citizens with the risk of implicitly suggesting (e.g. through labelling) that the products of biotechnology are less safe than their conventional counterparts, with the GM label effectively appearing to consumers as a product warning. EU

regulations favour the consumer's right-to-know with mandatory labelling of GMOs, whereas Canada has opted for voluntary GMO-free certification. In Australia, Food Standards Australia New Zealand (FSANZ) requires that GM foods and ingredients (including food additives and processing aids) that contain novel DNA or novel protein to be labelled with the words 'genetically modified'.

A strong interpretation of the public right-to-know recognises that there is such a right even when there is no evidence of risks to human health or the environment. Similar considerations apply to the notification of field trials of GM products: notification may be required simply on the grounds that the public have right-to-know rather than as a consequence of assessed risks to human health or biosafety. The OGTR maintains an interactive map on its website showing locations of sites where field trials are underway or subject to post-harvest monitoring.

4.5 International regulatory landscape

This Section briefly summarises some of the different international approaches and relates them to the axes just outlined. The different approaches to these issues seen around the world highlight issues in harmonising with other governments, particularly with respect to market access for export products, which is of importance to Australia.

4.5.1 International conventions and agreements

International regulatory arrangements applicable to synthetic biology include those related to trade, conservation, and biosecurity. International trade-related regulatory arrangements (such as the World Trade Organization (WTO)) are understandably product-based and promotional. The overarching policy of regulation is to facilitate trade in the products to new biotechnology.

International conservation-related regulatory arrangements such as the Convention on Biological Diversity (CBD) tend to the precautionary end of the spectrum and take a broad view of the considerations to be assessed. Issues of distributive justice and of indigenous rights in genetic resources are explicitly recognised in some regulations of this type, the Nagoya Protocol on Access and Benefit Sharing to the CDB being a notable example. Signing and ratification of international regulatory agreements of this type has been patchy.

International biosecurity regulatory arrangements (such as the Biological and Toxin Weapons Convention) provide a mechanism for international cooperation regarding dual-use issues in the context of research oversight. The convention prohibits the development, production, stockpiling and transfer of biological weapons, or the means of their delivery. See Appendix E for an overview of the international regulatory frameworks applicable to synthetic biology.

4.5.2 Country-specific regulation

European Union

EU regulatory arrangements are complex. They appear primarily process-based, precautionary, and with greater breadth of considerations, and strong public right-to-know compared to some other jurisdictions. The European Food Safety Authority plays a central role in providing science-based risk assessments. However, the European Parliament has provided considerable latitude to member states for decision making within their own jurisdictions. Commercial cultivation of GMOs is limited, with what some

have described as a *de-facto* moratorium on approval of GMOs for cultivation (Papademetriou, 2014); there is a zero-tolerance policy on presence of unapproved GMOs in imports (USDA Foreign Agricultural Service and Salmon, 2016).

While the European Court of Justice is yet to rule on a formal opinion provided by its Advocate General in January 2018 that the EU Directive on GMOs should not apply when gene editing technologies are used to make changes comparable to those achievable by mutagenesis, which is exempt, existing regulations seem likely to cover emerging products of synthetic biology in the near term (Buhk, 2014; Court of Justice of the European Union, 2018).

United States

Regulation is both product-based and process-based. It is implemented through the Coordinated Framework for the Regulation of Biotechnology (Office of Science and Technology Policy, 1986) according to which three agencies are jointly responsibly for the regulation of genetically engineered products: the United States Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS); the Environmental Protection Agency (EPA) the Food and Drug Administration (FDA). The emphasis of regulation is on assessment of risks to human health and biosafety, in keeping with the historic mission of these agencies. There has been concern that "the jurisdictions of the EPA, FDA and USDA may leave gaps or redundancies" (The National Academies of Sciences Engineering and Medicine, 2017) and the 2017 update to the Coordinated Framework provides a clarification of their various roles (Environmental Protection Agency, Food & Drug Administration and US Department of Agriculture, 2017).

The framework creates the potential for a divergence in approach. During 2017 the FDA proposed to regulate any animal altered using gene editing as a new drug (US Department of Health and Human Services, 2017). In contrast, the USDA-APHIS proposed rule to revise the agency's biotechnology regulations with regard to modern biotechnologies that would have effectively exempted some gene edited crops from regulatory oversight (US Department of Agriculture, 2017a). This led to a call from US lawmakers for a consistent approach to federal regulation of biotechnology (Dreiling, 2017). In January 2018, the USDA-APHIS withdrew its proposal and undertook to re-engage with stakeholders to determine the most effective, science-based approach (US Department of Agriculture, 2017b, 2017a).

There is some indication that the balance of regulation leans towards promotion: "*Statutes may not empower regulators to require product sponsors to share in the burden of generating information about product safety, may place the burden of proof on regulators to demonstrate that a product is unsafe before they can take action to protect the public, […] and almost all of the statutes lack adequate legal authority for post-marketing surveillance, monitoring, and continuous learning approaches.*" (The National Academies of Sciences Engineering and Medicine, 2017). There has historically been less recognition than in the EU of a public right-to-know over and above human health and biosafety considerations. The US is in the process of establishing a labelling standard for GM food under a law passed in 2016 (114th Congress of the United States, 2016).

Canada

Canada is distinctive in having an entirely product-based approach to regulation: all Novel Foods (NFs) or Plants with Novel Traits (PNTs) are subject to a requirement for pre-market notification and a safety assessment. Products of Biotechnology are regulated

under the Federal Regulatory Framework for Biotechnology 1993, which is essentially a statement that products of biotechnology will be regulated under existing regulations that cover traditional products. Canada largely follows international standards (*Codex Alimentarius*) for the safety assessment of NFs and PNTs. In this and other respects Canada seems to occupy a moderate position on the spectrum between promotion and precaution. Canada has no compulsory labelling of GMOs but has a voluntary standard for non-GMO products; it has no measures in place to deal with co-existence of GM and non-GM crops – the onus falls on organic producers to take measures to avoid contamination.

According to Canada's submission to the Convention on Biodiversity (CBD), the various authorities responsible for the oversight of the products of biotechnology see no major issues, as regards the ability to regulate products, arising from emerging biotechnologies, including synthetic biology.

New Zealand

The New Zealand approach may be characterised as process-based and as relatively precautionary, with a relatively broad view of the considerations to be assessed when compared to other jurisdictions. There is recognition of a public right-to-know over and above human health and biosafety considerations. GM techniques are used for animal and plant research in contained facilities (often by Crown Research Institutes); no GMOs are cultivated or approved for cultivation and no GM fresh produce sold. Imported food and feed (Living Modified Organisms (LMOs)) must be approved by FSANZ; presence of GMOs must be clearly labelled; applications for release of a LMO via NZ's EPA requires public notification except for indoor-contained research activities.

A High Court case and 2016 legislative amendment have clarified the status of emerging gene-editing technologies relevant to synthetic biology as regulated under the existing definition of genetically modified organisms. The amendments clarified that all organisms developed through conventional and longstanding chemical and radiation treatments do not require Hazardous Substances and New Organisms Act approval as GMOs (Smith, 2016). In late 2017 the New Zealand Royal Society convened a multidisciplinary panel to consider the social, cultural, legal and economic implication of gene editing in New Zealand that will incorporate Maori and broader cultural contexts (see Royal Society of New Zealand, 2017).

Australia

The Australian regulatory scheme is based on a process trigger that captures all dealings with genetically modified organisms and focuses on the identification and management of risks to people and the environment. It gives the Gene Technology Regulator broad powers for licensing and enforcement, including intentional releases of GMOs to the environment (both field trials and commercial scale), research in physical containment facilities and the certification of those facilities, with oversight of notifiable low-risk dealings delegated to institutional biosafety committees.

As the definition of what constitutes gene technology is contained in legislation, the scheme is quite adaptable to emerging technologies. The primary legislation provides a broad definition of gene technology and GMO, and the regulations contain lists of excluded techniques and organisms based on an established history of safe use.

The OGTR is part of an integrated, national regulatory framework that includes several product-based regulators. This includes Food Standards Australia New Zealand, which requires prior approval of all GM products intended for use in food, and in labelling of food with more than one percent GM content.

Both agencies have initiated consultative approaches to determining whether and how their legislation may need to be amended in response to the emergence of new gene editing techniques. The status of these consultations as of February 2018 is summarised in Table 3.

Table 3: Proactive response of Australian regulators to new technologies.

Technical review of Gene Technology Regulations 2001 initiated by Gene Technology Regulator to provide an interim solution while broader policy considerations associated with new technologies are progressed through statutory Scheme Review (see below)	
17/10/16 to 16/12/16	Submissions invited on a Discussion Paper canvasing four options for how new technologies could be regulated (OGTR, 2016)
30/11/17 to 21/02/18	After consideration of issues raised in submissions, current scientific understanding, potential risks, regulatory burden implications, and the policy intent of the GT Act, submissions invited on proposed amendments to the Regulations (OGTR, 2017)
	Once finalised, proposed amendments are subject to the agreement of State and Territory Governments and the usual Commonwealth regulation-making process
Third statutory review of Gene Technology scheme initiated by Legislative and Governance Forum on Gene Technology (LGFGT) to enable Scheme to accommodate continued technological developments into the future (Australian Government, 2017b)	
25/7/17 to 2/9/17	Phase 1 – Request for submissions on key issues to be addressed and review of relevant reports and reviews
6/11/17 to 15/12/17	Phase 2 – Exploration of options and possible policy solutions using input from Phase 1 through submissions to issues papers, workshops, forums, surveys, targeted meetings, market research
29/03/2018	Phase 3 – Test proposed outcomes via request for submissions on draft findings
	Potential changes to the scheme will be considered by the LGFGT and, if endorsed, would be subject to the usual Commonwealth law-making processes
Consultation initiated by Food Standards Australia New Zealand (FASNZ) to review how the Food Standards Code applies to food produced using on new technologies (FSANZ, 2018c)	
15/2/18 to 12/4/18	Comments invited on consultation paper regarding whether and how foods derived from new technologies should be captured under Standard 1.5.2 and whether definitional changes are required to improve clarity (FSANZ, 2018b)
	If FSANZ determines that the Code needs to be changed, a proposal would be developed for a separate process involving further public consultation

4.6 Regulation of dual-use technologies

As for many technological advances, synthetic biology can be used to generate economic, social and environmental benefits, but could also be deliberately misused to produce biological weapons. Examples of such dual use research – a term long used in the arena of international arms control and disarmament – include the *de novo* assembly of dangerous human and animal disease-causing agents, or enhancing the ability of such organisms to cause illness and death – known as 'gain of function' (Table 4).

To date, the ability to generate dangerous human pathogens has been the most prominent example of synthetic biology's dual use potential. In 2002 live, infectious, poliovirus was assembled from customised small DNA molecules purchased from a commercial supplier using a map of the virus genome available on the internet, and in 2005 the US Centre for Disease Control and Prevention synthesised the Spanish influenza virus responsible for the 1918-19 flu pandemic (Tucker and Zilinskas, 2006). In 2006, infectious Marburg virus, which causes haemorrhagic fever, was similarly recovered from DNA (Enterlein et al., 2006) and in January 2018 the synthesis of horsepox, a close relative of the smallpox virus was announced as *"the first complete synthesis of a poxvirus using synthetic biology approaches"* (Noyce, Lederman and Evans, 2018).

This type of work can be immensely valuable in enhancing our understanding of pathogens, their infective processes and immunological responses, and fundamental to the proactive development of defences against bioterrorism. However, understanding and engineering pathogenesis, as well as *de novo* production of infectious viruses, has potential for malicious use. In comparison with traditional genetic modification, synthetic biology approaches can extend the risk profile in two ways. Firstly, synthetic biology increases the extent of the modifications that can be achieved, including new organisms that have no equivalent in the natural world. Secondly, the modular approach to synthetic biology, where parts are understood in isolation then reassembled into new biological modules and systems to build desired functions in living cells, reduces the level of technical proficiency and infrastructure requirements, enabling users outside of academia and industry to apply the technology ('biohacking').

Table 4: Gain of function research targets.

Pathogenic characteristics	Host-pathogen interaction
Environmental stability	Species tropism (host range)
Virulence factors such as: • Endotoxins and exotoxins • Adherens • Enzyme expression (e.g. catalase, peroxidase) • Resistance to antimicrobials	Tissue tropism (routes of infection)
	Infectious dose
	Antigenic variability
	Modulation of immune response
	Transmissibility/communicability

Table derived from Kanabrocki (2017).

The risks posed by nefarious applications of synthetic biology are not the primary focus of any of the national regulatory regimes described in 4.5.2, which are primarily focussed on biosafety. The potential for malicious use necessitates the imposition of regulatory measures that, while not inconsistent with achieving *biosafety*, primarily aim to maintain *biosecurity*. These include:

- maintaining awareness of, and controlling access to, pathogens of consequence and to nucleic acid sequences of concern;
- restricting access to sensitive information about such pathogens (e.g. host range, virulence, transmissibility and resistance to medical countermeasures);
- ensuring the reliability of scientists granted access to facilities.

