

# Macquarie Law Journal

VOLUME 15, 2015

Synthetic Biology: Legal, Social and Ethical Challenges to its Regulation and Governance



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# Macquarie Law Journal

VOLUME 15, 2015

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## EDITORS' NOTE

This themed edition of the *Macquarie Law Journal* was inspired by a workshop held by Macquarie University in December 2014 on the ethical, legal and social issues raised by synthetic biology research. The 'Ethics and Regulation of Synthetic Biology' workshop stemmed from Macquarie University's involvement in synthetic biology research and its desire to engage in a multi-disciplinary discussion of issues raised by such research. It was organised by Dr Sonia Allan of the Macquarie Law School and Professor Wendy Rogers of the Department of Philosophy, pursuant to a grant jointly received by them from the Faculty of Arts and administered by the Centre for Agency, Values and Ethics at Macquarie University. The university was honoured to have the workshop opened by Professor Mary O'Kane, the NSW Chief Scientist and Engineer, and chaired by Professor Catriona Mackenzie, Fellow of the Australian Academy of the Humanities and an Executive Board Member of the Centre for Agency, Values and Ethics.

This edition, the 15<sup>th</sup> volume of the *Macquarie Law Journal*, features a collection of very interesting and topical pieces that largely reflect discussions and presentations from that workshop. It differs from many earlier editions of the *Macquarie Law Journal* in that the pieces included are not limited to discussions of the law. Instead, the articles present a range of issues for discussion that are relevant to the ethical, legal and social dimensions of synthetic biology and beyond. All of them have possible implications that will need to be addressed by legislators, regulators and courts. Indeed, the discussion at the workshop, and the articles herein, highlight the fact that consideration of whether to regulate emerging technologies, and if so how, requires contributions from many fields and diverse stakeholders. Included therefore is discussion of perspectives from science, ethics, sociology, law, civil society, and more. It is only by taking a multi-disciplinary approach that issues raised by new technologies can be fully explored, and decisions taken about the best ways to proceed in an area that promises many benefits but also poses some risks. The contributions are ordered to reflect, firstly, the breadth and depth of issues discussed at the workshop and then some wider ranging issues to do with emerging technologies and future challenges.

We start the edition with an informative report by Sonia Allan on the proceedings of the workshop. The report includes an introduction to Macquarie University's involvement in synthetic biology research through the Synthetic Yeast (*Sc2.0*) project, a discussion of the field, and a synopsis of her presentation on the day of the workshop. In particular, it provides a summary of the following: the 'promises and perils' of synthetic biology; a discussion of various international and national regulations relevant to synthetic biology (and possible gaps); and responses to the technology, ranging from cautious support to calls for moratoria. It also provides discussion of 'soft law' regulatory approaches being adopted by some researchers involved in synthetic biology research, and specifically by all those involved in the *Sc2.0* project. The report notes that it should not be read as a stand-alone document. While introducing some of the key regulatory issues, Dr Allan's report highlights the importance of engaging with other disciplines to understand the ethical, legal and social issues raised by synthetic biology. It therefore provides the foundations for the discussion to be found in the subsequent articles and commentaries.

The report is followed by a commentary by Jane Calvert and Emma Frow on the Synthetic Yeast Project. Dr Calvert was the keynote speaker at the Macquarie University workshop. In their article 'The Synthetic Yeast Project as a Topic for Social Scientific Investigation', the authors discuss the *Sc2.0* project (and some of its precursors) in detail, identifying the technical, social and conceptual issues that they find particularly salient as researchers in Science and Technology Studies. They discuss design principles that are central to the project, and identify its preference for open intellectual property. Their article points out that

the project encourages consideration of the spatial and temporal dimensions of organisms, and discusses how the project may assist in exploring tensions between engineering and biology. This paper is an important contribution to the discourse as it provides insight into the project from a social scientist viewpoint. It has regulatory importance because it enables us to reflect upon different aspects of the emerging technology in a way that could not be done without such a perspective.

The short article by Wendy Rogers, titled 'Ethical Issues in Synthetic Biology: A Commentary' raises important considerations about agenda setting, the role of bioethics in synthetic biology, and the subject of 'professionalisation' in the synthetic biology context. Professor Rogers discusses not only the promise of new and exciting technologies such as synthetic biology, but also the challenges in shaping and directing the field to minimise the risk of harm. Hers is an important and insightful piece to consider and leads well into the article written by Ainsley Newson.

Ainsley Newson's contribution, 'Synthetic Biology: Ethics, Exceptionalism and Expectations', highlights that synthetic biology gives rise to ethical implications which, although well recognised in academic and lay literature, are now being given increasing attention from policy makers. Her article then explores the question of whether there is anything singular about such issues that might justify a distinctive or 'exceptional' approach to synthetic biology when compared to other emerging bio-technologies that also raise ethical issues. Her insightful paper argues that the field, while not perhaps warranting a purely exceptional approach, does require engagement with ethics. Dr Newson discusses some under-explored lines of enquiry, and places her discussion within the wider realm of ethical engagement with emerging technologies. Her article is important for considering both ethical engagement with synthetic biology and the insights such engagement may have when contemplating regulation of the field.

A short research note follows, jointly penned by Karolyn White and Subramanyam Vemulpad under the title 'Synthetic Biology and the Responsible Conduct of Research'. In their contribution, the authors contend that synthetic biology poses no special issues in respect of the Australian Code for the Responsible Conduct of Research or for Institutional Biosafety Committees. Their view is that researchers working in the area, as well as regulatory agencies, have been proactive in seeking appropriate governance and considering potential risks. They address, and offer an assessment of, existing regulatory frameworks that provide a structure for safe practices and the mitigation of risks in synthetic biology.

The article by Lisa Eckstein, 'Regulatory Challenges of Synthetic Biology Trials and Other Highly Innovative Investigational Products', discusses possible regulatory challenges for the future and focuses upon issues surrounding clinical trials in humans. In her contribution, Dr Eckstein recognises that while synthetic biology remains in the early stages of innovation, achieving one of its posited goals of improving human health will depend on future clinical trials. She therefore explores Australia's capacity to ensure that clinical trials involving these kinds of highly innovative investigational products have an acceptable initial and ongoing risk-benefit ratio. The author argues that none of the current regulatory bodies in Australia — as they currently operate — are equipped to undertake the necessary reviews that will be required in the future. She therefore canvasses strategies for better supporting them in this role. The article provides important insights into how regulatory approaches may need to be fine-tuned into the future.

We are also grateful to have a further contribution on the subject of synthetic biology by David Mercer, an accomplished academic in the field of Science and Technology who has previously published on the topic of synthetic biology. In his article "iDentity" and

Governance in Synthetic Biology: Norms and Counter Norms in the “International Genetically Engineered Machine Competition” (iGEM)’, Dr Mercer provides a critical evaluation of the ethos of the iGEM competition, which is an annual world-wide student-based synthetic biology competition. He contends that the often stated iGEM goals of collaboration, interdisciplinarity, sharing of results, and overt commitment to the consideration of social and ethical implications of scientific work may be hard to achieve in practice and do not always play out either in the competition or across the emerging field as a whole. To this end, his argument is that policy makers need to move beyond ‘symbolically important’ parts of the field, such as iGEM, when addressing the challenges of regulation and governance of synthetic biology.

Finally, we have a contribution from one of our own student editors that moves beyond the subject of synthetic biology. The case note by Valiant Warzecha reminds us that emerging bio-technologies pose regulatory challenges in many senses, and it explores this issue with an analysis of the recent Full Federal Court decision in *D’Arcy v Myriad Genetics*.

We wish to thank all the contributors for their submissions to this edition of the *Macquarie Law Journal* and their cooperation with the editorial staff during the production phase. Of course, particular thanks must also go to the hard working and enthusiastic student editors, students of Macquarie Law School, whose commitment and perseverance made the publication of Volume 15 possible.

Sonia Allan  
Ilija Vickovich

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# REPORT ON MACQUARIE UNIVERSITY WORKSHOP ON ETHICAL, LEGAL AND SOCIAL ISSUES RAISED BY SYNTHETIC BIOLOGY (10 DECEMBER 2014)

SONIA ALLAN\*

## I INTRODUCTION

In mid-2014 Macquarie University, partnered by the Australian Wine Research Institute, announced its involvement in the Sc2.0 synthetic biology project.<sup>1</sup> The project, which follows the synthesis of the third chromosome found in yeast by Professor Jef Boeke of New York University,<sup>2</sup> aims to build the world's first completely synthetic yeast (*Saccharomyces cerevisiae* (*Sc*)) genome by engaging in a global partnership to synthesise the remaining 15 chromosomes by 2017. This task involves a partnership between scientists across the globe from New York University, John Hopkins University, the Joint Genome Institute, Beijing Genomics Institute, Tianjin University, Tsinghua University, Imperial College London, the University of Edinburgh and Macquarie University. In Australia, the research has been backed by \$1 million in funding from the NSW Office of the Chief Scientist and Engineer, and the NSW Department of Primary Industries. The Macquarie University Sc2.0 project is led by Professor Sakkie Pretorius,<sup>3</sup> whose team will work to design and synthesise yeast chromosomes 14 and 16.

The Sc2.0 project is clearly a project of the future, building upon Macquarie University's active involvement in research and teaching in this area for some years. For example, Macquarie's undergraduate students have competed in the International Genetically Engineered Machine (iGEM) competition for the past four years, being the top Australian team in each of these years, and winning two silver and two bronze medals internationally. Macquarie also has several projects in its Faculty of Science that in some shape or form are linked with, or on the path of, synthetic biology.<sup>4</sup>

However, the field of synthetic biology goes further in that it focuses upon building novel and/or artificial biological parts, organisms, devices and systems. Thus, as is often the case with emerging technologies, an increasing discourse about the ethical, legal, and social issues raised by such research, and its potential applications, has also been seen alongside the rise of this technology. What is striking about the *Sc2.0* project is that the members have embraced such discussion, wanting to ensure a multi-disciplinary and collaborative

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<sup>1</sup> Macquarie University, *Yeast 2.0 Project Launched* (2 June 2014) <<http://mq.edu.au/thisweek/2014/06/02/yeast-2-0-synthetic-biology-project-launched/#.VSSYWuFlyXc>>.

<sup>2</sup> Narayana Annaluru et al, 'Total Synthesis of a Functional Designer Eukaryotic Chromosome' (2014) 344(6179) *Science* 55, 55–58; *The Economist*, *Synthetic Biology: DIY Chromosomes* (29 March 2014) <<http://www.economist.com/news/science-and-technology/21599754-first-synthetic-chromosome-creature-complex-cells-designed>>.

<sup>3</sup> Professor Pretorius is the Deputy Vice Chancellor of Research at Macquarie University and a leading scientist in the field.

<sup>4</sup> For example, Macquarie scientists are working on the design of synthetic cyanobacteria for biofuels (Professor Ian Paulsen); integrin gene cassettes for design of expression modular proteins (Mike Gillings); design of self-assembling proteins as nanofabrication tools (Bridget Mabutt); development of nanodiamonds for biomolecular tags (Louise Brown); development of fungi and bacteria protein factories (Helena Nevalainen, Nicki Packer); and design and synthesis of light activated biological switches and devices (Rob Willows).

environment from the start. The workshop held at Macquarie University on 10 December 2014 therefore introduced, identified and discussed issues pertinent to the ethics and governance of synthetic biology research and potential future applications.<sup>5</sup> It engaged with current international research in relation to these issues, and identified how we may add to discourse at domestic and global levels.

This report provides an overview of the proceedings of the day; provides a short summary of what synthetic biology research and the Sc2.0 project is; outlines the possible benefits and potential risks of research and application that have been identified thus far in the synthetic biology field; and provides an introduction to various approaches to regulation and governance around the world. It also highlights views concerning what more may (or may not) be needed, as per the discussion at the workshop. Most of the remaining papers in this themed edition of the *Macquarie Law Journal* are written by a number of speakers from the event. The papers provide more detail about ethical, social, and/or legal and governance issues that were considered by speakers on the day. However, they are not merely reflections or summaries of what was spoken about, as a number have been further researched and subjected to double-blind peer review before being accepted for publication.

The articles and shorter papers published in this edition are intended to provide the basis for further discussion, thought and research concerning ethical, legal and social issues raised by synthetic biology and emerging technologies generally.<sup>6</sup> The report is not a wide and exhaustive review of the field of synthetic biology, but it reflects and elaborates on the discussions at the workshop. It is noted that the contents in this journal, like the workshop and ongoing work in the field, reflect the interdisciplinary approach being taken in this field. Such an approach is now seen as essential to any consideration of emerging technologies.

## II OVERVIEW OF PROCEEDINGS

The day long workshop took place on Wednesday 10 December 2014 at Trinity Chapel, Robert Menzies College in Sydney, Australia. The workshop was opened by Professor Mary O'Kane, the NSW Chief Scientist and Engineer, and was chaired by Professor Catriona Mackenzie, Fellow of the Australian Academy of the Humanities and an Executive Board Member of the Macquarie University Centre for Agency, Values and Ethics.

Distinguished speakers included:

- Professor Ian Paulsen, Professor of Genomics and Deputy Director of the Macquarie Biomolecular Frontiers Centre, Australian Laureate Fellow, Macquarie University. Professor Paulsen gave an overview of synthetic biology research, potential applications, and the Sc2.0 project.
- Dr Jane Calvert, Reader, Science Technology and Innovation Studies, School of Social and Political Science, University of Edinburgh. Dr Calvert delivered the keynote speech in which she discussed ideas, practices and promises of synthetic biology, drawing upon her interdisciplinary work in the sociology and anthropology of science, the philosophy of biology, and science policy.

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<sup>5</sup> The workshop was made possible via a \$12,000 grant awarded to Dr Sonia Allan and Professor Wendy Rogers by the Faculty of Arts, and administered through the Centre for Agency, Values and Ethics. Administrative and organisational support was provided by Swantje Lorrimer-Mohr and Jenna McClellan from MQ Campus Life.

<sup>6</sup> Note that the contents of this report are a summary of other works and information presented at the workshop, and are drawn from other researched materials. The report is an overview of proceedings on the day. Information is presented for education and discussion purposes and to highlight some matters of importance when considering the ethical, legal and social issues raised by synthetic biology.

- Debra J H Mathews, Assistant Director for Science Programs for the Johns Hopkins Berman Institute of Bioethics, secondary appointment in the Institute of Genetic Medicine, Assistant Professor in the Department of Pediatrics, Johns Hopkins School of Medicine. Dr Mathews presented via live video from the United States and discussed the self-regulatory governance framework developed for the Sc2.0 project.
- Dr Ainsley Newson, Senior Lecturer in Bioethics in the Centre for Values, Ethics and the Law in Medicine (VELiM) at the University of Sydney. Dr Newson presented on the ethics of synthetic biology, drawing on her longstanding interest and experience in the field, including a project grant from the European Commission in 2009 for the Synthetic Biology and Human Health Ethical and Legal Issues Project.
- Professor Wendy Rogers, Professor of Clinical Ethics in the Philosophy Department and the Australian School of Advanced Medicine at Macquarie University, Deputy Director of the Macquarie University Research Centre for Agency, Values and Ethics, and Australian Research Council Future Fellow.
- Dr Karolyn White, Director, Research Ethics and Integrity at Macquarie University and Associate Professor Subramanyam Vemulpad, Chair of Biosafety Committee, Deputy Associate Dean (HDR) for the Faculty of Science and Co-director of the Indigenous Bioresources Research Group and the National Indigenous Science Education Program. Dr White and Associate Professor Vemulpad spoke about responsible conduct of research.
- Dr Lisa Eckstein, Lecturer, University of Tasmania. Dr Eckstein discussed possible regulatory challenges for the future, such as whether synthetic biology should provide outcomes that lead to clinical trials in humans.

The author of this report, Dr Sonia Allan, presented a summary of the 'promises and perils' of synthetic biology, regulatory approaches taken around the world (and possible gaps), and responses to the technology from cautious support to calls for moratoriums. That information is included in the report below.

The workshop was presented to an audience that included students and representatives from universities across the country; representatives from the NSW Department of Health, the Office of Health and Medical Research, and the Department of Primary Industries; private organisations; and people from the industry and civil society (including, but not limited to, Gene Ethics and Friends of the Earth). There were also members from the general community and industry in attendance. Additionally, the Deputy Vice Chancellor of Research, Professor Sakki Pretorius, and the Pro-Vice Chancellor of Research, Integrity and Development, Professor Lesley Hughes, were present. There was lively discussion during question time and breaks, and at the end of the day, amongst attendees and with the speakers.

### III OVERVIEW OF SYNTHETIC BIOLOGY AND THE SC2.0 PROJECT

A number of speakers noted that there is no accepted agreement upon what 'synthetic biology' includes (or does not include), with its meaning continuing to be debated in academic circles. The Convention on Biological Diversity Subsidiary Body on Scientific, Technical, and Technological Advice notes:

'[A]reas of research that are commonly considered as 'synthetic biology' include DNA-based circuits, synthetic metabolic pathway engineering, genome-level engineering, protocell construction, and xenobiology. Some see the insertion of synthetically designed and produced DNA sequences or pathways into an existing genome largely as rebranding conventional biotechnology. Others consider the building of non-natural pathways that would be difficult to achieve with traditional genetic engineering and the

systematic engineering circuits and pathways as approaches novel to synthetic biology and distinct from traditional genetic engineering.<sup>7</sup>

However, there is general agreement that, as a scientific endeavor, synthetic biology aims to 'exercise control in the design, characterization and construction of biological parts, devices and systems'.<sup>8</sup>

Synthetic biology has further been explained as being a confluence of developments and breakthroughs in many disciplines including the biological sciences (genetics and genomics, molecular biology, systems biology), chemical sciences, mathematical sciences, computational sciences, data sciences, informatics, physical sciences, and engineering. With such advances in these fields combined it has become possible for molecular biologists to engage with the technology and explore possibilities of gene synthesis and replacement.<sup>9</sup> To date, the development of such research has taken place predominantly in the United States, China and the United Kingdom. Recently there has also been a growing number of research institutes working in the field in Europe.

The Sc2.0 project is representative of the large scale collaborative nature of synthetic biology research, which will require significant human resources to achieve its goals. That is, the work is intense and costly, and the involvement of multiple centres around the world is seen as a way of achieving what might otherwise not be possible.