Governmental approaches to addressing biosecurity risks tend to comprise a combination of national and international efforts to control access to organisms of concern or information about them, largely conducted under the auspices of the Biological and Toxin Weapons Convention (BTWC).

In Australia, the Department of Health administers the Security Sensitive Biological Agents (SSBA) Regulatory Scheme, which regulates the handling of agents that the Minister for Health considers to be of security concern, with inspectors provided by the OGTR. The Defence Export Controls (DEC) within the Department of Defence is responsible for regulating the export of defence and dual-use goods and technologies. DEC's activities assist Australia to meet its obligations under the BTWC and Australia currently co-chairs the Convention's Australia Group – 43 countries that develop controls to limit international trade in weapons of mass destruction – and its New and Evolving Technologies Technical Experts Meeting.

The non-government sector, particularly scientific and industry organisations, has an important role to play in biosecurity. Since its inception the synthetic biology community has recognised the risks posed by nefarious applications of the technology and has proactively sought to address them (National Research Council, 2004; Conferees, 2006; Garfinkel, Endy, Epstein, & Friedman, 2007). The focus has been on the perceived bottlenecks for the technology, namely DNA synthesis machinery, commercial suppliers of oligonucleotides, and genome or synthetic biology foundries (Section 2.3.3.8). Public discussion of bioterrorism has emphasised the ease with which processes such as targeted DNA-insertion can be performed by individuals outside of any framework of institutional governance. However, most of these highly accessible aspects of synthetic biology are downstream of the synthesis of the novel nucleotide sequences. This remains an expensive and technically demanding process. Regulation of the creation and distribution of synthetic nucleotide sequences is the obvious first line defence against bioterrorism. DNA synthesis is an international industry, and because its products are easily moved across national borders, a purely national approach to regulation is impractical. Instead, regulatory efforts have been led by industry bodies and scientific organisations such as the Industry Association for Synthetic Biology (IASB) and International Gene Synthesis Consortium (IGSC) (Torrance and Kahl, 2013). These efforts have led to the establishment of international industry protocols for screening, recording, and potentially, reporting of orders, backed by databases of sequences of potential concern.

It is recognised, however, that additional efforts may be needed at other levels

within the synthetic biology ecosystem, namely academic institutions, individual laboratories, and individual scientists. Potential interventions at these levels include ethics education, issuing codes of conduct, strengthening institutional review arrangements (e.g. biosafety committees), and direct or indirect supervision of synthetic biology research by national governments. Recognition of scale of potential harm has led to calls for a precautionary approach to dual-use research (Kelle, 2013). The potential conflict between precaution and fostering innovation may be less than in some other regulatory domains, such as food and agriculture, but some conflict still exists. For example, it has been argued that restrictions on the publication of scientific results with potential dual-use applications could slow the progress of science (Journal Editors and Authors Group, 2003). However, there is strong support in the social science and ethics literature for a more proactive and collaborative approach to regulation at levels other than the creation and distribution of sequences (e.g. Kelle, 2013; Miller & Selgelid, 2007). In a particularly thorough analysis, Miller and Selgelid compare the strengths and weaknesses of a range of increasingly centralised regulatory regimes for dual-use biotechnology. They express severe reservations about approaches that place the full weight of ethical responsibility on individual scientists or individual institutions and suggest that an independent national regulatory authority may represent the best approach.

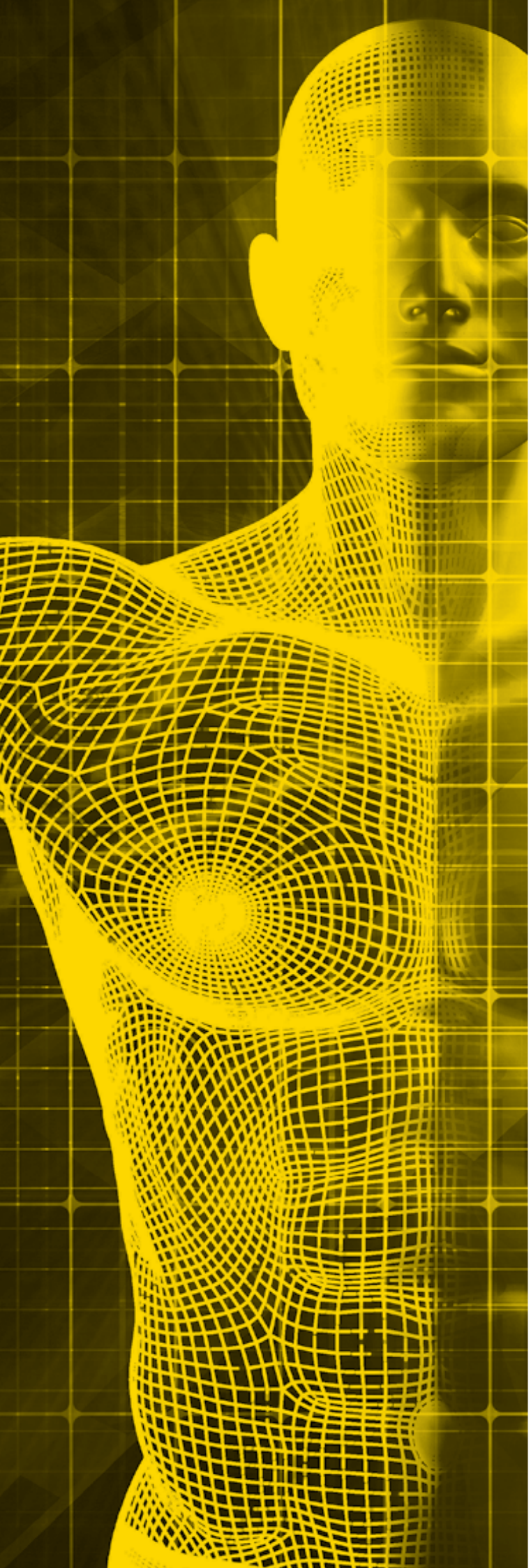
Maintaining robust and transparent regulatory arrangements for potentially dual-use synthetic biology techniques and products, and communicating the existence of these arrangements to the wider community will be important in earning and maintaining public trust.

4.7 Regulation of intellectual property

There is a good deal of similarity between the IP issues raised by synthetic biology and those raised by earlier phases of biotechnology. Patenting raises two main concerns. First, the granting of overly broad patents for basic technologies might be a bar to further scientific progress and industrial innovation. Second, the granting of a large number of patents in the same field to multiple applicants, any of which might be infringed by later work, has the potential to create a patent thicket of undue compliance burden on academic researchers and small start-ups.

Academic research on IP issues relating to synthetic biology has mostly focused on the US, and particularly on patent applications by the Venter Institute, many of which are related to their high-profile efforts to construct an entire synthetic genome for a bacterial cell. Data accessed from IP Australia suggests a very similar pattern of patent activity to that described in the academic literature on the US, albeit on a much smaller scale, and we tentatively assume that the conclusions of research on the US are applicable here. The consensus in the academic literature is that the patent system is working well, in the sense that overly broad patents for basic technologies are not being accepted and that there is little evidence of patent thickets obstructing research (Torrance and Kahl, 2013; McLennan, 2017).

Patents for synthetic biology constructs may be less controversial than patents sought in earlier phases of biotechnology. A central concern about patents for nucleic acid sequences has been that they seek to patent naturally occurring sequences. For example, this consideration was central to the invalidation of patents on the BRCA1 and BRCA2 sequences held by Myriad Genomics



in high-profile cases heard before the US Supreme Court in 2013 and the High Court of Australia in 2015. Synthetic biology constructs are less likely to be judged products of nature and more likely to meet patent criteria such as being new, involving an inventive step, or resulting from a method of manufacture.

Whilst synthetic biology is likely to lead to many patentable products and processes there is also considerable emphasis in the synthetic biology research community on the open source model, particularly in the development of standards, components and platforms for research (McLennan, 2012). The open-source approach has been pioneered by the Biobricks Foundation. The BioBrick Public Agreement provides researchers a means to licence use of components on open-source principles. In addition, the foundation's Open Material Transfers Agreement (OpenMTA) is one of a number of efforts to facilitate the transfer of materials between researchers (Chapter 1, Box 2).

The open-source model is associated with the effort to create technical standards and platforms to facilitate cooperation across the field. At present, despite the efforts of organisations such as the BioBricks Foundation and iGEM to encourage standardisation, activity in synthetic biology is not tightly constrained by a single set of widely adopted standards. Concern has been expressed that such an outcome could constrain future research, as well as enable it (Torrance and Kahl, 2013). Other authors have argued that nation states may need to play a role in ensuring that the synthetic biology landscape that emerges as a result of efforts towards standardisation is a genuine commons and not one that gives excessive power to individual players, as has been seen in the emergence of dominant platforms on the internet (Grewal, 2017).

4.8 Conclusions

The ethical, legal and social issues raised by synthetic biology are for the most part continuous with those realised by earlier phases of biotechnology, albeit with some original features.

Earning and maintaining public trust is an essential prerequisite for the successful development and application of synthetic biology. Such information as is available suggests a degree of public openness to biotechnology innovation in Australia that is higher than in some other jurisdictions, and broad interest in the potential applications and implications. To maintain and improve upon this situation it will be necessary to implement international best practice in Responsible Research and Innovation (Box 21). Issues of concern to society must be addressed early in the development of new technology and allowed to influence the direction of research and innovation. This approach has already been embraced by CSIRO (Section 4.3.1).

Australia is also a world-leader in the regulation of gene technology and is at the forefront of efforts to clarify where regulatory oversight is required for emerging technologies to protect the health and safety of people and the environment. This should be seen as a key comparative advantage in the future development of synthetic biology. Many aspects of the regulation of synthetic biology, such as the use of gene drives and control of access to potentially dual-use products and technologies, are transnational, necessitating active engagement with other regulators and international synthetic biology organisations.

The development of synthetic biology seems very likely to involve the development of uniform standards, components and platforms. This process appears likely to be led, as it is currently, by non-government or quasi-governmental international organisations such as the BioBricks Foundation. Australia will need to be an active participant in these organisations and processes.

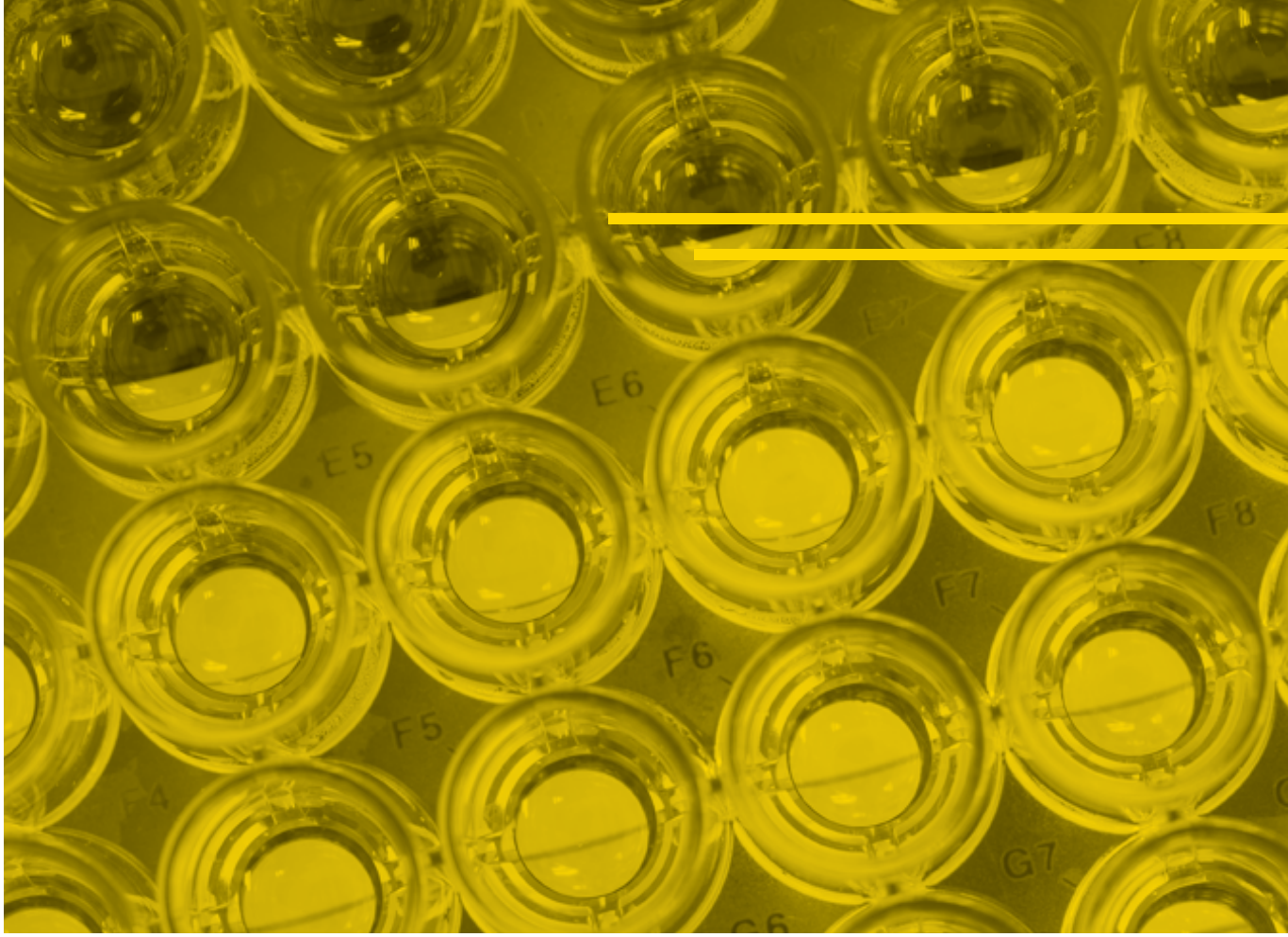
CHAPTER 5
CONCLUSIONS

The convergence of biology and engineering in the field of synthetic biology is truly transformational. These advances are leading to a range of applications that will deliver triple bottom line benefits in a wide variety of areas including industry and energy, agriculture, the environment and health and medical innovation sciences.