Yeast has been chosen as a focus for the Sc2.0 project as it is a eukaryote, a single cell fungus which is considered a 'safe food-grade organism'.<sup>10</sup> It is easy to propagate, has well defined genetics, and is one of the most intensively studied biological model systems. It is seen as an 'industrial workhorse' as it is heavily involved in baking, brewing, winemaking, food production (such as Vegemite), biofuel production, and production of enzymes for pharmaceuticals, vaccines and other medicines.<sup>11</sup> Its potential for developing possible applications of synthetic biology is considered 'promising'.<sup>12</sup> However, while in some areas of research commercial or near-to-market products from, or related to, synthetic biology exist (for example, certain biofuels, organic chemicals, natural vanillin, synthetic biology produced squalene and semi-synthetic artemisinin), the Sc2.0 project is a first instance project that is not focused upon application. The research is aimed at developing the ability to synthesise the full 16 chromosomes contained in yeast. Macquarie University's task, as mentioned above, will be to synthesise chromosomes 14 and 16. Professor Paulsen noted that this is a very early stage project, and that significant applications may be a while off. However, that does not mean that there is not a lot of discussion about the potential promise

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<sup>7</sup> Convention on Biological Diversity Subsidiary Body on Scientific, Technical, and Technological Advice, *New and Emerging Issues Relating to the Conservation and Sustainable Use of Biodiversity – Potential Positive and Negative Impacts of Components, Organisms and Products Resulting from Synthetic Biology Techniques on the Conservation and Sustainable Use of Biodiversity*, 18<sup>th</sup> mtg, Agenda Item 6, UN Doc UNEP/CBD/SBSTTA/18/INF/3 (20 May 2014) 4.

<sup>8</sup> Ibid.

<sup>9</sup> Sakki Pretorius, *News Briefing: Man-made Life – Announcing Australia's Role in DIY DNA* (23 May 2014) Australian Science Media Centre <<http://www.smc.org.au/briefing-man-made-life-announcing-australias-role-in-diy-dna/>>.

<sup>10</sup> In the United States the classification of *Saccharomyces cerevisiae* by the Food and Drug Administration authority is that of 'GRAS' (generally recognized as safe); in Europe it is classified as 'QPS' (qualified presumption of safety). See, eg, US Environmental Protection Agency, *Saccharomyces Cerevisiae Final Risk Assessment* (February 1997) Biotechnology Program under the Toxic Substances Control Act <[http://www.epa.gov/biotech\\_rule/pubs/fra/fra002.htm](http://www.epa.gov/biotech_rule/pubs/fra/fra002.htm)>; R Leuschner et al, 'Qualified Presumption of Safety (QPS): A Generic Risk Assessment Approach for Biological Agents Notified to the European Food Safety Authority (EFSA)' (2010) 21 *Trends in Food Science and Technology* 425, 430–431.

<sup>11</sup> Sakki Pretorius, above n 9.

<sup>12</sup> Ibid.

such research holds. For example, in quoting the UK Science Minister, Professor Sakki Pretorius has noted that 'it is a technology that promises to heal us, feed us, fuel us, and to power our economy, improve our wellbeing, and protect our environment'.<sup>13</sup>

Alongside such discussion are concerns about synthetic biology, and a consciousness that, along with potential benefits, lies the potential for harm. It has therefore been recognised that an approach that ensures research and technology only moves in a direction beneficial to society is crucial to research and potential future applications.

#### IV THE PROMISES AND POTENTIAL PERILS OF SYNTHETIC BIOLOGY

A theme that was discussed by all speakers at the workshop was that it is important to recognise both the wide and varied intended benefits of synthetic biology as well as the potential risks to biological diversity and human livelihoods associated with the components, organisms and products resulting from synthetic biology techniques. It was noted that both benefits and concerns are well documented in synthetic biology literature,<sup>14</sup> as is the fact that some aspects of synthetic biology may raise dual use issues (ie may have the potential for use for good and for harm).<sup>15</sup> A recent comprehensive survey conducted by the Convention on Biological Diversity Subsidiary Body on Scientific, Technical, and Technological Advice, was used as a basis for discussion at the workshop in order to outline some of the key areas and issues that display the potential for both benefits and risks.<sup>16</sup> The following key areas and issues were noted and discussed.

##### *Bioenergy Applications*

Potential benefits: reduce global dependence on fossil fuels; cut harmful emissions; next generation biofuels; biomass as feedstock.

Potential risks: decrease soil fertility; displacement of local sustainable uses; environmental harm; encroachment on traditional uses; biosafety concerns (for example, accidental release of organisms).

##### *Environmental Applications*

Potential benefits: more effective and 'green' pollution control and remediation; biosensors to identify contamination.

Potential risks: biosafety considerations regarding deliberate release of micro-organisms.

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<sup>13</sup> Ibid.

<sup>14</sup> See, eg, Brian Rappert and Michael J Selgelid, *On the Dual Uses of Science and Ethics* (Australian National University Press, 2013); Hans-Jürgen Link, 'Playing God and the Intrinsic Value of Life: Moral Problems for Synthetic Biology?' (2013) 19 *Science and Engineering Ethics* 435; Presidential Commission for the Study of Bioethical Issues, 'New Directions: The Ethics of Synthetic Biology and Emerging Technologies' (Research Report, December 2010); Andrew Balmer and Paul Martin, 'Synthetic Biology: Social and Ethical Challenges' (Independent Paper, Institute for Science and Society, University of Nottingham, 2008).

<sup>15</sup> For a comprehensive coverage of the dual uses of science, see Rappert and Selgelid, above n 14, 45.

<sup>16</sup> Convention on Biological Diversity Subsidiary Body on Scientific, Technical, and Technological Advice, *New and Emerging Issues Relating to the Conservation and Sustainable Use of Biodiversity – Potential Positive and Negative Impacts of Components, Organisms and Products Resulting from Synthetic Biology Techniques on the Conservation and Sustainable Use of Biodiversity*, 18<sup>th</sup> mtg, Agenda Item 6, UN Doc UNEP/CBD/SBSTTA/18/INF/3 (20 May 2014).

### *Wildlife-targeted Applications*

Potential benefits: identify and treat wildlife diseases; restore extinct species; new paradigms for biodiversity advocacy; target threats such as disease vectors.

Potential risks: diversion of funds and resources from conservation efforts; move policy makers away from addressing underlying causes for biodiversity loss; moral hazard — decrease will to conserve endangered species.

### *Agricultural Applications*

Potential benefits: sustainable intensification; land sparing; reduce chemical pesticides and fertilizers; drive land use.

Potential risks: biosafety considerations regarding the deliberate release of SynBio organisms.

### *Replacing Natural Materials*

Potential benefits: plant and animal conservation currently unsustainably harvested from the wild or through unsustainable cultivation.

Potential risks: displacement of products key to in-situ conservation; biosafety considerations around accidental release of micro-organisms.

### *Replacing Materials Made with Synthetic Chemistry*

Potential benefits: decreased use of non-renewable resources and less environmentally harmful manufacturing processes; sustainable production and consumption (which also protects biodiversity).

Potential risks: may not actually be greener (for example, bioplastics); drive significant land use changes towards feedstock production; biosafety considerations regarding accidental release of micro-organisms.

### *Biosecurity*

Potential benefits: better identification of pathogenic agents; response to biosecurity threats (for example, accelerated vaccines).

Potential risks: dual use challenge (for example, creating destructive pathogens).

### *Economic Applications*

Potential benefits: bioeconomy; economic growth, human health and environment; products such as artemisinin may improve human health in developed countries and therefore their economies.

Potential risks: product displacement harming economies; displacement of livelihoods of small-scale farmers and pickers; extraction and use of biomass may be ecologically unsustainable.

### *Health Applications*

Potential benefits: study of disease mechanisms; aid in diagnostics; drug discovery; drug screening; organisms that produce drugs and vaccines; therapeutic treatments.

Potential risks: possibility of direct harm to patients' health if engineered organisms/viruses trigger unanticipated adverse events; direct harm to workers in labs; patents restrict access to drugs and therapies.

### *Open Intellectual Property*

Potential benefits: innovation, transparency and openness; avoidance of patenting issues that relate to natural DNA.

Potential risks: may extend private ownership of genetic material, restricting public access; restricts access to information for carrying out independent risk assessments.

In addition, two further significant concerns were noted at the workshop: whether the transfer of genetic material from an organism resulting from synthetic biology techniques to another organism would change biodiversity at a genetic level and spread undesirable traits; and whether synthetic biology could result in radically different forms of life, with 'unpredictable and emergent properties'.

The following statement by Dana et al was therefore also considered:

'No one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data.'<sup>17</sup>

The statement highlights that there are also 'unknown unknowns' that need to be identified, considered, and addressed.

However, there are also considerations to be had about the benefits of such research. The following statement was also considered:

'It is easy (and perhaps appropriate) for an enumeration of the potential risks of synthetic biology to sound alarming. But these must be weighed against the benefits, not least in the sense that there is an ethical component to the decision to forego a new technology too: there can be socially significant penalties to the seemingly 'safe' option of 'doing nothing.' For one thing, the powerful capabilities synthetic biology might provide for developing and manufacturing drugs, including ones sorely needed in developing countries, should not lightly be set aside, just as we do not prohibit all drugs that have side-effects. It is conceivable that in the long-term, synthetic biology might offer one of the most powerful approaches for ameliorating natural biological and ecological hazards such as the spread of infectious diseases.'<sup>18</sup>

It was highlighted in the workshop that the tensions between promises and potential perils were great, and further ethical issues were highlighted and discussed. These tensions raise questions rather than give answers. What level of governance and regulation is needed? How do we allow the science to move forward while not ignoring risks? What level of risk are we as a society willing to accept? Should a precautionary approach be preferred? This led into the next part of the discussion concerning governance and regulation.

## V DIFFERING VIEWS REGARDING GOVERNANCE/REGULATORY APPROACHES THAT SHOULD BE TAKEN TO ADDRESS THE PROMISES AND PERILS OF SYNTHETIC BIOLOGY

Two differing views regarding how to address the promises and perils of synthetic biology by way of governance/regulatory options were highlighted (and discussed) at the workshop. These were a soft law approach, which would enable research to move forward under

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<sup>17</sup> Dana Genya et al, 'Four Steps to Avoid a Synthetic Biology Disaster' (2012) 483(7387) *Nature* 29.

<sup>18</sup> Mukunda et al, 'Guidelines for the Appropriate Risk Governance of Synthetic Biology' (Policy Brief, International Risk Governance Council, 2010).

guidelines, codes of practice and ethical undertakings by researchers, as contrasted with a complete moratorium on, at the very least, the release and commercial use of synthetic biology. The latter may prohibit or prevent certain types of research and it generally calls for the prevention of all release or commercialisation of research products or outcomes. The two approaches are further discussed below.

#### A *Soft Law (and Self-Regulation) as a Governance Option*

Attendees at the Macquarie University workshop were asked to consider the following statement made by Mandel and Marchant concerning the atypical characteristics of synthetic biology, and their suggestion to fill gaps with soft law options:

'The rapidly emerging technology of synthetic biology will place great strain upon the extant regulatory system due to three atypical characteristics of this nascent technology:

- synthetic biology organisms can evolve;
- traditional risk structures do not apply; and
- the conventional regulatory focus on end-products may be a poor match for novel organisms that produce products ...

[However] due to the uncertainty present at this early stage of synthetic biology development, and the practical political context, it is unlikely that the significant statutory and regulatory gaps identified could be cured directly. ... [A] selection of soft law alternatives ... could more quickly provide flexible and adaptive measures to help fill regulatory gaps in a manner that allows this promising technology to develop as rapidly as possible, while still adequately guarding against risks to human health and the environment.'<sup>19</sup>

The significance of the statement was discussed in relation to the three atypical characteristics that Mandel and Marchant highlight. Particular focus was had upon the challenges faced in using strict laws to regulate rapidly changing technologies.

It was noted that in referring to soft law options, Mandel and Marchant refer to such things as voluntary programs, consensus standards, partnership programs, codes of conduct, principles and certification programs. They note that 'such tools can impose substantive expectations or requirements, but unlike traditional hard law government regulations, are not directly enforceable'.<sup>20</sup>

The workshop highlighted that the soft law approach is very much the approach taken in the United States (the lead centre for the Sc2.0 project) for the regulation and governance of synthetic biology. Much governance of synthetic biology takes place there via the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, which, along with the Recombinant DNA Advisory Committee (RAC), have governed DNA research for decades in the United States. The guidelines are used to determine risk and biosafety levels of organisms used in research, to ensure proper handling and containment, and to minimise risk stemming from use.

In addition, the United States Department of Health and Human Services (DHHS) has issued a set of voluntary guidelines for companies producing and selling DNA to ensure that a DNA sequence ordered for synthesis does not code for harmful agents or toxins. The guidelines also provide for and validate the identity and credibility of the individual ordering

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<sup>19</sup> Gregory N Mandel and Gary E Marchant, 'The Living Regulatory Challenges of Synthetic Biology' (2014) 100 *Iowa Law Review* 155.

<sup>20</sup> *Ibid.*

the DNA. If a company has concerns and cannot resolve them, the company is advised to contact the FBI Office of Weapons of Mass Destruction.

The International Risk Governance Council (IRGC) has also published a set of guidelines which address biosafety and biosecurity; engagement of the public and other stakeholders; and ongoing, interdisciplinary dialogue to inform policy. The IRGC guidelines call for an internationally uniform method for DNA synthesis companies to screen requests; the conduct of regular audits to ensure that labs are following the appropriate safety precautions; and continued development of built-in safeguards that can mitigate risks in the event of accidental release.

Dr Debra Mathews, a member of the Sc2.0 project, also spoke about a specific statement of ethics and governance, which is the self-regulatory agreement made by all participants in the project.

### *1 The Sc.2.0 Project Statement of Ethics and Governance*

Dr Matthews gave an overview of the Sc2.0 project before discussing the history of governance in the field. She highlighted that synthetic biology research falls upon a continuum of recombinant DNA research (rDNA) and that, as such, it has a long history of self-governance. In the early 70s, scientists made a decision to look at self-governance to prevent risks in relation to rDNA. This took place starting with the 'Asilomar Conference' and moved to the above noted NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, and RAC. Dr Mathews noted that the remit of the current guidelines and RAC have developed and are quite different to their original form.

Moving to discuss synthetic biology specifically, Dr Mathews said that in the United States there is not a lot of 'formal governance', so the abovementioned NIH and DHHS guidelines are important. Nevertheless, in relation to the Sc2.0 project, she noted that early consideration was given to the issue of having a further unifying document that articulates the major policy and ethical issues related to the project, and the collective approach to be taken in relation to these issues. This document is important due to the global nature of the project that relies upon over 300 scientists from different backgrounds, working in diverse settings together. After much discussion and consultation, the result was a Sc2.0 ethics and governance document which was finalised and circulated to all project scientists in 2013. The document is incorporated in all new agreements that each participating site must sign prior to joining the project, and is added as an amendment to all previously executed partnership agreements. The document was circulated at the workshop.

Dr Mathews described the document as containing 11 statements to which all Sc2.0 participants agree to adhere. She further described the statements as falling into four main categories, being societal benefit, safety, intellectual property, and governance. The following is a summary of the Statement of Ethics and Governance set out pursuant to those four categories.

#### *(a) Societal Benefit*

##### *(i) Statement 1: Do No Harm*

The first statement in the ethics and governance document is as follows:

'As scientists and humans participating in the Sc2.0 Project, we wish for our work to contribute to the benefit of society and not to bring harm. The work on Sc2.0 will be

done only in service to peaceful purposes. Further, individual participants and the Sc2.0 Executive Committee will make efforts to ensure that all the benefits from Sc2.0 are maximized and any potential harms of Sc2.0 are minimised.'

The statement is of course aspirational and cannot guarantee that all people will work as described, but nevertheless requires that anyone working on the Sc2.0 project undertakes to act in this manner.

*(ii) Statement 2: Transparency and Public Engagement*

The second statement requires a commitment to 'transparency and public engagement'. It notes that the Boeke lab maintains an Sc2.0 website,<sup>21</sup> which is viewed as their 'public engagement venue with the broadest reach'. It states that project participants will 'contribute information to the resource in a timely fashion'. It is assumed that such information would include, for example, information about the science, ethics, governance and funding of the project — although this is not explicit. Information on such matters can also be found on various websites around the world describing respective participants' involvement and funding.<sup>22</sup> Statement 2 also refers to the Boeke lab being primarily responsible for public outreach. In addition, 'all Sc2.0 participants are encouraged to hold public lectures' (and will be supported via powerpoint slides and handouts from the Boeke lab).

The statement notes that the public are directly involved in the project, through partnerships with the LA Biohackers (a group of amateur scientists with a lab based in Downtown LA who provide space and equipment for people to work on their own biology projects and experiments)<sup>23</sup> and students at New York City's private Dalton High School, and that 'outreach will continue throughout the duration of the project'. Finally, it states that all Sc2.0 project participants are 'encouraged to make efforts to publicize both the potential and actual benefits *and* potential risks of Sc2.0 and other synthetic biology projects, in a way that lay people can understand'.

*(b) Safety*

*(i) Statements 3 to 6: Safety Concerns*

Statement 3 supports the use of the DHHS 'Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA' and requires that all sequence providers generating DNA for use in the Sc2.0 project are compliant with those guidelines.

Statement 4 requires that members of the Sc2.0 team access individuals requesting Sc2.0 project data/materials prior to shipment of such data/materials to 'help reduce the chance ... [of members] distributing materials to those with nefarious intent'.

Statement 5 is that the Sc2.0 project embraces and employs rigorous safety practices. It notes that there are no plans to intentionally release the completed synthesized yeast (or any components or intermediaries) into the environment. Nevertheless, all strains are to contain a number of 'auxotrophic mutations' which are intended to render them unlikely to be able

<sup>21</sup> Boeke Lab, *Home* (9 January 2015) Synthetic Yeast 2.0 <<http://syntheticyeast.org/>>.

<sup>22</sup> See, eg, Research Councils UK, *The Sc2.0 UK Genome Engineering Resource (SUGER)* (26 March 2015) Gateway to Research <<http://gtr.rcuk.ac.uk/project/E7645B9A-1C1D-47A4-82ED-6E3D606525C9>>; Macquarie University, *Yeast 2.0 Project Launched* (2 June 2014) <<http://mq.edu.au/thisweek/2014/06/02/yeast-2-0-synthetic-biology-project-launched/#.VSWfAuGEPT9>>.

<sup>23</sup> Los Angeles Biohackers, *Home* (7 February 2015) <<http://www.biohackers.la/>>.

to survive long-term outside of the laboratory. Research is required to further ensure that this process is appropriate and ongoing.

Statement 6 addresses safety concerns by providing that all faculty and staff will receive training on biosafety, dual-use concerns, and other ethics issues as appropriate. Dr Mathews explained that such training included lectures, the use of the National Science Advisory Board for Biosecurity's (NSABB) educational module for individual learning, and group discussion. Additionally, the group has been developing an online course on the ethics and policy issues related to synthetic biology that will be freely-available to all.

*(c) Intellectual Property*

*(i) Statements 8 and 9: Open Source Attitude*

Statement 8 notes the Sc2.0 project members' 'commitment to facilitating innovation and maximizing the beneficial use of Sc2.0'. Members of the Project agree that no intellectual property rights or restrictions on data and materials sharing should be exercised on the clones used to generate novel strains, intermediary strains, or the final Sc2.0 strain.

Statement 9 provides that data and materials of the Sc2.0 project will be made available to other scientists. All primary products of the Sc2.0 project, including the clones used to create novel strains, intermediary strains, or the final Sc2.0 strain will be made available at a cost to the broader community through a central repository.

*(d) Governance*

*(i) Statements 7, 10 and 11: Governance Structure*

Statement 7 provides that all work on the Sc2.0 project will comply with any relevant laws and policies.