This report examines synthetic biology from varying perspectives: its emergence and increasing importance in mainstream research, commercial and industrial applications; Australia's contribution to the global efforts to use this technology to benefit humankind – which in an increasingly populous world is being challenged by climate change, increasing energy demand, food security, environmental degradation, invasive pests and diseases; and finally, by considering the social, ethical and regulatory frameworks that will be needed to inform and govern synthetic biology in Australia.

Catching the wave

The desire to achieve social and economic prosperity through innovation is leading to strong global competition in synthetic biology. Leading innovation nations have been quick to establish a sound research infrastructure base and support industry development to hasten progress. Australia aspires to be in the top tier of innovation nations by 2030, the realisation of which will be enhanced only if the abundant opportunities being pursued, including leadership in synthetic biology, occur within a highly supportive national innovation system.



The US and the UK are leading the world in the development of synthetic biology. Government agencies in both countries are investing heavily in the development of foundational science and technologies. With the prospect of significant commercial returns being generated through the use of synthetic biology platforms, over US$1 billion was invested globally by companies in 2016, mostly in the US. By comparison, Australia's overall synthetic biology effort is modest and developing research-industry partnerships that can generate significant economic activity over time will require a more extensive infrastructure base and more sustained investment than exists currently. Without such focused investment, Australia risks falling behind its main competitors and will be unable to capitalise fully on its extensive research capability.

Australia does not yet have an integrated approach for the coordinated advancement of synthetic biology across its higher education, research and industry sectors. Importantly, the expertise within Australia's research-intensive universities will be complemented by initiatives such as CSIRO's recently established Synthetic Biology Future Science Platform. Initiatives such as these, alongside improved collaboration with industry and other research groups, will help drive innovation in this rapidly evolving interdisciplinary field, in which Australia has strengths in many relevant disciplines.

Understanding the benefits and risks

The application of engineering principles to the design and fabrication of recombinant DNA is still evolving. Synthetic biology is based on computational design and construction of synthetic DNA sequences, something considered a revolutionary advancement in recombinant DNA research, which until recently has involved only the transfer of naturally-occurring genes from one species to another. As this field develops, new and innovative applications will arise and provide benefits to industry and across the economy.

Past advances in technology have had both positive and negative impacts, where technological breakthroughs designed to improve our lives have had unintended consequences. For this reason, it is essential that all stakeholders – policy makers, regulators, private investors, the public and the researchers themselves – understand the and ethical and social issues raised by synthetic biology. This understanding should develop in tandem with the research since that research may result in potential innovations for which adequate governance arrangements have not yet been firmly established.

Educating our future workforce, policy makers and the community

Synthetic biology is a highly interdisciplinary field and there is a need to bring together experts from both the STEM and HASS disciplines to balance the science-driven approaches of researchers with an awareness of inherent social issues. Several Australian universities are ranked highly in fields including computer science, engineering, technology, life sciences, physical sciences, law and philosophy. These disciplines may provide a strong grounding for the development of teaching in the field of synthetic biology. Improving interdisciplinary education would strengthen Australia's capacity for synthetic biology. There could be dedicated joint-degree programs and the promotion and facilitation of cross-faculty education including the physical co-location of graduate and academic staff from both STEM and HASS disciplines.

The successful development and implementation of synthetic biology will require multi-disciplinary teams comprised of discipline-specific experts in the fields of social sciences, molecular biology, bioengineering, programming, analytics and data sciences analysis, as well as experts in ethics, and cultural and communication studies, who are good team players and are able to communicate their activities in an accessible way.

Earning public confidence and trust

Synthetic biology is a promising platform to tackle many major societal challenges. Due to the increasing global exploitation of natural resources, the future production of chemicals, materials, biosensors and biofuels for use in industry and energy, agriculture and food production, environmental protection and healthcare may need to rely on synthetic biology. However, the rational design, fabrication and, in some cases, insertion of synthetic DNA into natural biological systems or their component parts, will be viewed with

concern by some people. Hence it cannot be assumed that research and innovation in synthetic biology will continue without being challenged. The need for effective public community consultation has increased significantly since the genetic engineering of crop plants caused a severe backlash in Australia and overseas in the 1990s. It is therefore vital that the scientific and research community, policy makers, industry and the public begin to cooperatively consider the ethical, social, and legal challenges posed by synthetic biology, as well as the science involved and the place of synthetic biology in society. Public awareness about synthetic biology is low, and a shared vision will not be attainable if communication channels are not open to all and if the processes for conveying knowledge and building trust are poorly developed.

As synthetic biology is still in an early phase, societal oversight is timely and potentially as important to the success of the field as the conduct of the research itself. Earning public trust and confidence will require a genuine commitment to integrating societal oversight into the research and innovation process, an approach known internationally as responsible research and innovation (RRI). Lessons learned from earlier debates (such as those over genetically modified crops) can provide valuable insights to inform the development of engagement strategies for synthetic biology.

Regulation and governance

Australia has a well-established and integrated regulatory framework for gene technology, enabling the effective assessment and management of risks to human health and environmental safety associated with genetically modified organisms. Australia's regulatory scheme for gene technology and GMOs is process-based and allows for the consideration of new technologies as they emerge, as exemplified by the current technical review of the Gene Technology Regulations (Table 3). It is important to ensure that the level of regulation is proportionate to the risks that are posed to provide a regulatory environment that also enables Australian innovation to flourish.

Ultimately, public policy will be shaped by consideration of the scientific, social, ethical, regulatory and legal aspects of synthetic biology, which, in turn, will shape the future of synthetic biology.

Future scenarios

The full potential of synthetic biology is yet to be realised. However, a clearer vision is emerging of how it may contribute solutions to some of the world's major societal challenges. A supportive innovation system that builds public confidence and trust, embeds interdisciplinary education and training within our teaching institutions, and maintains a regulatory and governance framework within which contemporary approaches to the responsible advancement of research in this emerging and powerful field are closely aligned, will contribute to building a suitable Australian framework to apply synthetic biology techniques to many of society's grand challenges. Australia is well positioned to be both an active contributor and a major beneficiary from synthetic biology's many and varied uses and applications.

APPENDIX A
DEFINING SYNTHETIC BIOLOGY

A.1 Definition of synthetic biology

A definition of synthetic biology should include the key philosophies behind the field:

- rational design
- modularity
- abstraction
- novel, unnatural

Ideally, it should also exclude related concepts as *not* synthetic biology, such as directed evolution, random mutagenesis, descriptive systems biology and tissue engineering.

Synthetic biology has been defined in multiple ways previously. Three issues stand out as unresolved or incongruous between these different definitions:

- the inclusion (or not) of cell-free systems within synthetic biology
- the degree of overlap with traditional genetic engineering (largely defined by existing legislation on genetically modified organisms)
- the relative emphasis on the process of synthetic biology (design and engineering) versus the outcome (novel biological parts)

As a field, synthetic biology sits on a continuum of genetic technology approaches, ranging from basic molecular biology-based manipulations to complex genetic circuitry and whole genomes. Where this continuum moves from classical molecular biology into synthetic biology is a matter of debate. Some of the debate focuses around the complexity of the manipulations, some around the specific approaches, and some around the outcomes. For example, single gene knockout is not generally considered to constitute synthetic biology, whereas generating a microbe that uses a synthetic gene circuit to sense its environment and control production of a heterologous product in response to a certain stimulus would be considered synthetic biology by all members of the community. Therein lies an important element: synthetic biologists are a self-identifying community. It is a young community, and the boundaries of the field are still being defined.

The most commonly used definitions of synthetic biology resemble that adopted by the UK Royal Academy of Engineering, and subsequently used in the UK Synthetic Biology Roadmap 2012, as well as the UK Synthetic Biology Strategic Plan 2016: *"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"*. Like most definitions of synthetic biology, although it encompasses both the process (design and engineering) and the outcome (biologically based parts, novel devices and systems), the focus appears to be more on the manner in which the research is done than in the goal of that research.

The European Commission (EC) defines synthetic biology as *"the application of science, technology and engineering to facilitate and accelerate the design, manufacture or modification of genetic materials in living*

organisms". The EC definition is purposely broad and covers all types of GMOs capable of reproduction, with the main objective of making sure that all new developments in the field of synthetic biology will be included and therefore covered by the existing GMO legislation. The EC definition limits the use of the term to GMOs and products that have been manufactured using GMOs, while most other definitions (including the UK Roadmap definition given above) would also cover cell-free systems that do not contain biomolecules produced in GMOs. In addition, the UK Roadmap definition does not make it clear whether GMOs that are modified in more subtle ways are considered as products of synthetic biology.

In Australia, the CSIRO Synthetic Biology Future Science Platform defined synthetic biology as follows. *"Synthetic Biology (SynBio) is the design and construction of biological parts, devices, and organisms, usually based on DNA-encoded componentry; and their application for useful purposes"*. Like many other definitions, because of an emphasis on process rather than outcome, is ambiguous as to what biological systems and devices would be considered synthetic biology.

To resolve these issues, this report uses a definition that a) does not exclude cell-free systems, and b) emphasises and defines the outcome to make it clearer what research and applications we consider to be included: *'synthetic biology is the rational design and construction of nucleic acid sequences or proteins – and novel combinations thereof, using standardised genetic parts'*.

A.2 Examples of synthetic biology

As a field, synthetic biology sits on a continuum of genetic technology approaches, ranging from basic genetic manipulations to highly complex and extensive genetic engineering. Furthermore, synthetic biology exists across multiple levels of complexity (as described in Section 1.3.1). This section provides examples of what does – and does not – constitute synthetic biology. The examples provided here have been selected to provide an overview of type, scale and range of complexity, but are by no means exhaustive with respect to these aspects.

A.2.1 Xeno-nucleic acids and non-natural amino acids

At the level of nucleic acids, some scientists are exploring chemical units that can behave as nucleic acids, but differ from those in natural DNA, so-called xeno-nucleic acids (XNA) (Anosova et al., 2016). XNA encodes information similarly to DNA, however it is less susceptible to breaking down inside cells making it highly suited for diverse biotechnological applications that could include a new generation of medicines (Morihiro, Kasahara and Obika, 2017). Similarly, modifying the cellular machinery that switches genes into making proteins also makes it possible to use non-natural building blocks in proteins (Zhang, Otting and Jackson, 2013). One of the long term aims of research in this area is to build a novel gene expression system within cells that acts in parallel to the natural system and that is optimised for the production of synthetic biology products (Filipovska and Rackham, 2008).

A.2.2 Parts design

The next scale of synthetic biology involves modification of DNA-encoded parts to improve or alter their function, or to perform entirely novel functions. Examples of parts include (i) sequences that control the production of a protein by modifying the way genes are turned on and off, (ii) a sequence encoding the protein itself, and (iii) a structural element such as a DNA scaffold

to which other components are attached. Encoded proteins are typically enzymes, which can be thought of as molecular machines but can also act as structural or control elements.

Protein engineering aims to improve or modify protein function using rational sequence changes, or to create entirely new proteins using computational design from chemically-synthesised DNA. The engineered protein may have applications by itself (e.g. as a biomaterial), may be incorporated into devices, or may be combined with other genetic parts into devices and systems for higher order biological engineering (e.g. circuit construction, Section A.2.4). In an Australian example, proteins have been engineered and integrated into a chip that can be attached to a standard smart phone to detect a range of compounds important in health diagnostics (Guo et al., 2016; Molecular Warehouse, 2016). These biosensors are similar to glucometers that monitor the daily blood glucose levels of diabetic patients. Unlike the naturally occurring proteins used in glucometers, the engineered proteins in the new devices combine parts that detect the target compounds with other parts that translate these into an electrical output. The rational engineering of novel protein arrangements such as this makes this innovative application an example of synthetic biology. Biosensors are discussed in more detail in Sections 3.5.2 and 3.6.2.

A.2.3 Device design

While parts can be used in isolation, such as in the diagnostic devices discussed in Section 3.6.2, they can also be assembled into devices of multiple DNA-encoded parts that operate as a functional unit (Figure 3). The assembly of different parts into novel combinations constitutes synthetic biology at the level of device design, although the individual parts may not themselves be engineered. The most commonly engineered devices are metabolic pathways reliant on sets of genes responsible for the synthesis of diverse chemicals from more basic starting blocks. Metabolic pathways that are already present in the target organism can be optimised, or new pathways using genes from other species can be introduced. In this way, novel functions can be added to the target organism, such as the cellular manufacture of a specific high-value product, which could have many potential applications in the production of food, biofuels and pharmaceutical compounds.

An example of biosynthetic pathway design in crop breeding is the introduction of long chain omega-3 fatty acids in high yielding cultivars of oilseed varieties such as canola. Long chain omega-3 fatty acids are thought to have important health benefits. However, a primary source of this essential fatty acid in the Australian diet – oily fish in particular – risks becoming depleted due to concerns about overfishing and other environmental problems associated with factory farming and the harvesting of fish with potentially high levels of mercury. Consequently, researchers have transferred a set of marine algae genes into canola using synthetic biology techniques to produce long chain omega-3 fatty acids (Petrie et al., 2012). This example is discussed in more detail in Section 3.4.3.

A.2.4 Genetic circuity

Genetic circuits are composed of different devices that are organised to achieve a desired outcome. A simple genetic circuit generally consists of one or more devices sensitive to input signals connected to one or more devices that produce an output, conceptually similar to the function of a transistor in an electronic circuit.

An example of genetic circuit design is an engineered biosensor. These include a device to sense the desired small molecule (e.g. a

device that produces a receptor protein that can identify molecules specifically produced by a pathogenic bacterium) connected to a signal transduction/amplification system (e.g. devices that produce a series of proteins that form a communication response that can trigger gene expression) and a device that produces a reporter protein in response to the signal (e.g. a fluorescent protein), alerting observers to the presence of the pathogen. These engineered biosensors can be deployed either *ex vivo* in cell-free systems (by producing the required proteins and arranging them in a suitable device) or *in vivo* (by encoding them on a cell's genome for expression in a living whole cell biosensor). Circuits can be connected together, for example by replacing the reporter device with devices that produce an antibiotic effective against the pathogenic bacterium, thus forming a sense-and-kill system. The latter results in an engineered (non-pathogenic) bacterial cell that can sense small molecules produced by a pathogenic bacterium and produce an antibiotic to specifically kill that pathogen in response (Jayaraman et al., 2017).

Another example of a genetic circuit is one that gives rise to a switch (St-Pierre et al., 2013; Hao, Shearwin and Dodd, 2017). This type of circuit allows a cell carrying that circuit to exist stably in one of two states of gene expression, conceptually similar to a light switch where the light is either on or off. There are several different circuit designs that can give rise to alternative states of gene expression, and many types of trigger that allow a user to flip the switch from one state of gene expression to the other. Such switches can be used as a tool for optimising the industrial scale production of medically or chemically useful compounds (themselves the product of a separate, engineered genetic circuit), for example by turning on production of a desired compound only when sufficient biomass has accumulated in the culture.

A.2.5 Genome engineering

Genome scale engineering is a top-down approach that involves constructing the entire genome of an organism from fragments of synthetic DNA. The first living organism with a fully synthetic genome was generated in 2010 by assembling a copy of the genome of the bacterium *Mycoplasma mycoides* from fragments of chemically synthesised DNA and inserting the genome into a bacterial cell emptied of its own DNA (Gibson et al., 2010). The synthetic genome was based on the naturally occurring genome sequence but contained deliberate gene deletions as well as DNA watermarks demarking it as a synthetic sequence. The project developed methods for large-scale DNA assembly and answered fundamental biological questions such as which sequences are required for the organism viability under laboratory conditions (Hutchison et al., 2016).

The long-term objective of genome engineering is to construct designer microbes with genomes optimised for useful applications such as the production of biofuels, therapeutic compounds or other valuable biomolecules. To date, genome engineering has only been performed on microbial genomes. However, the Yeast 2.0 project, an international partnership of experts from ten laboratories in the US, China, UK and Australia, aims to construct the first synthetic eukaryotic genome in the yeast *Saccharomyces cerevisiae* (Synthetic Yeast, 2017). Eukaryotic cells are much more complex than bacterial cells and contain DNA in multiple large chromosomes. Within the project, each participating laboratory is assembling one or more of the 16 yeast chromosomes required for the synthetic genome. The Australian team, based at Macquarie University, is focusing on the chromosomes XIV and XVI. The project is expected to increase our understanding of how eukaryotic genomes function and hence facilitate the construction of synthetic microorganisms.

APPENDIX B
INTERNATIONAL SYNTHETIC BIOLOGY COMPETITIONS

There are several global synthetic biology competitions. The most influential, iGEM, is considered instrumental in the establishment of synthetic biology as an internationally recognised field (OECD, 2014). These competitions help drive innovative thinking and encourage students to pursue education and careers in synthetic biology. They provide students with hands-on experience of project management, design and problem-solving skills.

B.1 iGEM

igem.org/Main_Page

Since 2004, the global synthetic biology community has sought the involvement of undergraduate students through the International Genetically Engineered Machine (iGEM) competition, which challenges teams of students from around the world to develop useful tools using synthetic biology and contribute their novel components to the open repositories. The iGEM competition is run by an independent, not-for-profit organisation dedicated to the advancement of synthetic biology, education, and the development of an open, cooperative community and friendly competition. The iGEM competition gives students (primarily university students) an opportunity to apply synthetic biology solution to real world problems. Multidisciplinary teams compete to build, design, test and measure their own designs using biological parts and standard molecular biology techniques. Parts that are produced are added to the BioBricks registry and are provided as open source parts to the synthetic biology community. The competition has increased in size from 31 students (5 teams) in 2004 to 5,500 students in 2017 (310 teams), which compete and present their work at the annual jamboree. Australia joined iGEM in 2007 with a team from University of Melbourne, one of 88 teams competing that year.

B.2 BIOMOD

biomod.net

BIOMOD is an annual biomolecular design competition for undergraduate students that has been running since 2011. The competition provides opportunities for students internationally to design projects that use RNA, DNA and proteins to build products ranging from molecular robotics to nanoscale therapeutics and autonomous robots. The competition develops entrepreneurial skills through project design and securing funding, materials and work spaces. The teams convene to present their work at the BIOMOD jamboree.

B.3 BioMaker Challenge

www.synbio.cam.ac.uk/biomakerchallenge

The BioMaker Challenge is a more recent competition hosted by the University of Cambridge, John Innes Centre or the Earlham Institute. The Challenge encourages interdisciplinary teams to interface synthetic biology approaches with electronics, 3D printing, and instrumentation to develop low-cost sensors and instruments for biology. Teams from the University of Cambridge, John Innes Centre or the Earlham Institute are provided with four months lab support to undertake the projects. There is a focus on developing cheap solutions and open source sharing of information and inventions. It is open only to teams headed by members from University of Cambridge, John Innes Centre or the Earlham Institute, but it is planned that the program will expand beyond the three organisations.

B.4 Bio-start

www.bio-start.uk

Bio-start is an annual not-for-profit competition designed to commercialise the engineering of biology through an accelerator program. It is hosted by SynbiCITE, a synthetic biology commercialisation institute based at Imperial College in London, UK. The competition is a 10-week intensive program that includes mentorship, entrepreneurial training, workshops and access to global networks and opportunities. The competition seeks applications from businesses and researchers in industrial biotechnology, clean technology, agriculture technology, healthcare, or any sector where engineering DNA is an essential component and makes use of synthetic biology. Applicants must demonstrate that they can license the relevant intellectual property and have support from their technology transfer office or employer.

APPENDIX C
SYNTHETIC BIOLOGY PUBLICATIONS BY COUNTRY

Table 5: Synthetic biology publications by country.

Country	Publications 2000-2018		Synthetic biology publications per 100,000
	Total publications	Publications in synthetic biology-associated areas	
USA	10,493,994	10,978	104.6
China	3,834,016	2,657	69.3
UK	3,092,338	2,746	88.8
Germany	2,378,810	2,816	118.4
Japan	2,008,314	1,862	92.7
France	1,625,963	1,170	72.0
Canada	1,505,382	1,054	70.0
Italy	1,423,743	787	55.3
Spain	1,175,733	824	70.1
Australia	**1,148,838**	**626**	**54.5**

Number of total and synthetic biology publications in the top ten countries by research publication output since the year 2000. Data are from ISI Web of Science 16 January 2018.

APPENDIX D
ACOLA SURVEY FOR INPUT TO THE REPORT

D.1 ACOLA survey

As part of this report, ACOLA developed a survey examining synthetic biology research underway in Australia, the national capacity for developing a strong synthetic biology industry, and future skills and training needs. Input was requested from stakeholders and researchers at Australian universities, publicly funded research organisations (including CSIRO and Health and Medical Research Institutes), and the Synthetic Biology Australasia Society. Participants were asked to comment on their own research activities, the definition of synthetic biology, gaps in synthetic biology research capabilities, education and training needs, infrastructure, and strategic areas for synthetic biology development in Australia. In total, over 100 stakeholders responded to the survey (including two international responses). This appendix provides an overview of the survey questions and data collected. All data is de-identified.

D.2 ACOLA survey design

Details of the ACOLA survey sent to stakeholders can be found below.

Australia's Synthetic Biology Capabilities and Capacity: Survey

Question 1. In the event we would like to follow up with you, please provide your full name and contact details.

Definition of Synthetic Biology

Question 2. For the purpose of this survey and the project, the working group has adopted the CSIRO Synthetic Biology Future Science Platform definition of Synthetic Biology, namely:

"Synthetic biology is the application of engineering principles to biology. It involves the design and construction of biological systems and devices, as well as the re-design of existing, natural biological systems, usually based on DNA-encoded componentry; and the application of these systems and devices for useful purposes. Components include DNA, RNA, and proteins (commonly enzymes); these are used to build genetic circuits encoding cellular machinery, which may be applied either in vivo (inside cells) or ex vivo (in test tubes or other non-cellular environments). It is a highly interdisciplinary science, drawing on biology, engineering, and computer science, as well as many other fields".

In your view, is this an appropriate and complete definition of synthetic biology? If yes, what do you like about the definition? If the definition is not appropriate, what is your alternative?

Question 3. The project will need to provide parameters of what is considered synthetic biology and what isn't. Please indicate if you agree or disagree with the following areas being considered synthetic biology.

	Strongly disagree	Disagree	Borderline	Agree	Strongly agree	Not sure
Designing proteins that don't exist in any organism	⊙	⊙	⊙	⊙	⊙	⊙
Rational re-engineering of natural proteins to give them new functions	⊙	⊙	⊙	⊙	⊙	⊙
Creation of novel genetic regulatory circuits	⊙	⊙	⊙	⊙	⊙	⊙
Transfer of entire metabolic pathways between organisms	⊙	⊙	⊙	⊙	⊙	⊙
Creation of new chromosomes or genomes	⊙	⊙	⊙	⊙	⊙	⊙
Creation of artificial cells/compartments	⊙	⊙	⊙	⊙	⊙	⊙
Transgenesis using a gene from an unrelated organism	⊙	⊙	⊙	⊙	⊙	⊙
Gene drives	⊙	⊙	⊙	⊙	⊙	⊙
CRISPR-Cas9-induced or oligonucleotide-directed mutagenesis	⊙	⊙	⊙	⊙	⊙	⊙
Cisgenesis (i.e. deliberate transfer of genes between sexually compatible organisms)	⊙	⊙	⊙	⊙	⊙	⊙
Radiation- or chemical-induced mutagenesis	⊙	⊙	⊙	⊙	⊙	⊙
Induced pluripotent stem cells	⊙	⊙	⊙	⊙	⊙	⊙
Protoplast fusion	⊙	⊙	⊙	⊙	⊙	⊙
Tissue engineering, prosthetics, pacemakers	⊙	⊙	⊙	⊙	⊙	⊙
Biosensors using natural organisms or macromolecules	⊙	⊙	⊙	⊙	⊙	⊙
Non-biological nanotech applications of nucleic acids (e.g. DNA origami, DNA-based sequence sensors)	⊙	⊙	⊙	⊙	⊙	⊙

Are there any other areas that the project should include in the definition of synthetic biology? (please specify)

Question 4. What are your research focus areas in synthetic biology? Please also provide information about your specific research within these areas.

Question 5. Are you aware of any other research groups, industry groups, companies or individuals that are actively involved in synthetic biology research and development in Australia that we should contact as part of this project? Please list them and if possible provide the name of a contact person.

Question 6. How many funded synthetic biology research projects are you currently running and what is the total grant value received for these? How many FTEs (including PhD students) do you employ in this area?

Question 7. Are there gaps in your synthetic biology focus area in terms of capabilities, skills and knowledge? If yes, what are these gaps, are they at a national or international level, and in your view how can they be addressed?

Question 8. What will be the future education and training needs to prepare students and employees for synthetic biology opportunities in Australia? Please consider all levels of education and training in your response.

Question 9. What facilities and other infrastructure do you have access to for your synthetic biology work and what is missing? Are there specific challenges obtaining the materials needed for synthetic biology research?

Question 10. Is there a need for Australia to increase its capacity in certain synthetic biology focus areas? If so, which areas and how do you think this could best be achieved?