Statement 10 provides that oversight of safety and compliance with the statement is the responsibility of the Sc2.0 project Executive Committee — a committee that consists of individuals with scientific, ethics and policy expertise. Safety or compliance issues or concerns may be brought to the attention of that committee by anyone. The Committee has the authority to remove from the Sc2.0 project any partner that violates the Statement of Ethics and Governance.

The final statement provides that '[u]nderstanding that science advances very quickly and that local and national policies may also change over time, the Executive Committee will regularly review the Statement to ensure that the project policies appropriately reflect the risks and regulatory status of the project. If the risks increase, so will oversight and accountability'.

It was noted by Dr Mathews that while project-level accountability will not suffice to regulate all of synthetic biology, the Sc2.0 Statement of Ethics and Governance provides a valuable model for component self-regulation in the field. It may serve to fill the gaps in current oversight mechanisms via voluntary self-regulation, and aims to support work being conducted in a scientifically justifiable and ethically sound way.

*B Moratorium on the Release and Commercial Use of Synthetic Biology until Robust Regulation and Rigorous Biosafety Measures are Established*

The second approach to governance that was discussed at the workshop was the call for a world-wide moratorium on the release and commercial use of synthetic organisms until more robust regulations and rigorous biosafety measures are established. Such a call was issued on 13 March 2012 by over 100 environmental and civil society groups.<sup>24</sup> The following Executive Summary of that document was displayed for discussion:

Synthetic biology, an extreme form of genetic engineering, is developing rapidly with little oversight or regulation despite carrying vast uncertainty. Standard forms of risk assessment and cost-benefit analyses relied on by current biotechnology regulatory approaches are inadequate to guarantee protection of the public and the environment.

The Precautionary Principle is fundamental in protecting the public and our planet from the risks of synthetic biology and its products. A precautionary approach requires synthetic biology-specific oversight mechanisms that account for the unique characteristics of synthetic organisms and their products. Additionally, it assesses the novel consequences of synthetic organisms and products of synthetic biology as well as full consideration of alternative options.

Ensuring public health, worker safety and ecosystem resilience requires a committed focus on developing a critical public interest research agenda that includes risk research and development of alternatives, a robust pre-market regulatory regime, strong enforcement mechanisms, immediate action to prevent potential exposures until safety is demonstrated and ongoing monitoring for unintended consequences and immediate action to prevent potential exposures until safety is demonstrated.

Protection of the public includes a ban on using synthetic biology to manipulate the human genome in any form, including the human microbiome. Decisive action must also be taken to protect the environment and human health and to avoid contributing to social and economic injustice. Developers and manufacturers must be responsible for the safety and effectiveness of their processes and products and must retain liability for any adverse impacts.

Throughout, research and regulation shall be transparent and provide public access to all information regarding decision-making processes, safety testing and products.

Open, meaningful and full public participation at every level is essential and should include consideration of synthetic biology's wide-ranging effects, including ethical, social and economic results.

No synthetic organism or their synthetic building blocks should be commercialized or released without full disclosure to the public of the nature of the synthetic organism and results of safety testing.

This document outlines the following principles necessary for the effective assessment and oversight of the emerging field of synthetic biology:

<sup>24</sup> Friends of the Earth, International Center for Technology Assessment and ETC Group, 'The Principles for the Oversight of Synthetic Biology' (Declaratory Report, 13 March 2012).

- I. Employment of the Precautionary Principle
- II. Mandatory synthetic biology-specific regulations
- III. Protection of public health and worker safety
- IV. Protection of the environment
- V. Guaranteed right-to-know and democratic participation
- VI. Corporate accountability and manufacturer
- VII. Protection of economic and environmental justice.

It was noted that the manifesto called for:

‘[G]overnmental bodies, international organizations and relevant parties to immediately implement strong precautionary and comprehensive oversight mechanisms enacting, incorporating and internalizing [the above] principles. Until that time, there must be a moratorium on the release and commercial use of synthetic organisms and their products to prevent direct or indirect harm to people and the environment.’

It was further noted at the recent United Nations Conference of the Parties to the Convention of Biodiversity in October 2014 that:

- many countries have stressed the need to apply the precautionary approach to synthetic biology;
- there has been a call to set up systems to regulate the environmental release of any synthetic biology organisms or products; and
- there has been great emphasis on risk assessment to conservation and sustainable use of biodiversity as well as human health, food security and socio-economic considerations.

It was proposed by some countries (Malaysia and the Philippines) that a global international legal regulatory framework should be developed. The call was supported by a number of African countries, including Cameroon, Kenya, Liberia and South Africa. In Latin America, Bolivia and the Dominican Republic also supported a precautionary approach. Yet other countries opposed such suggestions including Australia, Canada, New Zealand the UK and the European Commission.

In addition to a call for a moratorium, some nations called for there to be discussion of whether it is necessary:

- to license and regulate the limited number of firms that provide raw materials for DNA synthesis;
- to regulate DNA synthesis machinery; and
- to expand the Nagoya Protocol (discussed below) to cover digital genetic sequences.

It was noted that the call for a moratorium is not arguing for the prevention of all research. Rather, it is based on the view that there are significant risks that have not yet been properly assessed and/or lack robust regulation, and that soft law options may fill the gap in some areas but are not enough to prevent serious impacts upon human health, biodiversity, food security, and the economy of some nations.

### C Discussion

Reflecting upon the above information, as well as the presentations given by other speakers at the workshop who discussed ethical issues raised by synthetic biology research, both the positives and negatives of soft law governance options, and/or the proposed moratorium, were noted.

Soft law options are particularly useful in areas of emerging technology that are developing at a rapid pace, such as synthetic biology. They enable decisions to be revisited and amended in response to new information on risks and potential benefits. They can also include measures and actions that provide a broader approach to governance. For example, the education of potential users of synthetic DNA can inform them about ethical practices, risks, and consequences; the compilation of a manual for biosafety in synthetic biology laboratories might provide more immediate information and guide practices within the laboratory; and broad roles for Institutional Biosafety Committees to identify and review experiments for both safety and security concerns may enhance the enforcement of, and compliance with, biosafety guidelines. Mandel and Marchant also note that soft law measures can be extended beyond national and regional boundaries, are collaborative rather than adversarial, and promote a 'moral sense of ownership within a professional culture of responsibility'.<sup>25</sup>

However, Mandel and Marchant also emphasise that such measures may not provide the normal procedural safeguards that are an important part of traditional regulation, and may serve to reduce transparency or exclude relevant stakeholders from the decision-making process.<sup>26</sup> In addition, there is some evidence that voluntary soft law programs are less effective than traditional regulation in 'providing consumer confidence that a technology or industry is being kept in check by government regulation, and providing certainty to companies and investors about regulatory requirements'.<sup>27</sup> Although soft law options play an important role in the governance of emerging technologies, they are not generally seen as an answer to *all* issues raised by such technologies.

At the workshop there was no opposition shown to using soft law options as part of an approach to the governance of synthetic biology. However, the extent to which they were adequate was the subject of some disagreement. The discussion regarding whether a moratorium was required provided for strong reactions from audience members who both supported and rejected the notion. Some were of the view that synthetic biology is no different to other forms of emerging technology; some were wholly supportive of the research and saw a cautious but progressive approach as necessary; others were adamant that the science is moving too fast, and poses unacceptable (and perhaps catastrophic) risks to humankind and/or the environment. Others still noted that differentiation within the field concerning what is good and what may be harmful also needs to occur. For example, Newson notes that it is obviously important not to leave populations or environments worse off in any way as a result of synthetic biology, but 'not everything that is produced in synthetic

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<sup>25</sup> Presidential Commission for the Study of Bioethical Issues, above n 14, 36–50.

<sup>26</sup> Mandel and Marchant, above n 19.

<sup>27</sup> *Ibid.* Mandel and Marchant point to a number of studies showing that the public has less confidence in voluntary programs providing adequate oversight. See, eg, Elenore Pauwels, 'Public Understanding of Synthetic Biology' (2013) 63 *BioScience* 79, 86 (52% of public thought government should oversee synthetic biology, while 36% believed voluntary guidelines developed jointly by government and industry would provide adequate oversight); Jennifer Kuzma, Pouya Najmaie and Joel Larson, 'Evaluating Oversight Systems for Emerging Technologies: A Case Study of Genetically Engineered Organisms' (2009) 37 *Journal of Law, Medicine and Ethics* 546.

biology research will have biosafety [or other negative] implications' and some products may be benign or not capable of infection.<sup>28</sup>

It was noted by a number of speakers and audience members at the workshop that the history of recombinant DNA research has always included discussion and fears of new kinds of diseases, altering human evolution or irreversibly altering the environment, and similar arguments about what to do in relation to perceived risks. For example, in its earliest stages, the ability to clone DNA segments resulted in a voluntary moratorium on certain rDNA experiments in mid-1974 due to concerns that the unfettered pursuit of the research might result in unforeseen and damaging consequences for human health and the earth's ecosystems.<sup>29</sup> The moratorium was universally observed, providing time for a conference to evaluate the state of the new technology and any risks associated with it. The conference, held at the Asilomar Conference Center in California, United States (which would famously go on to be referred to as 'the Asilomar Conference'), included scientists from around the world, lawyers, government officials and members of the press. One outcome of the conference was the decision to proceed with research under strict guidelines, which were subsequently promulgated by the National Institutes of Health and by other comparable bodies around the world. Despite opposition to this decision, the research has persisted.

Regulatory approaches have continued to differ around the world. For example, some nations enacted legislation that prohibits or restricts genetically modified plants and animals from entering their food supply. However, it was noted that no such embargo had been placed upon certain drugs and therapies currently used in the treatment of serious diseases that were created with the same technology.

It is clear that there are large ongoing questions and different points of views from people all over the world. It is also important to recognise that the issues discussed at the workshop are ones with a long history that has occurred along a continuum of scientific research and development. Therefore, it is also important to consider what regulation and governance currently exists, while also considering what more (if anything) is needed.

## VI CURRENT REGULATION OF SYNTHETIC BIOLOGY AROUND THE WORLD

Current regulation relevant to synthetic biology was therefore discussed at the workshop, although comprehensive discussion was not possible due to limited time. It was noted that there are some existing national and international regulatory regimes that serve to regulate the components, organisms and/or products resulting from synthetic biology to some degree, but they do not form a coherent and comprehensive international framework. There are gaps at both international and domestic levels.<sup>30</sup>

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<sup>28</sup> Ainsley Newson, 'Synthetic Biology: Ethics, Exceptionalism and Expectations' (2015) 15 *Macquarie Law Journal* 45.

<sup>29</sup> Paul Berg, *Asilomar and Recombinant DNA* (26 August 2004) Nobel Prize <[http://www.nobelprize.org/nobel\\_prizes/chemistry/laureates/1980/berg-article.html](http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/berg-article.html)>.

<sup>30</sup> Note that the information included in the overview of regulatory approaches was extracted from a number of documents that have considered these issues in more detail, and was used for education and discussion purposes. For detailed discussion of these issues, see, eg, Mukunda et al, above n 18; Margo A Bagley and Arti K Rai, 'The Nagoya Protocol and Synthetic Biology Research: A Look at the Potential Impacts' (Research Report, Woodrow Wilson International Center for Scholars, November 2013); Committee on Science, Technology and Law et al, *Positioning Synthetic Biology to Meet the Challenges of the 21st Century: Summary Report of a Six Academies Symposium Series* (National Academies Press, 2013); Shlomiya Bar-Yam et al, 'The Regulation Of Synthetic Biology: A Guide to United States and European Union Regulations, Rules and Guidelines' (Discussion Paper, NSF Synthetic Biology Engineering Research Center, 10 January 2012).

## A *International Regulation, Governance and Oversight*

At an international law level several protocols, conventions and agreements were noted.

### 1 *The Cartagena Protocol on Biosafety for Living Modified Organisms*

The Cartagena Protocol on Biosafety for Living Modified Organisms (LMOs) to the Convention on Biological Diversity regulates international trade in LMOs and establishes an advanced informed agreement procedure, based on risk assessment, regarding acceptance/rejection decisions of LMOs by countries to which they are being shipped. The Protocol also allows the recipient nation to invoke precautionary regulation if, in its judgment, there is not enough scientific information to make a proper assessment of the potential adverse effects of the LMO on the conservation and sustainable use of biodiversity or risks to human health. There are 157 parties to the agreement.

There are a number of outstanding issues relating to the oversight of genetic manipulation technologies even after adoption of the Protocol text. These include:

- LMOs is a more restricted category than genetically modified organisms (GMOs), since it excludes those that are no longer alive, and their products;
- 'intentional introduction into the environment' may not address situations where the exporter knows that some shipped modified grain, for instance, will be planted within the importing country, but does not necessarily intend this to happen;
- many important countries are not members of the Protocol, including the largest growers and exporters of LMOs: the United States, Canada, Argentina and Australia;
- the Protocol's provisions on trade in LMOs between a party and a non-party state does not require that its procedures be followed; and
- the Protocol says nothing about any regulatory oversight within a country.

Developments in synthetic biology could also lead to gaps in the risk assessment framework set out in the Cartagena Protocol, since established practices may not be capable of dealing with complex hybrids of genetic material (including some that are wholly synthetic in design and origin) and the properties and effects they display.

It was noted that on 14 October 2014, the United Nations Conference of the Parties to the Convention on Biological Diversity urged all member countries to:

- follow a precautionary approach to synthetic biology;
- establish, or have in place, effective risk assessment and management procedures and/or regulatory systems to regulate environmental release of any organisms, components or products resulting from synthetic biology techniques consistent with Article 3 of the Convention on Biological Diversity. These regulations must ensure that activities in one country cannot harm the environment of another;
- approve organisms resulting from synthetic biology techniques for field trials only after appropriate risk assessments have been carried out in accordance with national, regional and/or international frameworks, as appropriate;
- carry out scientific assessments concerning organisms, components and products resulting from synthetic biology techniques with regard to potential effects on the conservation and sustainable use of biodiversity. These assessments should take into account risks to human health and address other issues such as food security and socioeconomic considerations with the full participation of indigenous and local communities according to national and/or regional legislation;

- encourage the provision of funding for research into synthetic biology risk assessment methodologies and the positive and negative impacts of synthetic biology on the conservation and sustainable use of biodiversity, and to promote interdisciplinary research that includes related socioeconomic considerations; and
- cooperate in the development and/or strengthening of human resources and institutional capacities, including methodologies for risk assessments, in synthetic biology and its potential impacts on biodiversity in developing country Parties, in particular the least developed countries and small island developing States among them, and Parties with economies in transition, including through existing global, regional and national institutions and organizations and, as appropriate, by facilitating civil society involvement.<sup>31</sup>

The committee noted that ‘establishing or strengthening regulatory frameworks; and the management of risks related to the release of organisms, components and products resulting from synthetic biology techniques, should be taken fully into account in this regard’.<sup>32</sup>

The decision also:

- establishes an ongoing process within the Convention on Biological Diversity, including an expert group which will establish a definition of synthetic biology and identify whether existing governance arrangements are adequate; and
- invites other UN bodies to consider the issue of synthetic biology as it relates to their mandates.<sup>33</sup>

## 2 *The Nagoya Protocol to the Convention on Biological Diversity*

The Nagoya Protocol to the Convention on Biological Diversity<sup>34</sup> may also be relevant to synthetic biology. It has the stated purpose of ensuring ‘fair and equitable sharing of benefits arising out of the utilization of genetic resources’, which covers all organisms. The Protocol requires researchers to enter into ‘access and benefit sharing’ (ABS) arrangements concerning organisms being used. An ABS sets out who might profit, and how, from the organisms being used. It also stipulates how to distribute the benefits fairly, such as co-authorship of publications or sharing profits from products such as drugs, vaccines or crops.

A number of issues have been raised in relation to the Nagoya Protocol and synthetic biology. First is the issue of whether it applies to synthetic biology at all, and if so, to what extent. A 2013 report written for the Woodrow Wilson Foundation found significant uncertainty surrounding what sorts of genetic materials are covered.<sup>35</sup> The report noted three questions left unanswered: Would synthetic DNA or BioBricks be covered? Would genetic samples collected prior to the ratification of the treaty be covered? Would digital DNA sequences shared over the web be covered? Nevertheless, the report suggested that, at a minimum, researchers must verify the origin of the genetic material they use and ensure

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<sup>31</sup> See Conference of the Parties to the Convention on Biological Diversity, *New and Emerging Issues: Synthetic Biology*, 12<sup>th</sup> mtg, Agenda Item 24, UN Doc UNEP/CBD/COP/12/L.24 (17 October 2014).

<sup>32</sup> Ibid.

<sup>33</sup> Ibid.

<sup>34</sup> The *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization* was adopted by the Conference of the Parties to the Convention on Biological Diversity at its tenth meeting on 29 October 2010 in Nagoya, Japan. In accordance with its Article 32, the Protocol was opened for signature from 2 February 2011 to 1 February 2012 at the United Nations Headquarters in New York by Parties to the Convention. The Protocol entered into force on 12 October 2014. To date, it has 57 Parties, 59 ratifications and 91 signatures.

<sup>35</sup> Margo A Bagley and Arti K Rai, above n 30.

such material is taken in compliance with the domestic law of a provider country – regardless of whether they are signatories to the Nagoya Protocol.

Second, it has been suggested that the Nagoya Protocol rules will present challenges for synthetic biologists who combine genetic code from many different organisms to create drugs or sensors. In particular, if they do apply, there is a question of whether such practices could require dozens of ABS arrangements for a single product. Of note is that one CEO of a synthetic biology company suggested that, if this were the case, companies would simply move to a nation (such as the United States) that is not a party to the Protocol to avoid such ‘bureaucracy’.

### 3 *The Biological Weapons Convention*

The Biological Weapons Convention (which opened for signature in 1972 and entered into force in 1975) prohibits the development, production, acquisition, transfer, retention, stockpiling and use of biological and toxin weapons. It is a key element in the international community’s efforts to address the proliferation of weapons of mass destruction. This includes:

- microbial or other biological agents, or toxins that have no justification for prophylactic, protective or other peaceful purposes; and
- weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

However, there is a challenge regarding the monitoring of compliance. Ambassador Masood Khan, President of the Sixth Review Conference of the Biological Weapons Convention and Chairman of its meetings in August 2007 said:

‘[E]xtraordinary advances achieved in biosciences meant that biological weapons were – in theory – within reach of the smallest laboratory and most modest budget. No government, no international organization, could hope to monitor effectively the tens of thousands of small biotechnology facilities in operation worldwide. Clearly, this was a problem that needed a collective, multifaceted and multidimensional approach.’<sup>36</sup>

Ambassador Khan notes that in order to even begin to address this there needs to be a network of collaboration and coordination ‘that must weave international, regional and domestic strands into a flexible and resilient fabric of oversight and prevention’.<sup>37</sup>

The Australia Group was also noted as being relevant to considerations about the possibility of chemical or biological weapon development. The Australia Group is an informal association of 41 member states that aims to allow exporters or transshipment countries to minimise the risk of proliferation of chemical and biological weapons (CBW). It aims to limit the spread of CBW through the control of chemical precursors, CBW equipment, and biological weapon agents and organisms. All participating countries have licensing measures covering over 60 chemical weapon precursors.<sup>38</sup>

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<sup>36</sup> Masood Khan, ‘Strengthening a Global Biosecurity/Biosafety Framework and Coping with the Biotechnology Revolution’ (Speech delivered at the Biological Weapons Committee Meeting, Como, 25–26 October 2007).

<sup>37</sup> *Ibid.*

<sup>38</sup> See also The Australia Group, *Home* (2007) <<http://www.australiagroup.net/en/index.html>>.

#### 4 *The Agreement on Trade-Related Aspects of Intellectual Property Rights*

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is the most comprehensive multilateral agreement on intellectual property, setting standards to be met in domestic patent law. Most applications and techniques of synthetic biology would be patentable under Article 27.3(b) of the Agreement, which deals with intellectual property protection of genetic resources. Limits on the exploitation of intellectual property rights stem from other fields of law, such as human rights law and international environmental law. Trade-offs may be required where issues such as public access to innovative medicines are at stake. In this regard, compulsory licensing remains an option under the TRIPS agreement for patents in any field. In the 2001 Doha Declaration on TRIPS and Public Health, member governments of the World Trade Organization (WTO) stressed that it is important to implement and interpret the TRIPS Agreement in a way that supports public health.

#### B *Domestic Regulation, Governance and Oversight*

Domestic regulation, governance and oversight of synthetic biology differs across the world. The workshop presented some information regarding Australia's domestic system, as well as a brief discussion of some other countries/regions as comparators (including China, Canada, the European Union, and the United States). As the information was discussion-based, and not detailed enough to provide a comprehensive review of various domestic approaches to regulating synthetic biology, that such discussion was had is only noted here.<sup>39</sup> However, below are some specific points about Australia and the United States which were found to be useful in highlighting the complexities of current regulatory regimes. Some discussion of what more is needed was had, as well as noting that the drive by both Australia and the United States (as well as the European Union, United Kingdom and China) to engage with the research has been criticised as ignoring (or working against) calls for a moratorium on certain types of research and commercialisation.

##### 1 *Australia*

The current scheme of gene technology regulation in Australia is complex. Live and viable GMOs are regulated in Australia by the Gene Technology Regulator under the *Gene Technology Act 2000* (Cth) and corresponding state and territory legislation. An integrated framework involving other agencies then makes up Australia's gene technology regulatory system (which operates at the Commonwealth level) for regulating GMOs or genetically modified (GM) products. The agencies include:

- Food Standards Australia New Zealand (FSANZ), which is responsible for examining the safety of GM foods (Food Standards Code);
- The Australian Pesticides and Veterinary Medicines Authority (APVMA), which operates the national system that evaluates, registers and regulates all agricultural chemicals (including those that are, or are used on, GM crops) and veterinary therapeutic products under the *Agricultural and Veterinary Chemicals Code Act 1994* and the *Agricultural and Veterinary Chemicals (Administration) Act 1994*;
- The National Industrial Chemicals Notification and Assessment Scheme (NICNAS), which provides a national notification and assessment scheme to protect the health of the public, workers and the environment from the harmful effects of industrial chemicals under the *Industrial Chemicals (Notification and Assessment) Act 1989*;

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<sup>39</sup> For further discussion of such regulatory regimes see OECD, *Emerging Policy Issues in Synthetic Biology* (OECD Publishing, 2014).

- The Therapeutic Goods Administration (TGA), which administers the *Therapeutic Goods Act 1989* that provides a national framework for the regulation of medicines, medical devices, blood and tissues in Australia, including GM and GM-derived therapeutic products, and ensures their quality, safety and efficacy; and
- The Australian Quarantine and Inspection Service (AQIS), which regulates the importation into Australia of all animal, plant and biological products that may pose a quarantine pest and/or disease risk. Import permit applications must indicate the presence of a GMO and the Office of the Gene Technology Regulator authorisation.

The Gene Technology Ethics and Community Consultative Committee (GTECCC) considers ethical issues raised by synthetic biology to be qualitatively similar to those raised by gene technology. It provided the following information about the GTECCC third face-to-face meeting of the 2011–2014 Triennium in Canberra on 24 May 2013:

[T]he GTECCC noted that whether synthetic biology raises new ethical issues had been discussed by GTECCC at previous meetings. At its sixth meeting in May 2012, GTECCC concluded that synthetic biology did not raise any new ethical issues, and that the known proposed applications of synthetic biology would be regulated under the *Gene Technology Act 2000* ... GTECCC also agreed to maintain a watching brief on developments and reports regarding synthetic biology. At the seventh GTECCC meeting, members were provided with a presentation from a PhD candidate from the Australian National University Law School on research into the ethical and legal issues around synthetic biology and its regulation. Members also received a report on a Scoping Workshop on ‘Synthetic Biology Futures in Australia?’ from an officer from the National Enabling Technology Strategy (NETS). GTECCC noted the updates in the area of synthetic biology and agreed that:

- GTECCC will continue to maintain a watching brief on developments and reports regarding synthetic biology, noting the rapid and ongoing developments in this field;
- most techniques related to synthetic biology to date would be regulated under the Act, noting that this is predicated on the definitions in the legislation. GTECCC understands that the 2011 review of the Act considered the issue of the definitions keeping pace with technological advances, and would be interested in being consulted on future proposals to change the definitions;
- GTECCC notes that synthetic biology in relation to animals is subject to additional regulation by animal ethics committees;
- GTECCC has considered several reports by expert groups that discuss synthetic biology. These reports have comprehensively covered scientific issues and also underline the importance of continuing social and ethical responsibility of scientists;
- the reports all discuss deliberative democracy and emphasize the need not only for public consultation, but for public engagement; and
- GTECCC notes that the context for this issue also includes the debate around traditional intellectual property and the rapid expansion of open access science.<sup>40</sup>

It was further noted at the workshop that an independent review of the *Gene Technology Act 2000* in 2011 recognised that scientific and technological advances in gene technology and biotechnology continue to be rapid. Submissions included suggestions for improvements in regulation — which to date do not appear to have been realised. For example, in their submission to the review, the Department of Innovation, Industry, Science and Research and

<sup>40</sup> See Office of the Gene Technology Regulator, *Gene Technology Ethics and Community Consultative Committee Meeting 24 May 2013 Canberra* (26 August 2013) <<http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/gteccc-comm-May2013-htm>>.

the Commonwealth Scientific and Industrial Research Organisation noted that Australia's regulatory system regarding genetically modified organisms is complex and is in need of simplification; that issues of scale, containment and organisms with multiple modifications may create problems for regulators in the future; that there is a risk of the technology outpacing the regulation; that there is a need to ensure that consultation seeks to actively solicit input beyond the most active interest groups (for example, to the broader community); and that risk assessment should include an assessment of benefits as well as potential negative implications.<sup>41</sup>

The 2013 'All Governments' Response' to the review agreed to undertake further investigation of ways to ensure that the Act remains up to date with advances, including mechanisms to expeditiously amend legislative definitions, exclusions and the scope of regulation.<sup>42</sup> Friends of the Earth have expressed deep concern with Australia's flat rejection of the proposal for a moratorium that was discussed above.<sup>43</sup>

## 2 United States

It was noted at the workshop that the dominant idea in the United States regarding the regulation and governance of synthetic biology is that the existing policy and regulatory framework for biotechnology applies, with minor adaptations, to synthetic organisms. Details of the regulatory system were noted as having been discussed regarding the soft law approach to regulation that dominates the United States environment.

It was further noted that laboratory research is overseen by the National Institute of Public Health (NIPH), and that the NIPH biosafety system for risk assessment and categorisation of biological risk applies to synthetic biology research. This system has served as a reference document for the development of legislation and guidelines worldwide and encompasses the use of biosafety levels 1 to 4. It was again noted that the NIH Recombinant DNA Advisory Committee has concluded that, in most cases, biosafety risks for synthetic nucleic acids are comparable to rDNA research and that the current risk assessment framework can be used to evaluate synthetically produced nucleic acids with attention to the unique aspects of this technology. The NIH Guidelines for research involving rDNA molecules were adapted to specifically cover and provide principles and procedures for risk assessment and management of research involving synthetic nucleic acids. Synthetic DNA segments which are likely to yield a potentially harmful polynucleotide or polypeptide (for example, a toxin or a pharmacologically active agent) are regulated in the same way as their natural DNA counterpart.

Assessment and regulation of biotechnology products, including their intended environmental releases of organisms, fall under a coordinated framework put in place by the Environmental Protection Agency (EPA), the United States Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) and the Food and Drug Administration (FDA). This coordinated framework is considered appropriate for regulating most of the organisms obtained by near-term SynBio applications. Challenges and gaps have also been identified in United States regulations. These include that:

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<sup>41</sup> The Department of Innovation, Industry, Science and Research and the Commonwealth Scientific and Industrial Research Organisation, Submission to the Australian Government Department of Health, *2011 Review of the Gene Technology Act (2000)* (2011).

<sup>42</sup> Australian, state and territory governments, 'All Governments' Response to the Recommendations of the 2011 Review of the Gene Technology Act (2000)' (Response, Australian Government Department of Health, 2011).

<sup>43</sup> Louise Sales, 'Throwing Precaution to the Wind: The Government's Attempts to Thwart Regulation of Synthetic Biology' (2014) 122 *Chain Reaction* 18.

- unlike plants obtained by older genetic modification techniques, the engineering of organisms without the use of a (component of a) plant pest would shift them out of the regulatory review of APHIS;
- existing law may not provide the government with the authority to regulate genetically modified plants produced through synthetic biology; and
- it is expected that EPA regulators will face an increased influx of genetically engineered microbes intended for commercial use for which the risk assessment will pose a greater challenge for resources.

There have been proposals in the United States that additional funding, as well as a fast track for low-risk types of microbes, may become necessary in the future. Certain legislative actions that could strengthen the *Toxic Substances Control Act* as it applies to microbes may also become necessary.<sup>44</sup> However, commentators have also noted that although options for regulating synthetic biology within existing legislative authorities have been suggested, '[US] congressional resistance to passing strong environmental legislation of any type probably precludes the passage of new authority for [S]yn[B]io specific regulation'.<sup>45</sup>

## VII CONCLUSION

The regulation and governance of synthetic biology reflects the youth of the field. Not all countries have detailed policy agendas. A number have taken the position that synthetic biology at present falls under the regulatory structures in place that address biotechnology, gene technology, environmental issues and/or human health. However, there are gaps in regulation and governance, and issues about how regulation can keep pace. The indication is that regulators are 'keeping watch' at both national and international levels to assess issues related to this emerging technology. Some scientists have taken significant steps to 'fill the gaps' by designing soft law measures that guide them in their research and practice. Some nations are more concerned, and are calling for a moratorium on certain types of research, release into the environment, and commercial use. As research moves to products, increased regulatory attention may arise.

This report has highlighted some of the promised benefits and perceived perils of synthetic biology. It has detailed the discussion had at the Macquarie University workshop on the ethics and governance of synthetic biology, and presented information about ongoing areas in need of further discussion and exploration. However, this report is not a complete reflection of the issues discussed on the day. The papers, commentaries and notes that follow, written by the distinguished speakers who presented at the workshop on the day and other contributors to the journal, further explore ethical, social, legal and regulatory issues of note. We are all grateful to Macquarie University, the Office of the Deputy Vice Chancellor of Research and the Faculty of Arts for providing a grant to allow us — lawyers, ethicists, philosophers, scientists, members of civil society, industry, government and the community — to come together and join the conversation on the ethics and governance of synthetic biology.

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<sup>44</sup> For discussion of the US regulatory system and options for reform see Sarah R Carter et al, 'Synthetic Biology and the US Biotechnology Regulatory System: Challenges and Options' (Research Report, J Craig Venter Institute, May 2014) 24.

<sup>45</sup> Steve Suppan, *From GMO to SMO: How Synthetic Biology Evades Regulation* (7 August 2014) Institute for Agriculture and Trade Policy <<http://www.iatp.org/documents/from-gmo-to-smo-how-synthetic-biology-evades-regulation>>.

# THE SYNTHETIC YEAST PROJECT AS A TOPIC FOR SOCIAL SCIENTIFIC INVESTIGATION

JANE CALVERT\* AND EMMA FROW\*\*

*The synthetic yeast project (Sc2.0) is a visible example of the recent rise in prominence of eukaryotic synthetic biology. Drawing on an analysis of news stories, scientific papers, and our involvement with the scientific community, we describe the synthetic yeast project and some of its precursors, and we identify the technical, social and conceptual issues that we find particularly salient as researchers in Science and Technology Studies. We discuss the 'design principles' that are central to the project, and how these align Sc2.0 with the mainstream engineering agenda in synthetic biology. We identify the project's preference for openness regarding intellectual property, and compare this to ownership approaches in other branches of synthetic biology. We also argue that a study of yeast encourages us to consider more explicitly the spatial and temporal dimensions of the organisms used in synthetic biology. We conclude that social scientific investigation into the synthetic yeast project raises important questions that will help us better understand the movement of synthetic biology into more complex organisms and systems, and assist us in further exploring the tensions between engineering and biology that are central to this emerging field.*

## I INTRODUCTION

Yeast is a familiar microorganism. It is central to the production of everyday foods like bread and beer, and it is scientifically well understood. The familiarity of yeast makes the decision to build a synthetic 'designer' version of the entire yeast genome all the more significant. The goal of the synthetic yeast project (known as Sc2.0) is to create a novel, rationalised version of the genome of the yeast species *Saccharomyces cerevisiae* ('*S. cerevisiae*').<sup>1</sup> In March 2014, the complete synthesis of one of the chromosomes of *S. cerevisiae* was announced,<sup>2</sup> and received widespread scientific and media coverage. In this commentary we discuss the Sc2.0 project, paying attention to those features of the project, and of the synthetic organism, that we find particularly distinctive or noteworthy.

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<sup>1</sup> The National Science Foundation, *Synthetic Yeast 2.0, Building the world's first synthetic eukaryotic genome together* (2015) Synthetic Yeast 2.0 <<http://syntheticyeast.org/>>.

<sup>2</sup> Narayana Annaluru et al, 'Total synthesis of a functional designer eukaryotic chromosome' (2014) 344(6179) *Science* 55.

Synthetic biology is a field concerned with the design of new biological parts, devices and systems, and the re-design of existing biological systems for useful purposes.<sup>3</sup> The majority of synthetic biology research to date has been conducted on prokaryotic organisms (particularly bacteria) but there is growing interest in eukaryotic synthetic biology, with attention turning to yeast, plants, and even mammalian systems. For example, one of the research testbeds of the US Synthetic Biology Engineering Research Centre ('Synberc') focuses on mammalian systems.<sup>4</sup> Also, the UK Research Councils have recently made large investments in eukaryotic synthetic biology, including the establishment of OpenPlant,<sup>5</sup> a joint initiative of the University of Cambridge and the John Innes Centre, as well as the SynthSys-Mammalian research centre at the University of Edinburgh.<sup>6</sup>

We are social scientists in the field of Science and Technology Studies ('STS'), and we have been studying the emergence and formation of synthetic biology for the past seven years.<sup>7</sup> Our earlier work implicitly revolved around prokaryotic synthetic biology, because this was the focus of the scientists and engineers we were interacting with. But we have recently become involved in two large-scale synthetic biology projects: a multinational project titled 'Induced Evolution of Synthetic Yeast genomes',<sup>8</sup> and a UK research centre focused on mammalian synthetic biology.<sup>9</sup> As the research focus of scientists and engineers expands from prokaryotic systems to include yeast and multicellular mammalian systems, we reflect on how our own research questions are also being revised and expanded. In what follows, we show how recent activities, particularly in yeast synthetic biology, relate to our existing interests while also re-directing our attention to a somewhat different set of questions.

As STS researchers, we ground our work in empirical investigation of our subject matter, usually conducting interviews and extensive participant observation. This commentary piece marks the beginning of our investigations into synthetic yeast. It is not intended to provide a comprehensive overview of all the relevant issues, but instead highlights topics and themes that we identify as valuable to explore further. We draw on our previous research on synthetic biology, building on this through preliminary engagement with members of the yeast synthetic biology community and a survey of recent scientific publications on yeast synthetic biology. We have also conducted a thematic analysis of news stories (approximately 35 articles) accompanying the 2014 *Science* publication that reported successful construction of a synthetic version of yeast chromosome III.<sup>10</sup> Combining these different sources allows us to identify themes that we intend to pursue through further investigation of yeast synthetic biology.

After introducing yeast and describing the Sc2.0 project and its precursors, we outline some of the technical, social and conceptual issues we intend to explore in our future work. We end by asking how these different dimensions of the synthetic yeast project could help us to

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<sup>3</sup> This is a commonly used definition of synthetic biology. See, eg. <<http://syntheticbiology.org/>>.

<sup>4</sup> Synthetic Biology Engineering Research Centre, *Synberc building the future with biology* (2015) <<http://www.synberc.org/content/research-thrust-and-testbed-leaders>>.

<sup>5</sup> OpenPlant <<http://openplant.org/>>.

<sup>6</sup> The University of Edinburgh, *SynthSys Mammalian* <<http://www.synthsys.ed.ac.uk/research/funded-research/synthsys-mammalian>>.

<sup>7</sup> See, eg. Jane Calvert and Emma Frow, 'Social Dimensions of Microbial Synthetic Biology' in Colin Harwood and Anil Wipat (eds), *Microbial Synthetic Biology, Volume 40 (Methods in Microbiology)* (Burlington: Academic Press, 2013) 69.

<sup>8</sup> Projektträger Jülich (Germany), *ERASynBio 1st joint call 2013: 8 proposals selected for funding* (2015) ERASynBio <<https://www.erasynbio.eu/joint-calls/1st-call>>.

<sup>9</sup> University of Edinburgh, above n 6.

<sup>10</sup> Narayana Annaluru et al, above n 2.

deepen our understanding of the relationship between biology and engineering in synthetic biology.<sup>11</sup>

## II THE SIGNIFICANCE OF YEAST

Yeast is of great cultural importance for human societies, since it is essential to the brewing of alcohol and the baking of bread. The ancient relationship between yeast and humans is well known, and was frequently alluded to in several of the media stories we analysed (often with reference to the geographical origins of this relationship in the Fertile Crescent).<sup>12</sup> Indeed, the Latin name *Saccharomyces cerevisiae* means ‘beer sugar mould’, showing that even the name for this organism is inseparable from its common cultural use.<sup>13</sup> With its ability to ferment at industrial scale, yeast has been an essential part of the biotechnology industry from its beginnings,<sup>14</sup> and is currently in widespread use for the production of medicines, vaccines and biofuels. Thanks to its history of safe use in food products, yeast as an organism is categorised as ‘generally recognised as safe’ or ‘GRAS’ in the US, which streamlines its regulatory approval process.<sup>15</sup>

Given this longstanding relationship with human culture, yeast is a familiar everyday entity, and the news stories we analysed often transferred this sense of ‘domestication’ to their discussion of the synthesis of chromosome III. There were frequent associations made between yeast and consumer products (including Vegemite, in the Australian media),<sup>16</sup> with some sources also suggesting that synthetic yeast might lead to the production of ‘better beer.’<sup>17</sup>

Yeast is not only the object of widespread domestication, but scientifically it is ‘one of the most important model organisms for studying eukaryotic genetics.’<sup>18</sup> It was the first eukaryotic organism to have its full genome sequenced in 1996, and is described as well-suited to scientific investigation because it has a ‘relatively compact and stable genome’<sup>19</sup> and is simple compared to most eukaryotes. These features make yeast ‘an ideal candidate to extend synthetic genomics beyond bacteria.’<sup>20</sup>

<sup>11</sup> The relationship between engineering and biology is a central focus of a social scientific research project we are both involved with. See, European Research Council, *Engineering life: ideas, practices and promises* (2014) <<http://erc.europa.eu/engineering-life-ideas-practices-and-promises>>.