Question 11. Who are your industry or other research collaborators (both nationally and internationally) for your synthetic biology work?

Question 12. If you have international synthetic biology collaborators, is this due to a gap (e.g. skills, knowledge or technical) in Australia? If yes, please elaborate.

Question 13. In which areas of synthetic biology does Australia excel internationally? Are there areas where Australia could lead? Please provide examples.

Question 14. In which areas of synthetic biology does Australia demonstrate weaknesses as compared internationally? Where possible, please provide examples.

Question 15. What are the opportunities for synthetic biology in Australia?

Question 16. Is there anything we have not addressed in this survey that you think is important?

D.3 Overview of survey respondents

Survey responses were received from stakeholders at universities, publicly funded research organisations, commercial entities and government agencies. A breakdown of the respondents is provided in Figure 19.

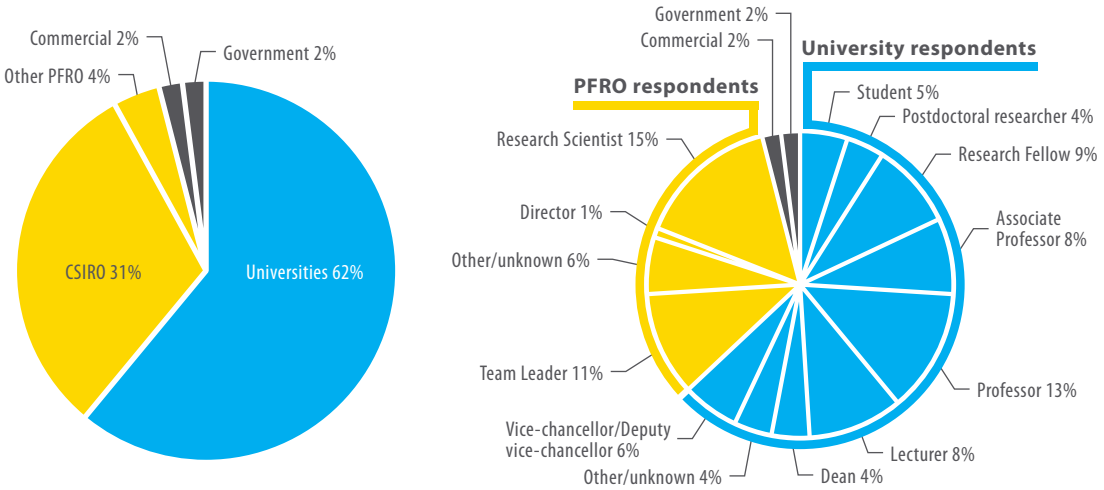


Figure 19: Breakdown of survey respondents by position at university and publicly funded research organisations (PFRO).

(A) Survey respondents by institution. The majority of survey respondents were from universities and CSIRO, with the remainder from other PFROs, commercial and government sectors. (B) Survey respondents by position at university and PFRO.

D.4 Survey results

D.4.1 Defining synthetic biology

Survey respondents were asked to comment on the definition of synthetic biology, via both an open-ended response (question 2), and in relation to specific examples (question 3). The final definition used in this report was developed in consultation with these responses.

	Strongly disagree	Disagree	Borderline	Agree	Strongly agree	Not sure	Total
Designing proteins that don't exist in any organism	1.94% (2)	2.91% (3)	4.85% (5)	26.21% (27)	**62.14% (64)**	1.94% (2)	103
Rational re-engineering of natural proteins to give them new functions	1.94% (2)	2.91% (3)	4.85% (5)	32.04% (33)	**56.31% (58)**	1.94% (2)	103
Creation of novel genetic regulatory circuits	1.92% (2)	0.00% (0)	0.96% (1)	25.00% (26)	**71.15% (74)**	0.96% (1)	104
Transfer of entire metabolic pathways between organisms	1.94% (2)	0.97% (1)	2.91% (3)	36.89% (38)	**54.37% (56)**	2.91% (3)	103
Creation of new chromosomes or genomes	2.94% (3)	0.00% (0)	3.92% (4)	25.49% (26)	**66.67% (68)**	0.98% (1)	102
Creation of artificial cells/ compartments	1.94% (2)	1.94% (2)	1.94% (2)	26.21% (27)	**66.99% (69)**	0.97% (1)	103
Transgenesis using a gene from an unrelated organism	6.80% (7)	**18.45% (19)**	**19.42% (20)**	**21.36% (22)**	**25.24% (26)**	8.74% (9)	103
Gene drives	4.90% (5)	8.82% (9)	9.80% (10)	**30.39% (31)**	**27.45% (28)**	18.63% (19)	102
CRISPR-Cas9-induced or oligonucleotide-directed mutagenesis	6.80% (7)	**23.30% (24)**	**18.45% (19)**	**21.36% (22)**	**21.36% (22)**	8.74% (9)	103
Cisgenesis (i.e. deliberate transfer of genes between sexually compatible organisms)	10.78% (11)	**26.47% (27)**	**17.65% (18)**	**19.61% (20)**	12.75% (13)	12.75% (13)	102
Radiation- or chemical-induced mutagenesis	**28.16% (29)**	**38.83% (40)**	19.42% (20)	7.77% (8)	2.91% (3)	2.91% (3)	103
Induced pluripotent stem cells	12.87% (13)	**31.68% (32)**	16.83% (17)	15.84% (16)	6.93% (7)	15.84% (16)	101
Protoplast fusion	18.45% (19)	**23.30% (24)**	15.53% (16)	13.59% (14)	5.83% (6)	**23.30% (24)**	103
Tissue engineering, prosthetics, pacemakers	**20.39% (21)**	**19.42% (20)**	**21.36% (22)**	16.50% (17)	15.53% (16)	6.80% (7)	103
Biosensors using natural organisms or macromolecules	2.94% (3)	10.78% (11)	15.69% (16)	**32.35% (33)**	**35.29% (36)**	2.94% (3)	102
Non-biological nanotech applications of nucleic acids (e.g. DNA origami, DNA-based sequence sensors)	3.88% (4)	10.68% (11)	15.53% (16)	**33.98% (35)**	**27.18% (28)**	8.74% (9)	103

D.4.2 Research focuses and areas of strength

Responses to questions 4 and 13 provide an indication of synthetic biology research activity and strengths in Australia. The most reported areas of research were: protein engineering (19 respondents), metabolic engineering (19 respondents), biosensors (11 respondents), modelling (8 respondents), synthetic genomes (5 respondents) and circuit design (4 respondents). Australian strengths identified by survey respondents were protein engineering (10 respondents), synthetic genomes (10 respondents), metabolic engineering (7 respondents), and plant synthetic biology (5 respondents).

D.4.3 Education

Responses to questions 7 and 8 suggested gaps in education or skills requirements and future training needs. Thirteen respondents identified improved interdisciplinary training as an education need or reported shortage of interdisciplinary skills as a research gap. Many of these respondents highlighted the importance of cross-faculty courses or building better links between faculties at universities. Specific joint-degree programs were suggested as a method of improving cross-faculty education. Seven respondents suggested that there should be specific synthetic biology training and courses available to students. Computational aspects including modelling, simulation and bioinformatics, is an area of perceived shortage both in Australia and overseas, with 17 survey respondents reporting an area of computational biology as either an education requirement or skill gap. Other skill areas identified as education requirements included engineering (8 respondents), molecular biology (6 respondents), biochemistry (6 respondents), chemistry (6 respondents) and mathematics (3 respondents). The importance of integrating ethical, legal and social aspects (ELSA) aspects in synthetic biology training was also highlighted (3 respondents).

D.4.4 Infrastructure

Questions 7, 9, 10 and 12 provided details on infrastructure used for synthetic biology research, as well as infrastructure gaps and requirements. Key infrastructure used in synthetic biology included omics facilities (8 respondents), computing facilities (7 respondents), DNA synthesis (4 respondents), DNA sequencing (4 respondents), microscopy (4 respondents) and high-throughput screening platforms (3 respondents). Two infrastructure gaps were reported by several survey respondents: insufficient scale-up facilities and the absence of an Australian synthetic biology (genome) foundry.

A genome foundry was suggested as a major infrastructure in gap in Australia (8 respondents), and 4 additional respondents reported that increased automation would improve their research capacity. One respondent noted that Australia currently does not have the skills required to run a genome or synthetic biology foundry and that international expertise would need to be brought in.

Six respondents reported scale-up facilities (including biomanufacturing facilities and large-scale protein production sites) as an infrastructure gap in Australia, with some respondents reporting they go overseas to access these facilities. The importance of scale-up facilities for research translation was highlighted. Local expertise in this area was also reported as a gap.

D.4.5 Barriers to synthetic biology

Two barriers to synthetic biology research identified from the responses to questions 7, 10, 12 and 14 were ELSA of synthetic biology, as well as difficulty in the translation and commercialisation of research. Seven respondents reported ELSA as a current gap or weakness in Australian synthetic biology research. It was also reported that there is a lack of support for ELSA research, as well as a gap in expertise, both of which encouraged researchers to collaborate internationally where support for ELSA research in synthetic biology was reported to be higher. It was noted that public acceptance will be required for the effective translation of research. Australia's capacity to translate research into commercial products was noted as one of the largest barriers to synthetic biology impact (14 respondents). The need to focus on research areas that can be translated, improve industry investment and entrepreneurship, and make funding available for early stage translation of research were all highlighted in survey responses. Research translation was described as a weakness in Australia compared to overseas, and lack of industry in Australia was reported as a reason for collaborating internationally.

APPENDIX E
INTERNATIONAL REGULATORY FRAMEWORKS APPLICABLE TO SYNTHETIC BIOLOGY

International regulatory frameworks

1992 Convention on Biological Diversity (CBD) has the stated goals of (i) preservation of biological diversity, (ii) sustainable use of its components, and (iii) fair and equitable sharing of benefits arising from genetic resources. The US has not ratified this convention.

1995 World Trade Organisation Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement): requires that measures to protect human, animal and plant health be based on scientific principles and not maintained without scientific evidence (The National Academies of Sciences Engineering and Medicine, 2016).

1995 WTO Agreement on Technical Barriers to Trade (TBT Agreement) recognises the right of governments to implement standards aimed at protecting the environment, promoting national security, protecting human health and safety etc.

2000 Cartagena Protocol on Biosafety (CPB) establishes the precautionary principle for dealing with products of new biotechnologies and the principle of Advanced Informed Agreement for the transboundary movement of LMOs.[6] This Agreement would appear to require consultation between parties to the convention before the release of a gene drive. Australia has not ratified this agreement and neither has Canada.

Codex Alimentarius Commission provides (i) Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants adopted in 2003, modified in 2008); (ii) Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms (2003); and (iii) Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (adopted in 2003, modified 2011), which form the basis of many national risk-assessment procedures.

2010 Nagoya Protocol on Access and Benefit Sharing (ABS) is dedicated to the implementation of the third goal of the CBD: fair and equitable sharing of benefits arising out of the utilisation of genetic resources. The ABS does not refer to synthetic biology, but does refer to Biotechnology, defined in Article 2 of CBD as *"Any technological application that uses biological systems, living organisms, or derivatives thereof to make or modify products or processes for specific use"*. Australia has not ratified this agreement; Canada has not signed; New Zealand has not ratified.

6 *"any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology"*.

GLOSSARY

Term	Explanation
adherens	Protein complexes that occur at the junction between cells in epithelial and endothelial tissues.
adnectins	A new family of therapeutic proteins designed to bind with high affinity and specificity to therapeutically relevant targets.
aldolase	An enzyme in energy metabolism.
amino acid	A class of organic compounds that are the structural units of protein.
antigens	Molecules that are capable of inducing an immune response in an organism.
Arabidopsis thaliana	A small flowering plant that is an important model system in plant biology for the study of plant genetics, physiology, biochemistry and development.
Artemisia annua	A common wormwood (plant) native to temperate Asia.
β-lactam antibiotics	A class of broad-spectrum antibiotics that have a β-lactam ring in their molecular structure.
biomass	Organic material from plants and animals that can be used as a renewable source of energy.
bioprocesses	Biological processes. A specific process that uses complete living cells or their components (such as enzymes and cellular machinery) to obtain desired products.
biosensor	A device that uses a living organism or biological molecules, especially enzymes or antibodies, to detect the presence of chemicals.
biosynthetic pathway	The sequence of enzymatic steps in the synthesis of a specific end-product in a living organism.
CAR T cell	Chimeric antigen receptor T cells. Immune cells that have had a synthetic receptor added to make them target a certain kind of disease cell.
Cas 9	An enzyme that cuts double-stranded DNA at a specific site, guided by a specifically selected RNA sequence. It originated in bacteria and is now widely used with CRISPR for gene editing.
cell	Structural unit of an organism, enclosed in a membrane, contains genetic material and cellular machinery.
chemotaxis	The movement of an organism in response to a chemical stimulus.
chromosome	Structure in which DNA is packed inside cells.
Codex Alimentarius	International food standards, guidelines and codes of practice recognised by the World Trade Organization (WTO). They are not imposed on member countries. As a WTO member, Australia is obliged, where possible, to harmonise its domestic regulations with Codex standards such as food additives, pesticide residues and veterinary drugs.
complex traits	Traits that are influenced by more than one factor (including genetic or environmental factors).
CRISPR	Short for 'clustered regular interspaced short palindromic repeats'. A technique that allows the introduction of specific changes into the genome of an organism.

cyanobacteria	A group of photosynthetic microbes that live in most inland waters. They can have major effects on water quality and health of aquatic ecosystems.
daptomycin	A cyclic lipopeptide antibiotic used for the treatment of systemic and life-threatening infections caused by Gram-positive pathogens.
DNA	Deoxyribonucleic acid. Macromolecule that in most living organisms contains the hereditary genetic information that is passed from one generation to the next.
ecosystem	Community of organism that interact with each other and their physical environment.
enzyme	Proteins that catalyse specific biochemical reactions.
epimerase	Any enzyme that catalyses structural changes within a molecule or chemical compound.
Escherichia coli (E. Coli)	A bacterium that normally lives in the intestines of healthy animals and people. Most varieties are harmless, however some can cause serious food poisoning.
eukaryotic	A type of cell that has internal structures and compartments, such as a nucleus. It is more complex than bacterial cells and includes the cells in plants, animals and fungi.
ex vivo	Experimentation or measurements conducted on tissue or cells that have been removed from the body.
Factor Xa	Activated factor X (where factor X is a coagulation factor, a substance essential to the normal blood clotting process).
foundry	A facility that can carry out every step of the process of creating a new synthetic biological system,
gene	Unit of heredity contained in DNA (or in RNA in some viruses). A region of the genome that produces a functional RNA or protein.
gene cluster	A fragment of DNA that contains multiple genes that have related functions.
gene drive	A molecular technique that drives the preferred inheritance of a particular gene with the aim of affecting a whole population.
genetic	Relating to genes.
genetic engineering	Introducing foreign genetic material into a living organism.
genetic material	Material that stores hereditary information. In most organisms it is DNA (RNA in some viruses).
genetic modification	Modifying the genetic material of an organism. Includes genetic engineering.
genome	The entire genetic material of an organism, made out of DNA (or RNA in some viruses).
genome editing	A scientific technique for making specific changes to the DNA of a cell or organism.
genome engineering	A top-down approach that involves constructing the entire genome of an organism from fragments of synthetic DNA.
glufosinate	A broad-spectrum herbicide.
glycopeptide antibiotic	A class of antibiotics originally isolated from plant and soil bacteria with structures containing either a glycosylated cyclic or polycyclic nonribosomal peptide.
glyphosate	A broad-spectrum herbicide.
Golden Gate cloning	A method of molecular cloning that allows a researcher to directionally assemble multiple DNA fragments into a single piece in one step.

hydrolases	An enzyme that catalyses the hydrolysis of a chemical bond.
in vitro	Experimentation or measurements conducted in a controlled environment outside of a living organism (e.g. in a test tube, culture dish or other controlled experimental environment).
in vivo	Experimentation or measurements conducted within a whole, living cell or organism.
logic gate	An engineering concept, building blocks of circuits.
macromolecule	A molecule containing a very large number of atoms, such as a protein, nucleic acid, or synthetic polymer.
metabolic	Relating to metabolism; the chemical reactions that maintain life and produce specific chemical compounds in living organisms.
metabolome	The total number of metabolites present within an organism, cell, or tissue.
microbe	A very small (microscopic) living organism.
mitochondria	An intracellular structure found in eukaryotic cells that produces energy for the cell through cellular respiration.
mutagenesis	The process of introducing changes into the genetic material of an organism.
mutation	A change in the genetic material of an organism.
Mycobacterium bovis (M. bovis)	A mycobacterium usually responsible for tuberculosis in cattle. The organism is also capable of infecting other species, including humans.
Mycobacterium tuberculosis (M. tuberculosis)	A species of pathogenic bacteria that is the causative agent of tuberculosis.
natural selection	An evolutionary process by which those individuals that are better adapted to their environment produce more offspring. Over many generations this leads to an increased occurrence of those genes that confer an advantage in that environment.
nuclease	A protein that cuts nucleic acid chains.
nucleic acid	Molecule that consists of nucleotides linked together in a chain, such as in DNA or RNA.
nucleotide	Structural unit of nucleic acids (DNA and RNA).
omics	An umbrella term that includes the fields of genomics, proteomics, metabolomics, microbiomics and transcriptomics, which are united by each studying a specific kind of biological product (e.g. proteins, microbes).
oomycete	Also known as water moulds, oomycetes are a group of several hundred organisms that contain some of the most devastating pathogens of plants and animals.
oxidoreductases	A class of enzymes that catalyse oxidoreduction reactions.
phage	Short for bacteriophage. Viruses that specifically target and infect bacteria, including multi-drug resistant strains.
Phytophthora cinnamomi (P. cinnamomi)	A soil borne water mould that spreads in plant roots in warm, moist conditions. *P. cinnamomi* causes severe root rot and dieback in certain plant species.
polyhydroxyalkanoate synthase	A bacterial enzyme that produces polyesters (polyhydroalkanoates) through fermentation of sugars.
population	A community of individuals that are capable of interbreeding.
post-zygotic	Taking place after a zygote has formed (i.e. after fertilisation).
progeny	A descendant or the descendants of a person, animal or plant.

promoter	A DNA region that controls a gene's activity.
protein	A class of organic compounds made from long amino acid chains. Proteins are the structural component of body tissues such as muscle and hair, and as enzymes and antibodies.
proteome	All of the proteins within a cell or organism at a given time.
Ralstonia eutropha (R. eutropha)	A bacterium found in soil that uses organic compounds and hydrogen as sources of energy. *R. eutropha* is used for a range of industrial and biotechnology applications, such as the production of polyesters and biomolecules.
ramoplanin	An antibiotic with broad-spectrum activity against Gram-positive bacteria. Used in the treatment of gastrointestinal vancomycin-resistant enterococci (VRE) and *Clostridium difficile* infections.
R-genes	Resistance genes. A gene involved in the process of resistance to a disease, pathogen, drug etc.
RNA	Ribonucleic acid. A nucleic acid that has many roles in living cells. Contains the hereditary information in some viruses.
RNAi	RNA interference. A biological process in which an RNA molecule inhibits gene expression by neutralising targeted messenger RNA (mRNA) molecules
Saccharomyces cerevisiae (S. cerevisiae)	Commonly known as baker's or brewer's yeast, *Saccharomyces cerevisiae* is a single-celled eukaryote that is frequently used in scientific research.
Staphylococcus aureus (S. aureus)	*S. aureus*, also known as golden staph, is a Gram-positive bacterium that lives on human skin or in the nose. However, if the bacterium enters the body through a cut in the skin it can cause a range of mild to severe infections.
Strain engineering	The design and development of a microbe with particular characteristics or traits.
Streptococcus pneumoniae (S. pneumoniae)	A bacterium that is the leading cause of bacterial pneumonia and middle ear infections. It is also a contributor to bacterial meningitis.
synthetic DNA	DNA produced in a laboratory.
T cell	A type of white blood cell that is of key importance to the immune system and is at the core of adaptive immunity, the system that tailors the body's immune response to specific pathogens.
teixobactin	A new antibiotic effective against gram positive bacteria including antibiotic-resistant strains without evidence of resistance development.
thrombin	The principle enzyme of haemostasis (blood clotting).
transcriptome	All of the RNA within a cell or organism at a given time.
transgene	A gene that is taken from the genome of one organism and introduced into the genome of another organism as a result of genetic manipulation.
transgenic	Organism that contains foreign genetic material received as a result of human manipulation, and therefore contains DNA sequences that do not typically exist in nature.
vancomycin	An antibiotic used to treat bacterial infections.

ABBREVIATIONS

PDO	1,3-propanediol
ABS	access and benefit sharing
ALL	acute lymphocytic leukaemia
ARC	Australian Research Council
ATCG	advanced tools and capabilities for generalisable platforms
BBSRC	Biotechnology and Biological Sciences Research Council
BDO	1,4-butanediol
BiKES	bispecific killer engagers
BIOMOD	biomolecular design
BPA	Bioplatforms Australia
BTB	bovine tuberculosis
BTWC	Biological and Toxin Weapons Convention
CAD	computer-aided design
CAM	computer-aided manufacturing
CAR	chimeric antigen receptor
CBD	Convention on Biodiversity
CoE	Centre of Excellence
CRISPR-Cas9	clustered regularly interspaced short palindromic repeats – CRISPR associated 9
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CVD	cardiovascular disease
DBTL	design-build-test-learn
DECO	Defence Export Controls Office
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
EC	European Commission
ELSA	ethical, legal and social aspects
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FSANZ	Food Standards Australia New Zealand
GDP	gross domestic product
GM	genetic modification/genetically modified
GMO	genetically modified organism
GMP	good manufacturing practice
HASS	humanities, arts and social sciences
hESC	human embryonic stem cell
IASB	Industry Association for Synthetic Biology
Ig	immunoglobulins
iGEM	international genetically engineered machine
IGSC	International Gene Synthesis Consortium
IP	intellectual property
iPC	inducible pluripotent stem cell
ktpa	kilotonne per annum
LCPUFAs	long-chain polyunsaturated fatty acids
LGFGT	Legislative and Governance Forum on Gene Technology
LMOs	living modified organisms
MGI	McKinsey Global Institute

MHC	major histocompatibility
MIT	Massachusetts Institute of Technology
MRC	Medical Research Council (UK)
Mtpa	megatonnes per annum
NCRIS	National Collaborative Research Infrastructure Strategy
NFs	novel foods
NHMRC	National Health and Medical Research Council
NISA	National Innovation and Science Agenda
NRPS	non-ribosomal peptide synthetases
OECD	Organisation for Economic Co-operation and Development
OGTR	Office of the Gene Technology Regulator
OpenMTA	Open Materials Transfers Agreement
PFAS	per-fluoroalkyl & poly-fluoroalkyl substances
PNTs	plants with novel traits
RNA	ribonucleic acid
RNAi	RNA interference
RRI	responsible research and innovation
SBA	Synthetic Biology Australasia
SBOL	synthetic biology open language
SDN	site-directed nuclease
SSBA	security sensitive biological agents
STEM	science, technology, engineering and mathematics
SynBioCDT	Centre for Doctoral Training in Synthetic Biology
TAR	transformation assisted recombination
TB	tuberculosis
TGA	Therapeutic Goods Administration
Treg cells	regulatory T cells
USDA	United States Department of Agriculture
USDA-APHIS	United States Department of Agriculture – Animal and Plant Health Inspection Service
WTO	World Trade Organisation
XNA	xeno-nucleic acids

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EXPERT WORKING GROUP

Professor Peter Gray AO FTSE FAICD (Chair)

Professor Peter Gray was appointed the inaugural director of the Australian Institute for Bioengineering and Nanotechnology (AIBN) at the University of Queensland in 2003 and served in this role until February 2016. He is currently Professor of Bioengineering at UQ, and an Emeritus professor at Fudan University in Shanghai and the University of NSW. Previously he was Professor of Biotechnology and Director of the Bioengineering Centre at UNSW, and a Senior Principal Research Fellow at the Garvan Institute of Medical Research in Sydney.

Professor Gray has had commercial experience in the USA working for Eli Lilly and Co and for the Cetus Corporation, and has held academic positions at University College London, and at the University of California, Berkeley.

His research interests are focussed on engineering mammalian cells to produce the complex proteins called biopharmaceuticals which are gaining rapid acceptance as human therapeutics, and on developing human stem cells bioprocesses suitable for producing the larger amount of cells required for clinical application. He is involved with a number of major metabolic engineering and synthetic biology programs at AIBN-UQ, focussed on the production of a range of molecules using the technologies.

Professor Gray was one of the founders and is a past president of the Australian Biotechnology Association, AusBiotech. He is a Fellow of the Australian Academy of Technology and Engineering (ATSE) and the Australian Institute of Company Directors, and has been named as one of Australia's 100 Most Influential Engineers. He is a past president and board member of ATSE. He is a member of the Boards of Bioplatforms Australia Ltd, Biopharmaceuticals Australia Pty Ltd, ACYTE Biotechnology Pty Ltd, Engineering Conferences International (ECI) Inc, New York, and serves on a number of State and Federal Government Councils and Committees.

Dr Sue Meek AO FTSE FAICD (Deputy Chair)

Dr Sue Meek specialises in working at the interface of academe, industry, government and non-government entities to increase awareness and understanding of the economic and social implications of science and technology and to facilitate the conduct, application and commercialisation of research and development.

As Principal of Sue Meek and Associates she aims to apply over 30 years of accumulated experience in science communication, advocacy and policy development, and expertise in research administration, commercialisation and regulation to the benefit of institutions, organisations and the community.

Until July 2016 Dr Meek was the Chief Executive of the Australian Academy of Science, her prior appointments include being Australia's inaugural Gene Technology Regulator and various senior State Government positions, most recently as Executive Director of Science and Technology with the WA Department of Commerce and Trade.