<sup>12</sup> See, eg, David Shukman, ‘Scientists hail synthetic chromosome advance’ *BBC News* (online), 27 March 2014 <<http://www.bbc.co.uk/news/science-environment-26768445>>.

<sup>13</sup> Anna Krzywoszynska, “*We produce under this sky*”: *making organic wine in a material world* (PhD Thesis, the University of Sheffield, 2012).

<sup>14</sup> Robert Bud, ‘Molecular biology and the long-term history of biotechnology’ in Arnold Thackray (ed), *Private Science: Biotechnology and the Rise of the Molecular Sciences* (University of Pennsylvania Press, 1998) 3.

<sup>15</sup> US Department of Health & Human Services, *Microorganisms & Microbial-Derived Ingredients Used in Food (Partial List)* (2013) US Food and Drug Administration <<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/MicroorganismsMicrobialDerivedIngredients/default.htm>>.

<sup>16</sup> Chris Pash, ‘Australia Has Joined the Global Effort to Create the First Synthetic Complex Organism, A Yeast to Make a Better Wine’, *Business Insider Australia* (online), 27 May 2014 <<http://www.businessinsider.com.au/australia-has-joined-the-global-effort-to-create-the-first-synthetic-complex-organism-a-yeast-to-make-a-better-wine-2014-5>>.

<sup>17</sup> William Herkewitz, *Scientists Create Synthetic Yeast Chromosome (And Unlock the Future of Beer)* (27 March 2015) *Popular Mechanics* <<http://www.popularmechanics.com/science/health/a10289/scientists-create-synthetic-yeasts-and-open-the-door-to-the-future-of-beer-16637455/>>.

<sup>18</sup> Stephen George Oliver et al, ‘The complete DNA sequence of yeast chromosome III’ (1992) 357 *Nature* 38, 38.

<sup>19</sup> Dejana Jovicevic, Benjamin Blount and Tom Ellis, ‘Total synthesis of a eukaryotic chromosome: Redesigning and SCRaMble-ing yeast’ (2014) 36(9) *Bioessays* 855, 856.

<sup>20</sup> *Ibid.*

### III THE SYNTHETIC YEAST PROJECT AND ITS PRECURSORS

To date, the highest-profile genome synthesis project has been the synthesis of the complete bacterial genome of *Mycoplasma mycoides* ('*M. mycoides*'). This was carried out by a team of researchers at the J Craig Venter Institute ('JCVI') and published in the journal *Science* in 2010.<sup>21</sup> The article describes how a synthetic copy of the natural *M. mycoides* genome was inserted into an already existing cell, where it was able to switch the cell from its original *Mycoplasma capricolum* phenotype to the new *M. mycoides* phenotype. This ambitious genome synthesis and assembly project is often invoked as a precedent to the synthetic yeast project.<sup>22</sup>

However, the Sc2.0 yeast genome synthesis project is an order of magnitude larger than the 1.08 million base-pair bacterial genome synthesised by the JCVI.<sup>23</sup> At 11 million base pairs, the synthesis of the *S. cerevisiae* genome is a considerably more challenging task. Because of its size, the Sc2.0 project is an internationally distributed effort, with different yeast chromosomes being synthesised simultaneously in different institutions around the world. For example, Macquarie University is synthesising chromosomes XIV and XVI in collaboration with the Australian Wine Research Institute, and the University of Edinburgh is working on the synthesis of chromosome VII and the 'neo-chromosome'. A commentary accompanying the 2014 *Science* publication includes an image illustrating the global distribution of the project, with each chromosome associated with the national flag of the country leading on its synthesis.<sup>24</sup>

This image is reminiscent of the Human Genome Project ('HGP'), which was a large-scale international genome sequencing project that ran from 1990 to 2003.<sup>25</sup> The HGP is often invoked in discussions of the synthetic yeast project.<sup>26</sup> Although the HGP's focus was on sequencing, not synthesis, it was a similarly ambitious, internationally distributed project that required coordination of tasks, milestones and timelines. In his analysis of how the HGP was governed, Hilgartner notes that special attention had to be paid to the division, organisation and peer recognition of work so as to ensure longer-term career viability of participating researchers, particularly postgraduate students and junior staff scientists.<sup>27</sup> To date, the yeast synthesis project has been relying heavily on undergraduate student contributions, which raises questions about how project allocation and authorship credit are being determined among the students contributing to this collective effort.

The geographical dispersion of the Sc2.0 project seems to be a key motivation behind the creation of a statement on ethics and governance, which has been agreed to by the Sc2.0 consortium participants and is published on the project's website.<sup>28</sup> The statement explains that 'this is a massive, collaborative project involving diverse scientists from academic and

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<sup>21</sup> Daniel Gibson et al, 'Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome' (2010) 329(5987) *Science* 52.

<sup>22</sup> See, eg, Ewen Callaway, *First synthetic yeast chromosome revealed* (27 March 2014) Nature International Weekly Journal of Science <<http://www.nature.com/news/first-synthetic-yeast-chromosome-revealed-1.14941>>.

<sup>23</sup> Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

<sup>24</sup> Elizabeth Pennisi, 'Building the Ultimate Yeast Genome' (2014) 343 *Science* 1426.

<sup>25</sup> Stephen Hilgartner, 'Constituting large-scale biology: Building a regime of governance in the early years of the Human Genome Project' (2013) 8(4) *BioSocieties* 397.

<sup>26</sup> See, eg, Elizabeth Pennisi, above n 24.

<sup>27</sup> Stephen Hilgartner, above n 25.

<sup>28</sup> Synthetic Yeast 2.0, *Sc2.0 Statement of Ethics and Governance* (24 November 2013)

<[http://syntheticyeast.org/wp-content/uploads/2014/04/Sc2\\_EthicsAndGovernanceAgreement\\_131124final.pdf](http://syntheticyeast.org/wp-content/uploads/2014/04/Sc2_EthicsAndGovernanceAgreement_131124final.pdf)> ('Statement').

commercial institutions across the globe.’<sup>29</sup> It goes on to say: ‘with scientists with such different backgrounds working together on this single project, it is essential that everyone involved is well informed and conscientious with regard to the ethics and related policy issues.’<sup>30</sup> It is notable that the size and geographical spread of the project is seen to demand that particular attention is paid to governance. This necessity for coordination, not only scientific but also ethical, may well be a feature of eukaryotic genome synthesis projects in the future. The Sc2.0 statement recognises this, saying: ‘we hope that this effort can serve as a model for other similarly collaborative, global endeavours in synthetic biology.’<sup>31</sup>

#### IV DESIGNING THE SYNTHETIC YEAST GENOME

To examine the technical features of the synthetic yeast genome project, it is helpful to return to the comparison with the JCVI’s synthesis of the *M. mycoides* genome. A key difference between the two projects is in the scope of genome (re-)design. The JCVI researchers created a synthetic version of an existing bacterial genome (adding a few unnatural, noncoding ‘watermarks’ to distinguish the natural and synthetic versions).<sup>32</sup> In contrast, the aim of the synthetic yeast project is not to produce a synthetic version of the wild-type *S. cerevisiae* genome, but rather to create a ‘designer genome’. The changes being made are described as ‘much more drastic alterations than those demonstrated by Venter and his team in 2010.’<sup>33</sup>

The synthetic yeast genome can be described as a ‘refactored’ genome. ‘Refactoring’ is a widely used approach in synthetic biology. The term is borrowed from software engineering and it means rationalising or cleaning up software code. Synthetic biologists have taken this idea and are applying it to *genetic* code, attempting to make it more ‘rational’ and streamlined.<sup>34</sup> Naturally occurring DNA<sup>35</sup> sequences, with their many repeats and redundancies, are rearranged in a way that is perceived of as ‘better’ (or perhaps ‘sleeker’).<sup>36</sup> The synthetic yeast project is an attempt to refactor the entire yeast genome.

The Sc2.0 project team is working to refactor the yeast chromosomes *in silico* before synthesising them. They are following three core (yet arbitrary) design principles: maintaining genomic stability, increasing genetic flexibility, and maintaining the fitness of the yeast.<sup>37</sup> These principles were applied to the redesign of chromosome III, and will be adhered to in the synthesis of the other chromosomes. Chromosome III was the first to be synthesised in the Sc2.0 project, and is described as a ‘sentimental favourite of yeast geneticists’<sup>38</sup> because it is one of the shortest, and it is also the chromosome containing the genes responsible for yeast sexual behaviour. It was also the first chromosome to be

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<sup>29</sup> Ibid 1.

<sup>30</sup> Ibid.

<sup>31</sup> Ibid.

<sup>32</sup> Daniel Gibson, above n 21.

<sup>33</sup> Ewen Callaway, above n 22.

<sup>34</sup> Karsten Temme, Dehua Zhao and Christopher Voigt, ‘Refactoring nitrogen fixation gene clusters from *Klebsiella oxytoca*’ (2012) 109(18) *Proceedings of the National Academy of Sciences of the United States of America* 7085.

<sup>35</sup> Deoxyribonucleic acid.

<sup>36</sup> Ian Sample, ‘Designer’ chromosome for brewer’s yeast built from scratch’, *The Guardian* (online), 28 March 2014 <<http://www.theguardian.com/science/2014/mar/27/designer-chromosome-brewers-yeast-eukaryotic-saccharomyces-cerevisiae>>.

<sup>37</sup> Jessica Dymond et al, ‘Synthetic chromosome arms function in yeast and generate phenotypic diversity by design’ (2011) 477 *Nature* 471.

<sup>38</sup> Jef Boeke quoted in David Biello, ‘Baker’s Yeast Gets a Genetic Makeover’, *Scientific American* (online), 27 March 2014 <<http://www.scientificamerican.com/article/bakers-yeast-gets-a-genetic-makeover/>>.

sequenced in 1992, and at that time was the first complete sequence of an entire chromosome from any organism.<sup>39</sup>

In an attempt to improve the genomic stability of the synthetic chromosome III, all known genome-destabilising elements were deleted, including small stretches of DNA called transposons and introns.<sup>40</sup> The ends of the chromosomes, called telomeres, were also removed and replaced by shorter, synthetic versions.<sup>41</sup> All told, the deletions have resulted in a synthetic chromosome that is 14% smaller than the original.<sup>42</sup> Another major change is that all of the yeast's transfer RNAs,<sup>43</sup> which are essential for making proteins from DNA, have been extracted from their original locations and will be combined to make a 'neo-chromosome'. This is because transfer RNAs can be sites of genomic instability, and it is predicted they will cause less damage if separated from the rest of the genome.<sup>44</sup>

The researchers have attempted to increase genetic flexibility in the synthetic genome by building in so-called 'SCRaMbLE' sites,<sup>45</sup> which 'will make it possible to reshuffle the genome at will.'<sup>46</sup> This will allow the researchers to evolve the yeast on demand, and to use evolution as a laboratory tool for obtaining new functionality,<sup>47</sup> which may prove to be an industrially relevant approach. Another aim is to find out more about biology, because it is hoped that the SCRaMbLE system 'will allow direct testing of evolutionary questions.'<sup>48</sup> Jef Boeke, the scientist leading the Sc2.0 project, says that he sees the synthetic yeast primarily 'as a learning tool.'<sup>49</sup> This tension between obtaining a greater understanding of biological systems and using this understanding in pursuit of industrial application runs through much of the current activity in synthetic biology.<sup>50</sup>

The intentional application of three 'design principles' shows that the synthetic yeast project, like much of synthetic biology, is strongly influenced by an aspiration to apply ideas from engineering to biology.<sup>51</sup> But the features that are being designed into the synthetic yeast compel us to think in new ways about the place of engineering in biology. For example, to what extent can we call the synthetic yeast genome a 'designer' genome if the SCRaMbLE system will yield unpredictable mutations? Evolution may be 'induced' in this project, but it is the power of the evolutionary process, not rational design, that is being harnessed. This raises questions about the relationship between evolution and rational design, questions that are becoming increasingly important to synthetic biology.<sup>52</sup>

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<sup>39</sup> Stephen George Oliver et al, above n 18.

<sup>40</sup> Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

<sup>41</sup> Elizabeth Pennisi, above n 24.

<sup>42</sup> Helen Thompson, *Scientists Build a Yeast Chromosome From Scratch. Next Up? Designer Genomes* (27 March 2014) *Smithsonian* <<http://www.smithsonianmag.com/science-nature/scientists-build-yeast-chromosome-scratch-next-up-designer-genomes-180950281/?no-ist>>.

<sup>43</sup> Ribonucleic acid.

<sup>44</sup> Elizabeth Pennisi, above n 24.

<sup>45</sup> Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

<sup>46</sup> Elizabeth Pennisi, above n 24.

<sup>47</sup> Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

<sup>48</sup> Narayana Annaluru et al, above n 2.

<sup>49</sup> William Herkewitz, above n 17.

<sup>50</sup> Maureen O'Malley et al, 'Knowledge-making distinctions in synthetic biology' (2008) 30(1) *BioEssays* 57.

<sup>51</sup> Pablo Schyfter, Emma Frow and Jane Calvert, 'Guest Editorial: Synthetic biology: Making Biology into an Engineering Discipline' (2013) 5(1) *Engineering Studies* 1.

<sup>52</sup> Jane Calvert, 'Evolution or design?' in Ginsberg et al, *Synthetic Aesthetics: Investigating Synthetic Biology's Designs on Nature* (Cambridge, MA: MIT Press, 2014) 259.

In contrast with much of the synthetic biology literature (particularly that from the 'BioBricks' school),<sup>53</sup> reporting about the synthetic yeast project discusses engineering mainly at the genomic or systems level<sup>54</sup> rather than focusing on standardised genetic 'parts', refactored genetic 'circuits',<sup>55</sup> and individual engineered 'devices' with specific functions.<sup>56</sup> In previous work, Calvert and colleagues distinguished between approaches to synthetic biology that focus on making standardised biological parts ('DNA-based device construction'), and those concerned with 'genome-driven cell-engineering', where the genome as a whole is regarded as the causal engine of the cell.<sup>57</sup> The synthetic yeast project is more strongly aligned with the latter approach. The ways in which engineering at the level of whole genomes might be considered similar to or different from engineering focused on parts (such as BioBricks), is a topic that would benefit from further investigation.

Interestingly, in our analysis of the media coverage surrounding the synthetic yeast chromosome, we find that some of the language departs from that typically associated with systematic engineering. For example, there are also many craft-like metaphors associated with the project — several sources use the language of 'stitching' and 'sewing' to describe the construction of the synthetic chromosome.<sup>58</sup>

## V OPENNESS AND OWNERSHIP

One area of strong similarity between the synthetic yeast project and the parts-based approach to synthetic biology is in their emphasis on openness and the sharing of synthetic biological constructs. The BioBricks approach has from its outset promoted the growth of a community of contributors who make their standardised biological parts freely and openly available for others to use. However, developing legal mechanisms to facilitate this has not been straightforward, given the strong emphasis on appropriation in biotechnology.<sup>59</sup> Similarly, those involved in the synthetic yeast project have decided that they will not claim intellectual property rights on the synthetic sequence. The Sc2.0 Statement of Ethics and Governance states this explicitly:

'We are committed to facilitating innovation and maximising beneficial use of Sc2.0. As such, no intellectual property rights will be exercised on the clones used to generate novel strains, intermediary strains, or the final Sc2.0 strain.'<sup>60</sup>

This has led to the synthetic yeast project being called 'the academic, open-source reply to what Venter did.'<sup>61</sup>

As this quotation suggests, the approach of the Sc2.0 consortium is very different from that taken in the JCVI's synthetic genomics work. The JCVI filed 13 patents in association with its synthetic *M. mycoides*, and their website maintains that:

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<sup>53</sup> Drew Endy, 'Foundations for Engineering Biology' (2005) 438 *Nature* 449.

<sup>54</sup> Priscilla Purnick and Ron Weiss, 'The second wave of synthetic biology: from modules to systems' (2009) 10(6) *Nature Reviews: Molecular Cell Biology* 410.

<sup>55</sup> Karsten Temme, above n 34.

<sup>56</sup> Although there is a passing reference to modularity in Dejana Jovicevic, Benjamin Blount and Tom Ellis above n 19.

<sup>57</sup> Maureen O'Malley et al, above n 50.

<sup>58</sup> Ewen Callaway, above n 22.

<sup>59</sup> Jane Calvert, 'Ownership and sharing in synthetic biology: a 'diverse ecology' of the open and the proprietary?' (2012) 7(2) *BioSocieties* 169.

<sup>60</sup> Statement, above n 28. It should be noted that intellectual property is allowed on derivatives of the yeast.

<sup>61</sup> Tom Ellis quoted in Ewen Callaway, above n 22.

'Intellectual property is important in the synthetic genomics/biology space as it is one of the best means to ensure that this important area of basic science research will be translated into key commercial products and services for the benefit of society'.<sup>62</sup>

Across the Sc2.0 project and JCVI's work, we thus see contradictory understandings of the relationship between intellectual property protection and innovation for 'beneficial use'.<sup>63</sup> More broadly, these two initiatives are grounded in different funding structures and institutional frameworks for supporting research and innovation, and draw different conclusions for how benefits (whatever they may be) are best derived.

The open norms we find in the yeast project may also owe something to the norms of the 'traditional' (non-synthetic) yeast research community. This is something we plan to investigate further. There may well also be parallels with other model organism research communities, such as the *Drosophila melanogaster* (fruit fly) community, which has traditionally adopted strong norms of 'sharing and free exchange',<sup>64</sup> and the *Caenorhabditis elegans* (worm) community, 'often celebrated as a model of scientific cooperation.'<sup>65</sup>

A striking feature of the synthetic yeast consortium is its emphasis on 'togetherness'. The tagline of the Sc2.0 website is 'Building the world's first synthetic eukaryotic genome together' (emphasis added), and the project has been called 'a great example of "do it together" biotechnology'.<sup>66</sup> Undergraduates in a popular 'build-a-genome' course at Johns Hopkins University carried out significant portions of the chromosome III synthesis.<sup>67</sup> The Sc2.0 project also officially involves a group of LA-based bio-hackers, and a class of high school students in New York.<sup>68</sup> With its language of togetherness, the Sc2.0 project undertakes a subtle but potentially meaningful shift away from the common 'do-it-yourself' description of synthetic biology activities involving bio-hackers and the lay public.<sup>69</sup> Social scientists have previously noted how 'do-it-yourself' communities are fundamentally dependent on the general infrastructure of science and engineering in order to operate,<sup>70</sup> but in the language chosen by the synthetic yeast project, the collaborative nature of synthetic biology endeavours becomes more explicit.

## VI SPATIALITY AND TEMPORALITY

Moving from the social organisation of the project to more conceptual issues, our preliminary discussions with scientists on the synthetic yeast project reveal the importance being placed on the spatial configuration of the yeast chromosome. For example, a key strand of the work in the 'Induced Evolution of Synthetic Yeast Genomes' project<sup>71</sup> will be to

<sup>62</sup> J. Craig Venter Institute, *First self-replicating synthetic bacterial cell* <<http://www.jcvi.org/cms/research/projects/first-self-replicating-synthetic-bacterial-cell/faq/#q11>>.

<sup>63</sup> Stephen Hilgartner, 'Novel Constitutions? New Regimes of Openness in Synthetic Biology' (2012) 7 *BioSocieties* 188.

<sup>64</sup> Robert Kohler, 'Moral Economy, Material Culture, and Community in *Drosophila* Genetics' in Mario Biagioli (ed), *The Science Studies Reader* (New York: Routledge, 1999) 243, 345.

<sup>65</sup> Rachel Ankeny, 'Fashioning Descriptive Models in Biology: Of Worms and Wiring Diagrams' (2000) 67 *Philosophy of Science* 260, 262.

<sup>66</sup> Drew Endy quoted in David Biello, above n 38.

<sup>67</sup> Jessica Dymond et al, 'Teaching synthetic biology, bioinformatics and engineering to undergraduates: the interdisciplinary Build-a-Genome course' (2009) 181(1) *Genetics* 13.

<sup>68</sup> Statement, above n 28.

<sup>69</sup> DIYbio, *An Institution for the Do-It-Yourself Biologist* (June 8 2015) <<http://diybio.org/>>.

<sup>70</sup> Alessandro Delfanti, 'Tweaking genes in your garage: Biohacking between activism and entrepreneurship' in Theo Hug and Wolfgang Sützl (eds), *Media Activism and Biopolitics: Critical Media Interventions in the Age of Biopower* (Innsbruck: Innsbruck University Press, 2012) 163.

<sup>71</sup> Projektträger Jülich (Germany), above n 8.

produce 3D images of the synthetic genomes to show how spatial organisation affects the design of new chromosomes, since ‘exactly how DNA is packaged up and put away is vitally important for the functioning of the organism.’<sup>72</sup>

This explicit attention to genome topology challenges the ‘flattened’ representations of genes and genomes that are often presented in circuit diagrams of gene regulation widely adopted in molecular biology and in parts-based synthetic biology.<sup>73</sup> Once we start conceptualising the yeast genome (in both its synthetic and non-synthetic forms), as an entity that is arranged, coiled, and packaged in 3D space, it becomes much harder to imagine it as ‘flattened’ and abstracted from its cellular context. This simplification is challenged even further by an acknowledgement of the temporal dimensions of this organism, which the scientists on the project also plan to address. They talk about wanting to conduct a 4D study of synthetic yeast (where the fourth dimension is time).<sup>74</sup>

We are not suggesting that spatiality and temporality are unique to yeast. They are of course essential features of all living systems and processes. Indeed, some maintain that it is their dynamic, processual nature that makes living things what they are — alive. As the philosopher of biology John Dupré puts it: ‘a static cell is a dead cell.’<sup>75</sup> We do see discussions of morphology and topology in other areas of both prokaryotic and eukaryotic synthetic biology, and there seems to be growing attention to exploring the physical constraints under which biological systems operate.<sup>76</sup> But spatiality and temporality are features of synthetic biology that are brought to life in our study of yeast. Growing attention to these characteristics might over time challenge dominant engineering approaches in synthetic biology, which tend to represent biological circuits as relatively static and flat. It seems that space and time are more easily ignored, eliminated or suppressed in some branches of synthetic biology than in others.

## VII THE PERSONALITY OF YEAST

A final feature of yeast to emerge from our analysis of the media coverage associated with chromosome III synthesis is that there was much discussion of its ‘personality’. For example, emphasis was placed on the familiar, ‘humble’ nature of brewer’s yeast, and there was also much talk of yeast as being ‘pliable’,<sup>77</sup> ‘tolerant’,<sup>78</sup> ‘robust’,<sup>79</sup> a ‘domesticated servant’,<sup>80</sup> and a ‘workhorse’.<sup>81</sup>

<sup>72</sup> Gregory E. Kaebnick, *Synthetic Chromosomes*, The Hastings Center (28 March 2014) <<http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6853&blogid=140>>.

<sup>73</sup> Nikolas Rose, ‘Molecular Biopolitics, Somatic Ethics and the Spirit of Biocapital’ (2007) 5(1) *Social Theory & Health* 3.

<sup>74</sup> Jef Boeke, personal communication. See also National Institutes of Health, *4D Nucleome* <<http://commonfund.nih.gov/4Dnucleome/index>>.

<sup>75</sup> John Dupre, ‘Living Causes’ (2013) 87(1) *Aristotelian Society Supplementary Volume* 19.

<sup>76</sup> Timothy Rudge et al, ‘Cell Polarity-Driven Instability Generates Self-Organized, Fractal Patterning of Cell Layers’ (2013) 2(12) *American Chemical Society Synthetic Biology* 705.

<sup>77</sup> Narayana Annaluru et al, above n 2.

<sup>78</sup> Dan Vergano, ‘Scientists Move Closer to Inventing Artificial Life’, *National Geographic* (online), 27 March 2014 <<http://news.nationalgeographic.com/news/2014/03/140327-functional-designer-chromosome-synthetic-biology/>>.

<sup>79</sup> Alan Boyle, ‘Gene Gurus Create Synthetic Yeast Chromosome From Scratch’, *NBC News* (online), 27 March 2014 <<http://www.nbcnews.com/science/science-news/gene-gurus-create-synthetic-yeast-chromosome-scratch-n63316>>.

<sup>80</sup> Jessica Dymond et al, above n 37.

<sup>81</sup> *Ibid.*

There seem to be attempts to preserve the character and ‘personality’ of yeast even in its synthetic form. This connects to one of the project’s three design principles: that the fitness of the yeast should be maintained. After publishing the synthesis of chromosome III, Boeke is reported as saying: ‘We checked everything by sequencing the whole chromosome and we also tested the “yeastiness” and saw essentially no difference with normal yeast.’<sup>82</sup> In another interview he explains: ‘we’ve actually got a yeast that looks like a yeast, smells like a yeast, and makes alcohol like a yeast’, adding ‘We can’t really tell it apart, and yet it’s so different.’<sup>83</sup>

Given the radical changes being made to the synthetic yeast genome (including the creation of a ‘neo-chromosome’), the extent to which preservation of ‘yeastiness’ is understood is an issue we hope to explore further. We speculate that such refactoring of existing genomes may challenge traditional species distinctions and give rise to questions about species identity and taxonomy.<sup>84</sup> This may, in turn, raise broader ethical questions about, for example, our responsibilities towards different ‘natural’ and ‘synthetic’ species of yeast or other refactored species (both prokaryotic and eukaryotic). Krzywoszynska<sup>85</sup> argues that we should see yeast as a ‘matter of concern’;<sup>86</sup> as a subject with its own ‘telos’ independent of human intentionality. Questions arise here about the telos of the *synthetic* yeast, a tool for understanding and manipulation, purposely designed to evolve on demand.<sup>87</sup> We plan to explore in more depth what is implied by the researchers’ attempt to ensure they have created a ‘happy, healthy yeast.’<sup>88</sup>

## VIII CONCLUSION

In closing, we reflect on how the relationship between biology and engineering — one of our key research interests in synthetic biology<sup>89</sup> — plays out in the synthetic yeast project, technically, socially and conceptually.

Technically, the synthetic yeast project is a large-scale refactoring exercise driven by intentional design principles, so to this extent it is well aligned with an engineering agenda. However, the media reporting about the project suggests that the drive for standardisation is not as strong as in other branches of synthetic biology. And the emphasis on the whole genome, rather than discrete ‘parts’, in the synthetic yeast project may lead to a different conception of biological engineering, which might require a greater recognition of the importance of context. Additionally, the attempt to harness the powers of evolution that we

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<sup>82</sup> Jef Boeke quoted in James Urquhart, *Synthetic yeast chromosome is fully functional* (27 March 2014) Royal Society of Chemistry <<http://www.rsc.org/chemistryworld/2014/03/synthetic-yeast-chromosome-fully-functional>>.

<sup>83</sup> Jef Boeke quoted in Helen Thompson, above n 42.

<sup>84</sup> Carrie Friese notes taxonomic conundrums facing zoo professionals creating interspecies ‘chimeric’ offspring of endangered species; the speculative designer Daisy Ginsberg has also drawn attention to possible challenges to current taxonomic practices with the advent of genome synthesis. See Carrie Friese, ‘Classification conundrums: categorizing chimeras and enacting species preservation’ (2010) 39(2) *Theory and Society* 145.

<sup>85</sup> Anna Krzywoszynska, above n 13.

<sup>86</sup> Bruno Latour, ‘Why Has Critique Run out of Steam? From Matters of Fact to Matters of Concern’ (2004) 30(2) *Critical Inquiry* 225.

<sup>87</sup> Gregory E. Kaebnick, above n 72.

<sup>88</sup> Jef Boeke quoted in Arielle Duhaime-Ross, *Scientists just took a major step toward making life from scratch* (27 March 2014) The Verge <<http://www.theverge.com/2014/3/27/5553044/first-functional-eukaryotic-chromosome>>.

<sup>89</sup> See, eg, Emma Frow and Jane Calvert, ‘Can simple biological systems be built from standardized interchangeable parts?’ (2013) 5(1) *Engineering Studies* 42.

see in this project perhaps gives away some of the control that we normally associate with engineering approaches.<sup>90</sup>

With respect to its social dimensions, we see that the large-scale, international synthetic yeast project is perceived to require specific guidelines and oversight precisely because of its distributed nature and size. Issues concerning the division of labour, credit, and reward also become more pertinent. 'Big science' as a term was originally associated with the physical sciences and engineering, with the HGP being one of the first 'big biology' projects.<sup>91</sup> The synthetic yeast project looks set to continue this trend. 'Scaling-up' is a key aspiration of engineering,<sup>92</sup> but this may take on novel forms and characteristics when the focus is biological.<sup>93</sup>

We have also mentioned the synthetic yeast project's preference for openness with regards to intellectual property, and compared this to similar norms in the BioBricks school of synthetic biology, and the more proprietary approach adopted in the JCVI's work on synthetic bacteria. The BioBricks approach explicitly draws on computer engineering, and is inspired by open-source software. The synthetic yeast project is influenced by this agenda, but its orientation towards openness may also be something that is carried over from the traditional yeast research community, since openness is often a feature of model organism communities.

More conceptually, we have shown how the synthetic yeast project encourages us to think explicitly about the spatial and temporal dimensions of the organisms used in synthetic biology — dimensions that are perhaps more easily ignored or overlooked in work on simpler organisms. Arguably, it is the dynamic and processual nature of living things that distinguishes them from engineered artefacts. We asked about the extent to which the organism's 'yeastiness', and perhaps even its telos, might be preserved in its synthetic form. The attempts to keep synthetic yeast 'happy' may go beyond the instrumentalisation that we expect of engineering approaches.

As researchers in STS, our primary concern is not with regulation, nor in attempting to draw a line between permissible and prohibited research. Instead, in this commentary we have highlighted key themes, issues and topics of investigation that the synthetic yeast project encourages us to think about, particularly with respect to the relationship between engineering and biology that is central to this emerging field. We hope that this brief foray into eukaryotic synthetic biology via the synthetic yeast project will prove useful in guiding our understanding of, and reflections on, the development of synthetic biology as it moves into more complex organisms and systems

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<sup>90</sup> That being said, directed evolution approaches are becoming increasingly widespread in synthetic biology, and are not limited to synthetic yeast. See Ryan Cobb, Tong Si and Huimin Zhao, 'Directed evolution: an evolving and enabling synthetic biology tool' (2012) (16) *Current Opinion in Chemical Biology* 285.

<sup>91</sup> Stephen Hilgartner, above n 25.

<sup>92</sup> Emma Frow, 'Making big promises come true? Articulating and realizing value in synthetic biology' (2013) 8 *BioSocieties* 432.

<sup>93</sup> Gail Davies, Emma Frow and Sabina Leonelli, 'Bigger, faster, better? Rhetorics and practices of large-scale research in contemporary bioscience' (2013) 8 *BioSocieties* 386.



# ETHICAL ISSUES IN SYNTHETIC BIOLOGY: A COMMENTARY

WENDY ROGERS\*

*This paper provides a brief overview of ethical issues associated with synthetic biology and identifies three ethical challenges to consider in the development and management of synthetic biology. First, the injunction to use synthetic biology for the good of humankind raises questions about who should determine the direction and uses of synthetic biology. This issue is discussed in terms of setting the research agenda. Second, there are questions about the extent to which bioethics is, and ought to be, a 'critical companion' for novel and emerging technologies. This question is stimulated by the observation that some of the most cogent criticisms of synthetic biology have come from within the field, rather than from external bioethical critiques. Finally, there are calls for professionalisation as a mechanism for self-regulation regarding ethical behaviour. However, as there are diverse disciplines engaged in synthetic biology, it may be difficult to settle on a single set of agreed professional norms.*

## I CONTEXTUALISING SYNTHETIC BIOLOGY

Debates about the ethics of synthetic biology tend to focus on a small number of what are seen as key issues, and to take a broadly consequentialist approach.<sup>1</sup> The potential benefits of synthetic biology are characterised as advancing knowledge and understanding, and creating useful practical applications.<sup>2</sup> Potential advances in knowledge relate to increasing our understanding of complex biological processes such as the functioning of DNA or the chemical processes necessary for life to exist. Prospective practical benefits include: the creation of 'biofactories' for manufacturing cheap medicinal products; new energy sources and biofuels; organisms engineered to clean up environmental degradation; and new materials for a range of applications.<sup>3</sup>

Despite the significance of these potential benefits, there are a number of serious ethical concerns about synthetic biology, regarding both physical and non-physical harms. Physical harms relate principally to safety and security. Given the novel nature of synthetic biology creations, the accidental or intentional release of engineered organisms may lead to extensive and unpredictable environmental damage, or damage to the health of human and non-human animals. This potential for harm leads directly to concern about biosecurity, and raises questions about the most appropriate ways to safeguard both knowledge and physical products.<sup>4</sup> Alongside these physical harms, concerns about broader issues of wellbeing have led to various normative and existential questions.

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<sup>1</sup> Ainsley Newson, 'Current Ethical Issues in Synthetic Biology: Where Should We Go From Here?' (2011) 18 *Accountability in Research* 181, 185.

<sup>2</sup> Eric Parens, Josephine Johnston and Jacob Moses, *Ethical Issues in Synthetic Biology: An Overview of the Debates* (Woodrow Wilson International Centre for Scholars, 2009), 14.

<sup>3</sup> Ibid 14.

<sup>4</sup> Ibid 17.

These include concerns about the fair distribution of benefits and harms from synthetic biology; the implications of 'playing god' through the creation of artificial life; and the potential impact of synthetic biology upon deeply held beliefs about the appropriate relationship between humans and the natural world.<sup>5</sup>

## II COMMENTARY

There is unresolved debate in the literature as to whether synthetic biology raises unique ethical issues.<sup>6</sup> Whether or not the issues are ethically unique, there is some agreement that the ethical management of synthetic biology requires a multidisciplinary response, a focus upon professional duties and responsibilities, and a commitment to transparency and public debate.<sup>7</sup> To this end, there has been discussion amongst synthetic biologists about their own roles and responsibilities, leading in some cases to formal commitments. The Synthetic Yeast 2.0 project ('Sc2.0'), for example, has its own statement of governance and ethics, which is binding upon all researchers involved with the multi-national collaboration to synthesise a yeast genome.<sup>8</sup> The statement enjoins researchers to work for the benefit of humankind; be open and transparent; comply with relevant national and local regulations; avoid providing materials to those with nefarious intent; embrace an ethos of personal and environmental safety; undertake ethics training; and have a commitment to open sharing of intellectual property. This statement identifies concerns about biosafety and bioterrorism, commits to only beneficent uses of synthetic biology, and seeks to guarantee ethical practice through strategies including legal and regulatory compliance as well as mandatory ethics training.

In what follows, I briefly explore three issues raised in this statement and elsewhere in the literature. In so doing, I hope to identify some of the complexities underlying what may be presented as relatively straightforward ethical issues raised by synthetic biology, and to question the role of bioethics in engaging with the ethical challenges of synthetic biology. The first is the injunction to use synthetic biology for the good of humankind, which I call the agenda setting question. The second concerns the role of bioethics in synthetic biology, and to what extent bioethics is and ought to be a 'critical companion' for novel and emerging technologies. Finally, I touch upon the subject of professionalisation, as many in the field consider that whether or not synthetic biology turns out to be a force for good in the world will depend upon the behaviours of those working in the field. Whilst none of these issues is unique to bioethics, familiar issues can play out in unfamiliar ways in this new field.

### A *Agenda Setting*

Agenda setting is one of the most critical, and most neglected, issues in research ethics. Most of the information we have about agenda setting in research comes from the medical arena. There are plausible claims that medical research has, to a significant extent, been diverted away from the ideal aim of knowledge generation in the service of healthcare, and instead is subject to the commercial aims of the pharmaceutical and biomedical industry.<sup>9</sup> That is, the agenda is not set by aims to do with improving human health, but rather is the result of

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<sup>5</sup> Ibid 18; Markus Schmidt et al, 'A Priority Paper for the Societal and Ethical Aspects of Synthetic Biology' (2009) 3 *Systems Synthetic Biology* 3, 5.

<sup>6</sup> David Heyd, 'Is There Anything Unique in the Ethics of Synthetic Biology?' (2012) 55 *Perspectives in Biology and Medicine* 581, 584; Newson, above n 1, 189.

<sup>7</sup> Newson, above n 1, 190; Schmidt et al, above n 5, 5.

<sup>8</sup> Synthetic Yeast 2.0, *Statement of Ethics and Governance* (24 Nov 2013) syntheticyeast.org <[http://syntheticyeast.org/wp-content/uploads/2014/04/Sc2\\_EthicsAndGovernanceAgreement\\_131124final.pdf](http://syntheticyeast.org/wp-content/uploads/2014/04/Sc2_EthicsAndGovernanceAgreement_131124final.pdf)>.