Dr Meek is a Fellow of the Academy of Technology and Engineering and of the Australian Institute of Company Directors, an Officer of the Order of Australia and an Honorary Professor at the Australian National University. She is a Director of Bioplatforms Australia Ltd, and chairs the Advisory Council of the Washington-based Centre for Environmental Risk Assessment (part of the International Life Sciences Institute Research Foundation).

Professor Paul Griffiths FAHA

A philosopher of science with a focus on biology and psychology, Paul was educated at Cambridge and the Australian National University, receiving his PhD in 1989. He heads the Theory and Method in Bioscience project node of the Charles Perkins Centre, a major new initiative at Sydney focused on interdisciplinary research into obesity, diabetes and cardiovascular disease. He served as Associate Academic Director for Humanities and Social Sciences while the Centre was being established, and continues to serve on the Executive Committee as Domain Leader for Society and Environment.

Paul is a Fellow of the American Association for the Advancement of Science, the Australian Academy of the Humanities and the Royal Society of NSW. He was President of the International Society for History, Philosophy and Social Studies of Biology from 2011-13 and from 2006-12 he was a member of the Australian Health Ethics Committee of NHMRC.

Professor Ian Small FAA

Professor Ian Small's research interests into the growth and development of living organisms is largely determined by the genes they contain, but converting the genetic information into biological activity requires intermediary processes involving ribonucleic acid (RNA) and proteins that bind to and process this RNA. Professor Small aims to understand how the largest class of RNA-binding proteins in plants recognise their target RNAs and aims to develop custom-designed proteins for switching genes on or off at will. This technology will be used initially to create new hybrid cereal varieties, but holds promise for more general applications in the new field of synthetic biology, including applications in human health.

Professor Small's PhD at Edinburgh University, awarded in 1988, was followed by a career with France's National Agronomy Research Institute (INRA), where he held the Vice-Director position at the Plant Genetics and Breeding Station in Versailles and the Plant Genomics Unit in Evry. In 2005, he was awarded a WA State Premier's Research Fellowship and moved to Perth to become the Director of the ARC Centre of Excellence in Plant Energy Biology from 2006-2013 and Director of the state-funded Centre of Excellence in Computational Systems Biology from 2006-2014. He is currently an ARC Laureate Fellow and was elected to the Australian Academy of Science in 2015.

Professor Small's early work on plant mitochondrial genomes and fertility restorer genes involved in cytoplasmic male sterility contributed significantly to the development,

patenting and commercialisation of technology for male-sterile brassicas used in the breeding of elite hybrid lines—much of the canola grown globally is now produced using this technology. His research interests later evolved to take advantage of large-scale functional genomics technology and bioinformatics. He is perhaps best known for the discovery and characterisation of the pentatricopeptide repeat (PPR) family of proteins, a huge family of proteins involved in controlling gene expression in mitochondria and chloroplasts.

Professor Joe Trapani FAHMS

Professor Joseph Trapani received his medical degree in 1977 and completed physician training (FRACP) in rheumatology in 1985. His PhD (The University of Melbourne, 1986) was on the immunogenetics of HLA-associated disease, particularly B27-related arthropathy. Professor Trapani first became interested in how the immune system defends the body against viruses and cancer while working as a postdoctoral fellow at Memorial Sloan-Kettering Cancer Institute, New York, where he worked in Bo Dupont's lab. Here, Professor Trapani discovered and characterised a number of the genes and proteins used by killer lymphocytes to eliminate virus-infected cells. He found that one protein (perforin) forms pores in the target cell surface and provides access for proteases (granzymes) to enter and trigger cell death via various programmed cell death pathways. With his colleagues, Professor Trapani has since devised novel ways of harnessing the power of these killer lymphocytes (CAR T cell therapy) and adapted their use to adoptive immunotherapy for various cancers.

In the late 1990s, Professor Trapani undertook a number of seminal studies showing that focal defects in the immune system of mice resulted in a remarkable susceptibility to cancer, particularly B cell lymphoma. This work is regarded as among the first incontrovertible evidence in support of Burnet's hypothesis of 'cancer immune surveillance', first postulated in the 1950s. Trapani's lab has also identified a rare group of children with inherited defects of perforin function and shown that they are also abnormally susceptible to leukaemia.

In 2012, Professor Trapani received a $12.3 million award from the Wellcome Trust (UK) to lead a consortium of Australian and New Zealand research teams, aiming to develop a new class of immune-suppressive drugs that protect transplanted bone marrow stem cells against immune destruction mediated by the pore-forming protein, perforin. The work is now approaching clinical development.

Professor Trapani is Executive Director Cancer Research at Peter Mac, Head of the Cancer Immunology Program and Head of the Cancer Cell Death Laboratory. Professor Trapani's research interests include the immunopathology of viral and auto-immune diseases, apoptosis induction by cytotoxic lymphocytes and cancer immunotherapy. He has authored more than 310 research papers, reviews and book chapters on these topics and his work is cited >22,000 times. Professor Trapani is also a member of the Executive (Board) of Cancer Council Victoria, Chair of CCV's Medical and Scientific Committee and a member of many peer-review and advisory bodies in academia and industry.

Associate Professor Claudia Vickers

A/Professor Vickers holds dual roles as Director of the CSIRO Synthetic Biology Future Science Platform at CSIRO and Group Leader in the Australian Institute for Bioengineering and Nanotechnology at the University of Queensland (UQ). She completed her PhD in cereal crop biotechnology at CSIRO Plant Industry and UQ in 2004. She held post-doctoral and Visiting Scientist positions at Essex and Lancaster Universities in the UK 2004-2007, where she worked on abiotic stress and the metabolic regulation and physiological function of volatile isoprenoids in plants. She returned to UQ in 2007, joining the Australian Institute for Bioengineering and Nanotechnology to expand her research program into microbial metabolic engineering. Since then she has headed a group focussed on converting agricultural biomass to industrially-useful biochemicals using advanced synthetic and systems biology approaches. Target compounds sit in the isoprenoid group of natural products, and include jet fuel, plant hormones for agricultural applications, food additives (flavours, colours, etc.), fragrances, and pharmaceuticals. Since January 2017 A/Professor Vickers has held a joint appointment with the Commonwealth Science and Industry Research Organisation (CSIRO) to lead the CSIRO Synthetic Biology Future Science Platform (SynBioFSP), a $30 million research and development program aimed at expanding Australia's capability in synthetic biology. She is also on the Executive of Synthetic Biology Australia as Immediate Past President.

Professor Catherine Waldby FASSA

Professor Catherine Waldby is Director of the Research School of Social Sciences at the Australian National University, and Visiting Professor at the Department of Social Science and Medicine at King's College, London. Prior to this, she was Professorial Future Fellow in the School of Social and Political Sciences at the University of Sydney. Her researches focuses on social studies of biomedicine and the life sciences, and she is the author of fifty-five research articles and seven monographs in this area. Her recent books include *The Global Politics of Human Embryonic Stem Cell Science: Regenerative Medicine in Transition,* (with Herbert Gottweis and Brian Salter, Palgrave 2009) *Clinical Labour: Tissue donors and Research Subjects in the Global Bioeconomy* (with Melinda Cooper, Duke University Press 2014) and *The Oöcyte Economy: The Changing Meanings of Human Eggs in Fertility, Assisted Reproduction and Stem Cell Research'* Duke University Press (in press). Her work has been translated into Italian, Korean, Chinese and German.

With Nikolas Rose and Ilina Singh, she is the editor of *BioSocieties,* an interdisciplinary journal for the social studies of life sciences. She is a Fellow of the Academy of Social Sciences in Australia and a member of the History and Philosophy committee of the Academy of Science. She is also the Deans and Directors' representative on the ANU Council. She has received numerous national and international research grants for her work on stem cells, embryology, blood donation and biobanking, from the Australia Research Council, the National Health and Research Council, the UK Economic and Social Research Council, and the European Union COST and FP7 programs. Her work has had extensive policy impact in relation to the regulation of human embryonic stem cell research, stem cell treatments, biobanking and tissue donation.

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We would particularly like to thank the following people for their valuable research assistance during the project: Mischa Davenport regarding the ethical, legal and social aspects of synthetic biology; Dr Suvi Honkanen regarding synthetic biology in agriculture and food production; Professor Lars Nielsen regarding synthetic biology in energy and industry; and Dean Tyler regarding health and medical synthetic biology. We would also like to thank Rebecca Wood for undertaking valuable research and writing across multiple aspects of the report and for providing ongoing support during the project.

We gratefully acknowledge the expertise and contributions from the many experts who have helped shape and develop the report.

In particular, we acknowledge the university stakeholders, researchers and industry stakeholders who took the time to respond to the project survey and calls for input. We would also like to thank the Association of Australian Medical Research Institutes (AAMRI) and Synthetic Biology Australasia (SBA), in particular Associate Professor Oliver Rackham, for sharing the survey with their networks.

Our thanks to the Expert Working Group who put a great deal of time, effort, and insight into the report's conceptualisation and production, and also to the ACOLA Secretariat, in particular Dr Lauren Palmer and Dr Angus Henderson, who made significant contributions to supporting the Expert Working Group and managing the project.

Further information on these contributions can be found under 'evidence gathering'.

Our special thanks to CSIRO, the Department of Health and the Office of the Chief Scientist for both financial and in-kind support.

EVIDENCE GATHERING

Workshops and meetings were held across Australia during this project. Many people have contributed their time and expertise to the project through written submissions, meetings with members of the Expert Working Group and participation at workshops.

The views expressed in the report do not necessarily reflect the opinions of the people and organisations listed in the following sections.

Workshops

The ACOLA Synthetic Biology Project held four workshops:

- Initial scoping workshop: held in Sydney on 5 December 2016 to discuss the scope of the horizon scanning project;
- Second scoping workshop: held in Canberra on 27 June 2017 to initiate the project and hold discussions with key stakeholders and the Expert Working Group;
- Expert Working Group face to face meeting: held in Sydney on 29 August 2017 to discuss the report.
- Synthesis workshop: held in Melbourne on 8 February 2018 to synthesise the report.

Stakeholders consulted at workshops, teleconferences or meetings

Adam Wright
Adrian White
Alan Finkel
Alison McLennan
Anne-Marie Lansdown
Bradley Schulz
Deborah Hailstones
Erica Kneipp
Feiya Zhang
Hugh Goold
Jack Steele
Jahla Gato
Jason Tong
John Bell
Katherine Leigh
Maryanne Shoobridge
Michelle McLaughlin
Paul Bertsch
Raj Bhula
Vidya Jagadish

Survey

The project survey involved over 100 stakeholders from universities, government and industry. Due to confidentiality we are unable to list these stakeholders, however we gratefully acknowledge their important contributions to this project. Our thanks to the Association of Australian Medical Research Institutes (AAMRI) and Synthetic Biology Australasia (SBA) for sharing the survey amongst their networks.

Input papers

Synthetic Biology: Economic and Market Analysis

ACIL Allen Consulting 2018, Synthetic Biology: Economic and Market Analysis, A report for the Australian Council of Learned Academies.

Energy and Industry

Lars Nielsen, 2018, Synthetic Biology: Energy and Industry, A paper for the Australian Council of Learned Academies

PEER REVIEW PANEL

Professor Chris Easton FAA

Chris Easton is Professor of Chemistry at the Australian National University, where his research interests evolve around understanding and exploiting the chemistry of biological systems. He graduated from Flinders University and the University of Adelaide, before holding positions at Harvard University, the Australian National University, the University of Canterbury (NZ) and the University of Adelaide, then taking up his current appointment. He is the author or coauthor of over 300 papers and 45 full and provisional patent applications, has been awarded a D.Sc. from the University of Adelaide, and is the recipient of the Royal Australian Chemical Institute Birch Medal and the Archibald Ollé Prize of the Institute. He is a Fellow of the Australian Academy of Science, the Royal Society of Chemistry and the Royal Australian Chemical Institute.

Professor Richard H Furneaux FNZIC FRSNZ

As Director of the Ferrier Research Institute of Victoria University of Wellington he leads a world-renowned team of 38 research scientists and 17 PhD students. A major focus is the discovery and commercialization of 'Glycotherapeutics'—drugs and dietary supplements based upon knowledge of the role of carbohydrate molecules in biological processes. They partner nationally and internationally for biology and biochemistry. Richard is a Fellow of the Royal Society Te Apārangi, was awarded the Hector Medal in 2006 and the Thomson Award in 2012, was selected as Wellingtonian of the Year in Science & Technology in 2013 and won both the KiwiNet Supreme Award and the Research Entrepreneur Award in 2017. He has authored 194 original papers, 26 reviews or book chapters and been named as an inventor on 22 international patent families. He is the Director of Discovery Chemistry at GlycoSyn, and Director of the NZ companies Humble Bee Limited and Hardie Health Limited and a former director of Avalia immunotherapies Ltd. Richard began his career in the Chemistry Division of DSIR in 1980 after completing his PhD at Victoria University of Wellington with Professor Robin Ferrier and subsequent Post-Doctoral work with Professor Fred Shafizadeh at University of Montana, USA.