<sup>9</sup> Wendy Rogers and Angela Ballantyne, 'Justice in Health Research: What is the Role of Evidence-based Medicine?' (2009) 52 *Perspectives in Biology and Medicine* 188.

commercial interests. The evidence for this claim is increasingly persuasive, to the point that there are credible estimates that 85 per cent of medical research is wasted, usually because it asks the wrong questions, is badly designed, remains unpublished or is poorly reported.<sup>10</sup>

These failures in medical research provide salutary lessons about the perils of allowing research agendas to evolve unprotected from market forces. This is an opportunity for the synthetic biology community to take stock, consider the forces at work on current research agendas in synthetic biology, and act together to shape these agendas. First, we need to ask what it might mean to have a research agenda in synthetic biology. Who would propose the agenda, and what values would it be based upon? Debate about medical research, although stopping short of suggesting some kind of overarching agenda, has led to various recommendations about prioritising research.<sup>11</sup> These include strategies for increasing the yield of basic research; increasing transparency about which projects are funded and why; taking account of the needs of end-users; building upon existing research; and increasing communication about what research is in progress.<sup>12</sup> These strategies are consistent with the focus in synthetic biology on transparency and open communication of results, but it is not clear who are the 'end users' and whose needs should be prioritised. Are they governments who want weapons, the private sector who seek profitable products, or the public? And if the latter, the public is clearly not homogenous in its attitudes towards synthetic biology, which would make development of a research agenda based upon public views difficult.<sup>13</sup> The Sc2.0 Statement refers to 'the good of humankind' but this does not translate easily into a consultation or prioritisation strategy, especially where funding comes from commercial sources. Taking agenda setting seriously will make decisions about which projects to pursue or abandon easier, by providing transparency about the grounds to justify such decisions.

## B *Bioethics as a Critical Companion for Synthetic Biology*

French philosopher Bernadette Bensaude-Vincent proposes that bioethics should be a critical companion for synthetic biology.<sup>14</sup> Bensaude-Vincent argues that bioethicists and critical activists have largely taken the claims of synthetic biologists at face value, that is, they have concurred with what she calls the 'visions of incredible futures'.<sup>15</sup> In so doing, programs aimed at identifying ethical, legal and social issues (ELSI programs) tend to reinforce rather than challenge the credibility of the promises made by synthetic biologists. She notes that, somewhat ironically, the most serious challenges to some of the more utopian promises of synthetic biology come from within the field rather than from either ethicists or critical activists.<sup>16</sup> Three of these challenges revolve around theoretical assumptions, experimental aspects and economic considerations, which are considered in this commentary.

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<sup>10</sup> John PA Ioannidis, 'How to Make More Published Research True' (2014) 11 (10) *Public Library of Science Medicine* <<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001747>>.

<sup>11</sup> Iain Chalmers et al, 'How to increase value and reduce waste when research priorities are set' (2014) 383 *Lancet* 156.

<sup>12</sup> *Ibid.*

<sup>13</sup> Hart Research Associates, *Awareness & Impressions Of Synthetic Biology: A Report Of Findings* (Hart Research Associates, 2010) 6, 7.

<sup>14</sup> Bernadette Bensaude-Vincent, 'Between the Possible and the Actual: Philosophical Perspectives on the Design of Synthetic Organisms' (2013) 48 *Futures* 23.

<sup>15</sup> *Ibid* 23.

<sup>16</sup> *Ibid* 24, 26.

### 1 *Theoretical Assumptions*

First, there is concern that some of the foundational theoretical assumptions underpinning synthetic biology may be flawed. For example, synthetic biology draws heavily on the analogy between cells and computers, where genetic expression is seen as the program/software, and the cell machinery or chassis taken to be the equivalent of computer hardware. However, although software may be self-replicating, the hardware is not and so the analogy between cells and computers is flawed. Computers do not replicate themselves.<sup>17</sup> Given the ubiquity of this metaphor, it is perhaps surprising that this criticism is not widely aired, because the way that we conceptualise objects such as cells has significant implications for the ways that research about them will develop. In addition, many of the imagined futures of synthetic biology assume that recipient cells will be receptive to the introduction of new genomic material and that the resulting organisms will be permanently reliable.<sup>18</sup> This assumption is questionable given the tensions between evolution and preservation in naturally occurring cells.

### 2 *Experimental Challenges*

Second, there are experimental challenges in applying the engineering principles of standardisation, decoupling and abstraction to biology. Bensaude-Vincent notes that 'unlike the parts assembled in mechanical engineering, the building blocks of synthesis inevitably interact'.<sup>19</sup> These interactions, which may be more or less unpredictable, affect the identity and behaviour of the ensuing organisms. That is, the rational principles of engineering come unstuck in the chaotically interactive world of biology. For example, there are claims that the majority of the parts in the international Registry of Standard Biological Parts (an open access repository of synthetic biology 'snippets') do not function as advertised.<sup>20</sup> Furthermore, engineering metabolic pathways is messy and painstaking work. It is notable that the successes of synthetic biology, such as the development of Artemisinin, have been plagued by unexpected interactions between parts, and proceeded by trial and error rather than by applying rational engineering principles.<sup>21</sup> The proclaimed principles of synthetic biology do not always, and perhaps only rarely, correspond with practice. It will be important for bioethicists who wish to engage, critically or otherwise, with synthetic biology, to understand experimental issues as well as to question dominant assumptions.

### 3 *Economic Assumptions*

Third, it is unclear whether the predicted bioeconomy is sustainable. Rob Carlson has noted that given current costs, the finances needed to upscale synthetic biology far exceeds plausible investment capacities.<sup>22</sup> The promise of course is that as critical mass builds, costs will fall, but it is unclear whether in fact this is the case. It is also unclear as to whether an open source system, such as is currently endorsed by many of the scientists, will encourage the investments thought to be necessary to create commercially viable synthetic biology. At least one economic analysis suggests that some kind of hybrid system that incorporates

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<sup>17</sup> Antoine Danchin, 'Bacteria as Computers making Computers' (2008) 33 *FEMS Microbiology Reviews* <<http://dx.doi.org/10.1111/j.1574-6976.2008.00137>>.

<sup>18</sup> Bensaude-Vincent, above n 14, 27.

<sup>19</sup> *Ibid* 27.

<sup>20</sup> Sam Kean 'A Lab of their Own' (2011) 333 *Science* 1240, 1241.

<sup>21</sup> Bensaude-Vincent, above n 14, 27.

<sup>22</sup> Rob Carlson, *Biology is Technology: The Promise, Peril, and New Business of Engineering Life* (Harvard University Press, 2010) 104–5, cited in Bensaude-Vincent, above n 14, 27.

limited proprietary protections may lead to greater rates of innovation than a completely open source system.<sup>23</sup>

Bensaude-Vincent's examples argue for bioethicists to engage deeply and critically with specific scientific claims and individual projects, as the issues that arise are complex and particular. Crucially, ELSI contributions can help to ask the hard questions, such as what would count as failure in particular avenues of investigation. Without such engagement, the humanities and social sciences will contribute little to shaping and enriching the field, but instead will be left to react to the promises made by perennially, and sometimes wildly, optimistic synthetic biologists.

### C Professionalisation

My final point concerns the behaviours that we might want synthetic biologists to engage in, and how to encourage these behaviours. Professionalisation has been suggested as a potential option for supporting high ethical and governance standards in synthetic biology.<sup>24</sup> Professionalisation has the flexibility of self-governance whilst incorporating elements of legal regulation, and mandating accountability for individuals and for a profession as a whole.<sup>25</sup> Another potential advantage of professionalisation is that members of a profession are seen as responsible, with clearly defined fiduciary duties and various standards that can be enforced.<sup>26</sup> Obviously there is a gap between being seen as, and actually being, responsible that cannot be bridged by membership of a profession alone, but membership may help to support an ethos of professional responsibility and accustom synthetic biologists to recognising and responding to the ethical dimensions of their work.<sup>27</sup> Fostering an ethic of responsibility and accountability through professionalisation may bridge the gap between engineers and molecular biologists, and encourage the latter to link their expert knowledge more explicitly with moral obligation.<sup>28</sup> Leadership is essential to building professional ethos, otherwise it is very difficult to instil ethical ideals and promote ethical practice, especially where members of the (new) profession come from different training backgrounds and cultures. Such fertile ground will be necessary for codes of ethical conduct, such as that in the Sc2.0 statement, to flourish. This will entail normalising practices, such as discussion of the implications of the work at hand, and having a constant willingness to ask questions about who may be harmed or benefited, and what values are at play in particular projects. Without deep and meaningful engagement at all levels, professionalisation is unlikely to achieve its intended goals. And of course, professionalisation will not stop those with truly nefarious intent, although an ethos of ethical practice may render those who pose a risk to biosafety and biosecurity easier to identify.

## III CONCLUSION

In summary, synthetic biology does hold the promise of new and exciting technologies, but as with any new field, there are challenges in shaping and directing the field and minimising the risk of harm. Some of the emerging ethical norms, such as the injunction to use synthetic biology only for the benefit of humankind, may prove difficult to implement unless care is taken with setting the research agenda. Bioethical engagement will hinge, to some extent,

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<sup>23</sup> Joachim Henkel and Stephen Maurer, 'The Economics of Synthetic Biology' (2007) 3 *Molecular Systems Biology* 117.

<sup>24</sup> Lorna Weir and Michael J Selgelid, 'Professionalisation as a Governance Strategy for Synthetic Biology' (2009) 3 *Systems and Synthetic Biology* 92.

<sup>25</sup> *Ibid* 95.

<sup>26</sup> *Ibid*.

<sup>27</sup> *Ibid*.

<sup>28</sup> *Ibid* 92.

upon bioethicists having a critical stance as well as an intimate knowledge of the science. Otherwise, they risk irrelevance. Finally, professionalism is touted as a potential ethical regulatory mechanism for synthetic biology but the success of this will depend upon strong and ethically sophisticated leadership.

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# SYNTHETIC BIOLOGY: ETHICS, EXCEPTIONALISM AND EXPECTATIONS

AINSLEY J NEWSON\*

*Synthetic biology gives rise to ethical implications. These are already well recognised, with an ever-increasing academic and lay literature and growing attention from policy-makers. What is less clear is whether analysis of ethics in synthetic biology should be 'exceptional'. That is, is there anything about synthetic biology that justifies a distinctive 'ethics of' approach? Likewise, what may or may not be fruitful directions for useful bioethical inquiry in synthetic biology remains under-explored. This paper first synthesises ethical issues arising in synthetic biology. A claim is then advanced that while a purely exceptionalist approach to ethics and synthetic biology is unwarranted, the field nevertheless requires engagement with ethics. Initial suggestions are put forward as to how this might be achieved. The paper then determines several hitherto under-explored lines of enquiry which serve to both further useful discussions of synthetic biology and contribute to the wider project of ethical engagement in emerging technologies.*

## I INTRODUCTION

Synthetic biology involves the deliberate application of engineering principles to well-defined molecular components to synthesise novel or augment existing biological entities.<sup>1</sup> One aim of this research area is to extend previously limited biological functionalities, or create entirely new ones, in a standardised, defined, and reproducible way. Synthetic biology has become possible due to rapid advances in technologies such as DNA synthesis and engineering.<sup>2</sup> While its practical applications remain putative, its theoretical utility is almost limitless. This combination of research approaches, and its broad array of uses in medicine and the environment, makes synthetic biology a potentially disruptive technology.<sup>3</sup>

This paper will address three interlinked topics. First, the ethical issues that arise, or are likely to arise, in synthetic biology research and its applications are synthesised. As Link has pointed out, these may not be 'debates' as such – discussions regarding ethical issues in the development and application of synthetic biology have been directed more towards

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<sup>1</sup> There is no single definition of synthetic biology that is adopted by all who identify as researchers in this field. The description offered in this paragraph is the author's own, based on eight years working in the field. However, a range of definitions of synthetic biology are used in practice. See, eg, News Feature, 'What's in a Name?' (2009) 27 *Nature Biotechnology* 1071, 1071–3; Alexander Kelle, 'Synthetic Biology as a Field of Dual-Use Bioethical Concern' in Brian Rappert and Michael J Selgelid (eds), *On the Dual Uses of Science and Ethics* (Australian National University ePress, 2013) 45, 46–49. Other papers in this special issue of the *Macquarie Law Journal (MqLJ)* also define synthetic biology.

<sup>2</sup> Jing Liang, Yunzi Luo and Huimin Zhao, 'Synthetic Biology: Putting Synthesis into Biology' (2011) 3 *Wiley Interdisciplinary Reviews: Systems Biology and Medicine* 7, 8–10.

<sup>3</sup> James Manyika et al, 'Disruptive Technologies: Advances That Will Transform Life, Business, and the Global Economy' (Report, McKinsey Global Institute, May 2013) 4.

*anticipating* potential issues.<sup>4</sup> Public attitudes to this technology have generally been positive.<sup>5</sup> However, groups that champion environmental and other interests have also shown an interest in synthetic biology.<sup>6</sup> This scrutiny of the field will no doubt continue.

The paper then examines two interrelated questions: the novelty of ethical issues arising in synthetic biology, and whether its ethical analysis should be regarded as exceptional. Both questions are answered in the negative. However, synthetic biology does give rise to ethical issues and, as such, warrants attention in the discipline of bioethics. Building on this discussion, the third part of the paper then discusses some possible future directions for ethical analysis in synthetic biology.

The paper concludes that there is unlikely to be one straightforward proclamation about the acceptability of synthetic biology. The challenge for bioethics is to develop a reasoned response to synthetic biology that can account for the field's novelty and promise, while at the same time not simply reiterating issues that have been raised in other contexts.

## II ETHICS AND SYNTHETIC BIOLOGY

This section will review and synthesise the ethical aspects of synthetic biology and its applications to date. Generally, ethical issues discussed in synthetic biology have not been raised in an attempt to prevent this field of research (unlike in similar fields such as genetic modification). Rather, engagement and bidirectional dialogue between ethicists, researchers and funders have prevailed.<sup>7</sup>

Deliberation over ethical issues has been included in the field of synthetic biology in numerous ways. For example, ethics has been included in programmes for synthetic biology conferences.<sup>8</sup> Research funders providing dedicated resources for synthetic biology research have required researchers to address ethical, legal and social implications.<sup>9</sup> An increasing number of reports are considering the ethical and policy implications of synthetic biology.<sup>10</sup>

The majority of ethics work has evaluated the synthetic biology *as a field*.<sup>11</sup> That is, ethical analysis has tended to examine the implications of synthetic biology research as a whole, as

<sup>4</sup> Hans-Jürgen Link, 'Playing God and the Intrinsic Value of Life: Moral Problems for Synthetic Biology?' (2013) 19 *Science and Engineering Ethics* 435, 436.

<sup>5</sup> See, eg, Suzanne King and Tara Webster, 'Synthetic Biology: Public Dialogue on Synthetic Biology' (Report, Royal Academy of Engineering (UK), June 2009), 15, 23, 28, 39.

<sup>6</sup> See, eg, ETC Group (Canada), 'Extreme Genetic Engineering: An Introduction to Synthetic Biology' (Report, Jan 2007).

<sup>7</sup> See, eg, Paul Rabinow, 'Assembling Ethics in an Ecology of Ignorance' (Paper presented at Synthetic Biology 1.0, Massachusetts Institute of Technology, Cambridge MA, 11 June 2004) <[http://syntheticbiology.org/Synthetic\\_Biology\\_1.0/Speakers.html](http://syntheticbiology.org/Synthetic_Biology_1.0/Speakers.html)>.

<sup>8</sup> See, eg, Rabinow, above n 7; *Synthetic Biology 3.0*, (24-26 June 2007) <<http://www.syntheticbiology3.ethz.ch/extra/SBProceedings.pdf>>; See generally *Synbio.org* (2015) <<http://syntheticbiology.org/Conferences.html>>, which provides a list of previous conferences in synthetic biology.

<sup>9</sup> See, eg, Philip Shapira and Abdullah Gök, 'UK Synthetic Biology Centres Tasked with Addressing Public Concerns', *The Guardian* (online), 30 January 2015 <<http://www.theguardian.com/science/political-science/2015/jan/30/uk-synthetic-biology-centres-tasked-with-addressing-public-concerns>>.

<sup>10</sup> See, eg, Andrew Balmer and Paul Martin, 'Synthetic Biology: Social and Ethical Challenges' (Institute for Science and Society, University of Nottingham, May 2008); Erik Parens, Josephine Johnston and Jacob Moses, 'Ethical Issues in Synthetic Biology: An Overview of the Debates' (Woodrow Wilson International Centre for Scholars, 2009); Presidential Commission for the Study of Bioethical Issues (US), *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (2010).

<sup>11</sup> Patrick Heavey, 'Integrating Ethical Analysis "Into the DNA" of Synthetic Biology' (2015) 18 *Medicine, Healthcare and Philosophy* 121, 121.

opposed to critiquing individual projects or applications within it. There are likely several reasons for this. First, when ethical analysis within synthetic biology commenced, not a great deal was known about particular applications and so it was necessary to take a broad approach. Second, synthetic biology has some novel unifying features. Despite there being no single definition or approach, these 'new' features provide a basis for ethical analysis.<sup>12</sup> Third, while individual projects in synthetic biology are beginning to give rise to novel data and results, such projects are more fundamental (and perhaps aligned with more 'standard' research in disciplines such as chemistry or physics) and may not have any significant ethical relevance beyond questions such as research integrity. Fourth, undertaking implications-based assessments of individual projects may not give much scope for novel ethical inquiry. Finally, there is much about synthetic biology when viewed *as a field* that is ethically relevant and interesting. For example, agenda-setting and reflection on modes of working can and should be subject to ethical inquiry.<sup>13</sup> Analyses are commencing to determine how the field as a whole should move forward. Looking at synthetic biology as a field, the ethical and conceptual issues raised in the literature can be classified as follows: defining and creating life; biosafety and biosecurity; benefit sharing; professional ethics and integrity; and regulation and policy-making. Each of these considerations will now be synthesised.

#### A *Synthetic Biology and the Definition and Creation of 'Life'*

Synthetic biology has already been used to generate a synthetic genome,<sup>14</sup> and efforts to synthesise minimal cells from simple organisms such as yeast are underway.<sup>15</sup> While not yet possible, future research in synthetic biology could generate novel 'living' entities capable of activities such as self-replication, energy consumption and use. Potential applications of synthetic biology raise numerous philosophical and ethical questions, among them: (i) What properties should an entity possess in order for it to be termed 'alive'? (ii) Is research in synthetic biology that gives rise to new biological entities that are alive warranted? (iii) Should the manner in which an entity came to be alive matter? (iv) If a living entity is created, at what point should that entity have rights normally ascribed to those possessing moral status and thus a right to life? It is beyond the scope of this paper to address these questions in depth, but each will be briefly considered.

With respect to (i) the definition of life, or the properties that an entity should possess to be termed 'alive', there are claims in the literature that a single definition is not possible nor would such a definition be stable.<sup>16</sup>

On question (ii), whether synthetic biology should be used to create new life forms, an absolutist approach is unlikely due to the varying kinds of entities that may be created in different contexts. Nevertheless, the question is a useful guide to the relevant ethical considerations. Those cautious about creating new life forms will point to the fact that as yet,

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<sup>12</sup> This point is considered further in the final section of this paper.

<sup>13</sup> Thomas Douglas and Julian Savulescu, 'Synthetic Biology and the Ethics of Knowledge' (2010) 36 *Journal of Medical Ethics* 687, 687; Wendy Rogers, 'Ethical Issues in Synthetic Biology: A Commentary' (2015) 15 *Macquarie Law Journal* 39.