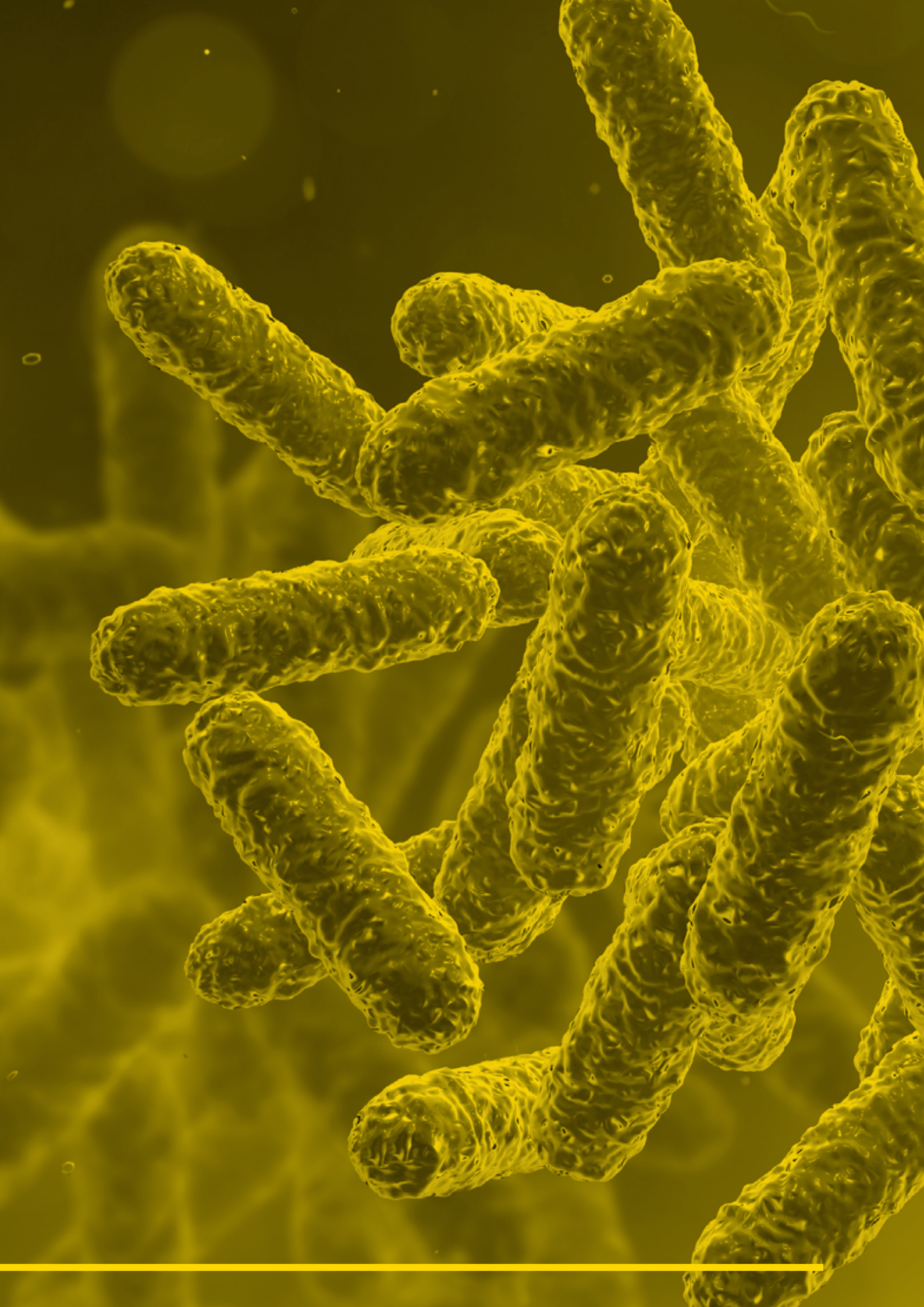
Professor Rob Sparrow

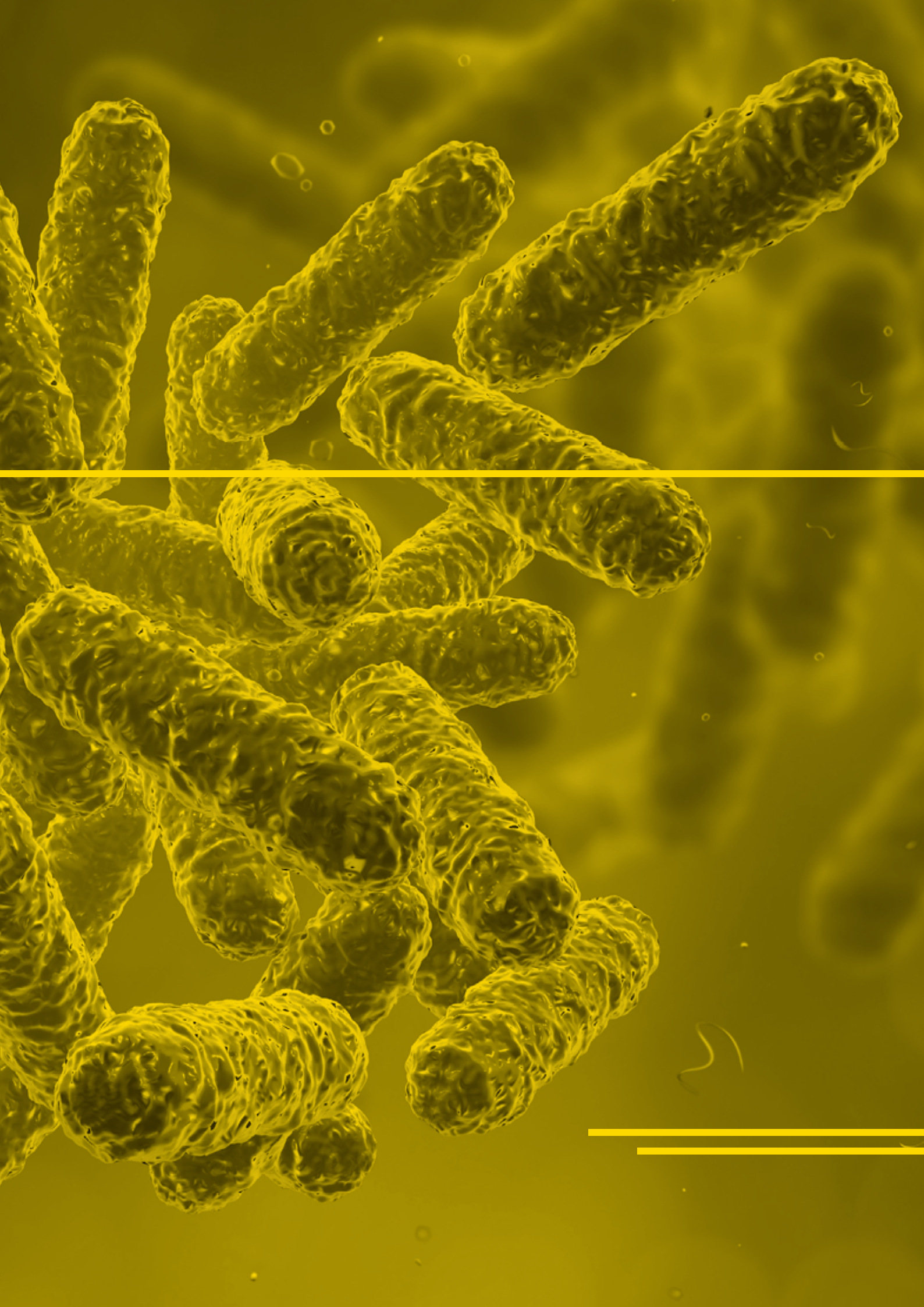
Rob Sparrow is a Professor in the Philosophy Program, a Chief Investigator in the Australian Research Council Centre of Excellence for Electromaterials Science, and an adjunct Professor in the Monash Bioethics Centre, at Monash University, where he works on ethical issues raised by new technologies. He has been an ARC Future Fellow, a Japanese Society for the Promotion of Science Visiting Fellow at Kyoto University, a Visiting Fellow in the CUHK Centre for Bioethics, in the Faculty of Medicine, at the Chinese University of Hong Kong, and a Visiting Fellow at the Centre for Biomedical Ethics, in the Yong Loo Lin School of Medicine, at the National University of Singapore. He has published widely, in both academic journals and the popular press, on the ethics of preimplantation genetic diagnosis, human cloning, artificial gametogenesis, and human enhancement.

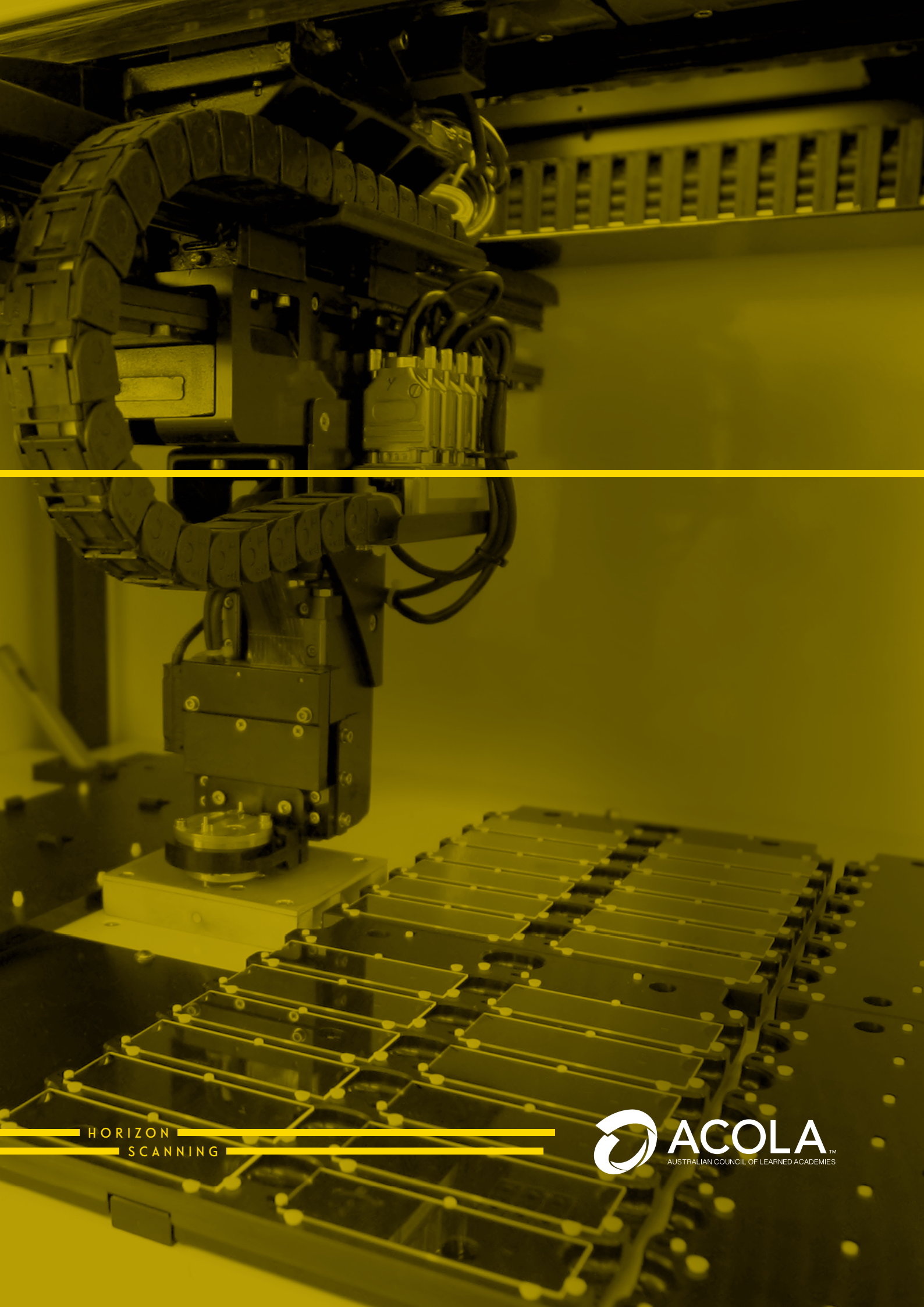
Professor Louis Waller AO FASSA

Emeritus Professor Louis Waller AO FASSA held the Sir Leo Cussen Chair of Law in Monash University from 1965 to 2000. His principal fields of teaching and research were Criminal Law and Evidence, and in the last two decades of his tenure, Law and Medicine and Forensic Medicine. He was Victorian Law Reform Commissioner in 1982 1984 and the first Chairman of the Law Reform Commission of Victoria in 1985. In 1982 he was appointed the Chairman of the Victorian IVF Committee, then Chairman of the statutory Standing Review and Advisory Committee on Infertility from 1985 to 1993, and Chairman of SRACI's successor, the Infertility Treatment Authority from 1996 until 2001. He was a member and then Chairman of the Ethics Committee of the Walter And Elliza Hall Institute from 1987 to 2001, and the first lay member and then Chair of the Appeals Committee of the Royal Australasian College of Surgeons.

He has published books, chapters and articles in both legal and medical journals.







HORIZON SCANNING

ACOLA
AUSTRALIAN COUNCIL OF LEARNED ACADEMIES