<sup>14</sup> Daniel G Gibson et al 'Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome' (2010) 329 *Science* 52.

<sup>15</sup> Jane Calvert and Emma Frow, 'The Synthetic Yeast Project as a Topic for Social Scientific Investigation' (2015) 15 *Macquarie Law Journal* 27.

<sup>16</sup> Balmer and Martin, above n 10, 26–29; Editorial, 'Meanings of "Life": Synthetic Biology Provides a Welcome Antidote to Chronic Vitalism' (2007) 447 *Nature* 1031, 1032. The European Commission has claimed that synthetic biology will give rise to calls for a more sophisticated definition of life. See New and Emerging Science and Technology (NEST) High-Level Expert Group, 'Synthetic Biology: Applying Engineering to Biology' (Project Report No EUR 21796, European Commission, 2005) 19 <[ftp://ftp.cordis.europa.eu/pub/nest/docs/syntheticbiology\\_b5\\_eur21796\\_en.pdf](ftp://ftp.cordis.europa.eu/pub/nest/docs/syntheticbiology_b5_eur21796_en.pdf)>.

very little is known about the possible benefits. Although researchers have established key components of biological knowledge, such as the sequence of the human genome, research to determine the *function* of genes and *regulation* of gene expression in complex organisms is less developed. The risks associated with creating completely new organisms, particularly if they are to be released into the environment, should be carefully considered.<sup>17</sup> There is also a concern that creating life may mechanistically reduce the complexities of life to engineering principles.

In reply, it may be claimed that the benefits of creating new life forms should not be discounted before research is undertaken. Some synthetic biology researchers are working towards developing new life forms, but only on a small scale, and with careful design and oversight. Creating new life forms will also give rise to intrinsic biological knowledge, valuable in its own right. It may inspire awe in life's complexity as opposed to viewing life mechanistically. While risk will be inherent when creating life, this on its own may not be enough to condemn the creation of new life forms, so long as there is accountability and risks are well assessed.

Related to these questions is (iii), whether the manner in which an entity came to be alive should matter. It could be claimed that the properties of an entity denoting it as 'living' are all that are needed. Others, perhaps those who value the 'natural' or 'naturalistic' concepts of life, may argue that the mode of creation of a life and the intent in such creation are also important. However, a consensus seems to be emerging that the former of these positions is more relevant to ethical deliberation. Namely, we should look at the properties of an entity to determine its moral status, not how that entity was made. To this end, demarcating between 'natural' and 'artificial' means of creating life is likely to be unhelpful and unnecessary.<sup>18</sup>

The final question (iv) asks at what point a new life form created by synthetic biology attains moral status. This question is motivated by a concern that if synthetic biology can create new (and potentially complex) entities, then we need to know how to treat them. It may be ethically inappropriate to create new entities that have moral status, but then treat those entities poorly. If the answer to (iii) is that it is justifiable to separate 'natural' and 'artificial' life forms, and to treat them differently depending on their origins, then this final question may be moot. However, consensus is emerging that the rights of artificially created living entities should not depend on their mode of creation.<sup>19</sup> If correct, this means it would be inappropriate to apportion different ethical significance to entities created in different ways. If mode of creation is irrelevant to moral status, then the focus shifts to a more classic investigation as to the properties of a living entity that afford it moral status, and accordingly, certain rights. These properties remain contested, but may include sentience, the ability to feel pain, and the ability to conceive of oneself as a being with a past and a future.<sup>20</sup> Mere biological life is not enough. It is therefore reasonable to suggest that not all living entities created through synthetic biology will have a status deserving of moral respect.

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<sup>17</sup> This point is considered further in the discussion of ethical issues and policy and regulation in synthetic biology.

<sup>18</sup> David Heyd, 'Is There Anything Unique in the Ethics of Synthetic Biology?' (2012) 55 *Perspectives in Biology and Medicine* 581, 583–584, 586; Simon Heuksen, 'Artificial Life and Ethics' (2014) 8 *Nanoethics* 111, 112–114; Thomas Douglas, Russell Powell and Julian Savulescu, 'Is the Creation of Life Morally Significant?' (2013) 44 *Studies in History and Philosophy of Biological and Biomedical Sciences* 688, 696.

<sup>19</sup> Bernard Baertschi, 'The Moral Status of Artificial Life' (2012) 21 *Environmental Values* 5, 16–17; Link, above n 4, 437; Douglas et al, above n 18, 696.

<sup>20</sup> Ainsley Newson, 'Personhood and Moral Status' in Richard Ashcroft et al (eds), *Principles of Health Care Ethics* (John Wiley, 2<sup>nd</sup> ed, 2007) 277, 281–282.

## B Biosafety and Biosecurity in Synthetic Biology

Concerns around biosafety and biosecurity are prevalent in the synthetic biology literature.<sup>21</sup> Other papers in this edition have addressed current regulations pertaining to biosafety in an Australian context.<sup>22</sup> From an *ethical* perspective, questions of biosafety and biosecurity can be framed as follows: What measures of safety are ethically appropriate for use in synthetic biology? How should nefarious and worthy applications of synthetic biology technologies be weighed and compared?

Biosafety refers to containment and other measures put in place to ensure safe working with, and use of, potentially hazardous biological agents. Regarding biosafety measures, a key ethical rationale is protection from harm. It is important to ensure the products of synthetic biology do not leave populations or environments worse off. However, it is also important to note that not everything produced in synthetic biology research will have biosafety implications. Some products may be benign or not capable of infection.

Ethical considerations will arise when a balance needs to be struck between regulating scientific conduct on biosafety grounds, which may impinge on scientific freedom, and facilitating open-ended research to encourage beneficial outputs. So-called 'garage biology' is one area where this balancing is relevant. The 'component' approach used in some domains of synthetic biology research lends itself to use by individuals who may not be working within a traditional sphere of scientific research, such as a university or research institute. Questions have been raised as to how the conduct and products of those undertaking garage biology should be monitored and controlled.<sup>23</sup> Another cause for concern builds on the above issue of creating new life forms which may be capable of evolving and changing if and when they are released into the environment. Ethical deliberation may assist in determining the appropriate risk trade-offs and standards of conduct.

Biosecurity can mean both the kinds of protections put in place to ensure biosafety, and the prevention and management of nefarious uses of synthetic biology. For example, with inexpensive DNA synthesis and publicly available virus sequences, it has been possible to construct virulent viruses using mail-order DNA fragments.<sup>24</sup>

Ethical questions relevant to biosecurity include consideration of how to trade off beneficial and potentially harmful uses of the same technology. This is termed the 'dual use' problem. It applies in contexts where the same research can be used for 'both good and bad purposes', specifically 'research that can be used for especially harmful purposes... where the consequences... would be potentially catastrophic.'<sup>25</sup> Dual use problems are not unique to synthetic biology. However, synthetic biology offers a good prototype for their

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<sup>21</sup> See, eg, Alexander Kelle, 'Synthetic Biology and Biosecurity: From Low Levels of Awareness to a Comprehensive Strategy' (2009) 10 *EMBO Reports* S23; Markus Schmidt et al, 'A Priority Paper for the Social and Ethical Aspects of Synthetic Biology' (2009) 3 *Systems and Synthetic Biology* 3, 4–5; Jonathan B Tucker and Raymond A Zilinskas, 'The Promise and Perils of Synthetic Biology' [2006] *The New Atlantis* 25 (Spring) 32–34, 37–42; Presidential Commission for the Study of Bioethical Issues (US), above n 10, 71–74, 129–131.

<sup>22</sup> Sonia Allan, 'Macquarie University Workshop on Ethical, Legal and Social Issues Raised by Synthetic Biology', (2015) 15 *Macquarie Law Journal* 5; Lisa Eckstein, 'Regulatory Challenges of Synthetic Biology Trials and Other Highly Innovative Investigational Products', (2015) 15 *Macquarie Law Journal* 65.

<sup>23</sup> Balmer and Martin, above n 10, 19–20.

<sup>24</sup> Jeronimo Cello, Aniko V Paul and Eckard Wimmer, 'Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template' 297 (2002) *Science* 1016.

<sup>25</sup> Michael J Selgelid, 'Ethics and Dual-Use Research' in Michael J Selgelid and Seamus Miller (eds), *On the Dual Uses of Science and Ethics: Principles, Practices, and Prospects* (Australian National University ePress, 2013) 3, 4.

consideration.<sup>26</sup> Douglas and Savulescu reflect on the deliberate misuse of synthetic biology and evaluate this dual use dilemma. They coin the term an 'ethics of knowledge' which asks 'whether to pursue and disseminate certain kinds of [potentially very harmful] knowledge' even though benefits would also arise.<sup>27</sup> They claim that this question has so far been overlooked in synthetic biology, as it has been also for other emerging technologies. This approach would complement retrospective ethical analyses of the production of scientific knowledge, as well as prospectively help to resolve dual use problems.

An ethics of knowledge for synthetic biology has not been universally endorsed. Pierce has critiqued this approach, pointing to a lack of consensus as to who should determine the ethics of knowledge.<sup>28</sup> She also rejects Douglas and Savulescu's claim that this is a job (purely?) for ethicists.<sup>29</sup> Pierce further points out the lack of clarity regarding whose interests such a consensus should serve,<sup>30</sup> and concludes by pointing to the complex deliberative processes that would be required to develop a truly representative ethics of knowledge. Would determining acceptable and unacceptable knowledge actually achieve the objective of preventing deliberate harm, or would it merely give that illusion?<sup>31</sup> As an alternative, Pierce suggests an 'ethics of knowledge priorities' to ask 'about which resources we should generate and which should be our priorities, and under what conditions.'<sup>32</sup> This approach is not solely guided by misuse, but by a range of considerations including resource allocation.

### C *Benefit Sharing*

Ethical aspects pursuant to benefit sharing in synthetic biology include questions such as whether patenting an artificially synthesised genome is appropriate. For example, the J Craig Venter Institute, which produced the first minimal synthetic genome, patented the sequence of the minimal genome in 2007.<sup>33</sup> Taking a very different approach, the BioBricks Foundation has adopted an open-source model in which anyone can upload or download biological components.<sup>34</sup> Questions also arise about the role of patents and other intellectual property in influencing pricing and availability of products of synthetic biology. For example, the medical and bioremediation applications of synthetic biology could have a significant impact in developing countries, especially where resources are low and needs are great.

Another question, though one not unique to synthetic biology, is how benefits should be justly distributed. For example, concerns have been expressed that synthetic biology could, in the short term, undermine the livelihoods of communities producing natural products that synthetic biology could replace. The paradigmatic example here has been that of anti-malarial drug artemisinin which is produced from a rare natural product by communities with minimal resources. Large-scale synthetic production of artemisinin is now all but a reality. While this could ease the global shortage of this much-needed drug, concerns have been expressed that synthetic artemisinin will be expensive and that the communities which currently produce the natural precursor will be worse off.<sup>35</sup>

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<sup>26</sup> Kelle, above n 1, 62.

<sup>27</sup> Douglas and Savulescu, above n 13, 687, 692.

<sup>28</sup> Robin L Pierce, 'Whose Ethics of Knowledge? Taking the Next Step in Evaluating Knowledge in Synthetic Biology: A Response to Douglas and Savulescu' (2014) 38 *Journal of Medical Ethics* 636, 636–637.

<sup>29</sup> *Ibid.*

<sup>30</sup> *Ibid* 637.

<sup>31</sup> *Ibid* 637–638.

<sup>32</sup> *Ibid* 638.

<sup>33</sup> Minimal Bacterial Genome, US 20070122826 A1 <<http://www.google.com/patents/US20070122826>>.

<sup>34</sup> iGEM, *Registry of Standard Biological Parts DNA Submission* (2015) <[http://parts.igem.org/DNA\\_Submission](http://parts.igem.org/DNA_Submission)>.

<sup>35</sup> Balmer and Martin, above n 10, 25–26.

Hunter has explicitly considered the role of claims that rely on the concept of justice in debates over emerging technologies, using synthetic biology as an example.<sup>36</sup> He claims that contrary to how they are often used, only rarely can justice considerations block the ingress of new technologies.<sup>37</sup> Hunter argues that while justice should certainly guide *how* a new technology is introduced, it is often problematic in that those supporting them tend to take a short-term view.<sup>38</sup> Instead, justice considerations regarding emerging technologies should be based on a long-term view, although he also claims that even justice concerns that take a longer-term view are not of concern for synthetic biology.<sup>39</sup>

A potential solution to concerns of justice in synthetic biology is to build mechanisms of benefit sharing into the technology's translation. In a different context, Schroeder has offered the following definition of benefit sharing for non-human resources:

Benefit sharing is the action of giving a portion of advantages/profits derived from the use of non-human genetic resources or traditional knowledge to the resource providers, in order to achieve justice in exchange.<sup>40</sup>

She then offers a separate definition of benefit sharing regarding human genetic resources:

Benefit sharing is the action of giving a portion of advantages/profits derived from the use of human genetic resources to the resource providers to achieve justice in exchange, *with a particular emphasis on the clear provision of benefits to those who may lack reasonable access to resulting healthcare products and services.*<sup>41</sup>

Schroeder justifies a two-definition approach on the basis that human genetic information is the common inheritance of humanity, whereas other resources are part of the sovereign rights of states. However, synthetic biology may challenge this dichotomous approach, or at least extend the application of the definition of human genetic resources to encompass chimeric resources. Synthetic biology may well see biological components or other artefacts being made that *combine* both human and non-human DNA.

It does not seem unreasonable to suggest that a laudable goal for synthetic biology is to reach end points at which benefit sharing is achieved and that this is done in line with a reasonable consensus definition of what it means to justly share those benefits. Where synthetic biology is used to negate the need for a natural resource (such as with the artemisinin example above), perhaps benefit sharing approaches could include assistance for those whose livelihoods in producing natural precursors have been affected.

#### D *Professional Ethics and Integrity in Synthetic Biology*

Given the open-endedness of research in synthetic biology and its applications, including possibly nefarious ones, engendering researcher responsibility and accountability is paramount. However, such a claim is not straightforward given the diverse methodologies and disciplines involved in synthetic biology, and the various cultural and other factors they incorporate. Engineering, for example, has historically been a discipline that has more overtly taught and addressed aspects of professional ethics, perhaps because many

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<sup>36</sup> David Hunter, 'How to Object to Radically New Technologies on the Basis of Justice: The Case of Synthetic Biology' (2013) 27 *Bioethics* 426.

<sup>37</sup> Ibid 428, 430.

<sup>38</sup> Ibid 433.

<sup>39</sup> Ibid 434.

<sup>40</sup> Doris Schroeder, 'Benefit Sharing: It's Time for a Definition' (2007) 33 *Journal of Medical Ethics* 205, 207.

<sup>41</sup> Ibid 207, 208 (emphasis added).

engineering graduates end up working in the profession. This is not to say that those working in the pure sciences have acted unethically, but perhaps these kinds of considerations have been more implicit. It may be that synthetic biology cannot (and perhaps should not) have *one* professional ethics. Determining researcher responsibility may also lead to similar 'ethics of knowledge' questions as those discussed above.

Synthetic biology could give rise to biological components that self-assemble, self-replicate or display other properties usually associated with living entities. If these components are considered for use outside the laboratory, stakeholders need to feel confident that they have been produced by researchers who have the necessary expertise, who have made a commitment to act with integrity and who appreciate any sensitivities in their chosen field. It has been a very positive occurrence in synthetic biology that so many researchers have been prepared to engage with experts in social sciences, ethics and law to deliberate on the implications of their work.

Beyond the initial question of acting ethically in scientific research, some are questioning whether professionalisation of the field of synthetic biology should be employed as a governance strategy.<sup>42</sup> Professionalisation would involve a central body setting standards for elements of practice such as training and conduct. The body would likely comprise peer-selected experts, thus promoting responsiveness to the community of researchers it will serve. Researchers seeking professional recognition would then be required to demonstrate adherence to these standards. The benefit of professionalisation is that it represents a compromise between internal and external regulation of conduct. That is, researchers would not be left to entirely self-regulate on an individual basis. Neither would researchers be subject to standards or limits that have been imposed from outside the discipline. The interests of broader stakeholders, such as community members and the state, could be incorporated into the standards that are set. Professionalisation would not be the only mechanism of governance, but would form part of a 'web of prevention' of improper conduct.<sup>43</sup>

While attractive, professionalisation is a new concept for science. Questions will arise as to how to agree on standards and training requirements. This would be a big task, one likely to be resource intensive, considering the number of disciplinary approaches and techniques used in synthetic biology research.

### E *How Should Synthetic Biology be Regulated?*

Potential regulatory or policy approaches, and possible gaps, regarding synthetic biology in an Australian context are discussed elsewhere in this issue.<sup>44</sup> However, there are also ethical aspects to questions of regulation of synthetic biology as an emerging technology. One such question is whether synthetic biology should be regulated at all. An in-depth answer to this question is beyond the scope of this paper, so for the purposes of this discussion it will be assumed that synthetic biology, like many other fields of inquiry, is already subject to regulation and that a degree of external oversight is warranted.

If it is correct to assume that synthetic biology does need regulatory oversight, a further question arises as to whether synthetic biology requires specific regulation. The answer to

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<sup>42</sup> Lorna Weir and Michael J Selgelid, 'Professionalization as a Governance Strategy for Synthetic Biology' (2009) 3 *Systems and Synthetic Biology* 91, 94–96. Governance options for synthetic biology are briefly surveyed in the next section.

<sup>43</sup> *Ibid* 95–96.

<sup>44</sup> Allan, above n 22; Eckstein, above n 22.

this question is more complex. On the one hand, as Allan and Eckstein have shown, there is already a range of oversight relevant to synthetic biology in Australia. It is also prudent not to over-regulate or exceptionalise an emerging technology to the detriment of what that technology might achieve. The broad range of disciplines, methodologies and potential applications of synthetic biology (such as in health or environmental remediation) mean that specific laws or regulations may be insufficient to effectively monitor the entire field. On the other hand, it seems clear that synthetic biology could have detrimental outcomes if misapplied or if control is lost. Potentially problematic outcomes may be mitigated, and stakeholder confidence optimised, if there is specific oversight of synthetic biology.

Assuming that some means of regulation will be put in place, even if just for the initial stages of the field's emergence in Australia, a third question that will arise is which regulatory approach to adopt. A brief sketch of some of the predominant regulatory approaches and concepts follows.

Three approaches to governance are anticipatory governance, adaptive governance and responsible research and innovation (RRI). All involve some kind of deliberative engagement with stakeholders. Anticipatory governance describes a set of procedural principles for how to collectively imagine, deliberate, design and influence emerging technologies.<sup>45</sup> Adaptive governance involves analysis of different aspects (such as social and economic) that contribute to multi-level governance, and how these help build resilience in a particular society. It is an integrated and holistic theory. RRI encourages *responsible* practice in research and innovation, undertaking a transparent and interactive process.<sup>46</sup> It involves collective stewardship now to protect the future. RRI has become a predominant framework in which to discuss regulation of emerging technologies, particularly in Europe, where a number of funders have built RRI considerations into funding documentation.<sup>47</sup>

An alternative approach to these kinds of governance strategies is to have more informal oversight, or partnership between researchers and other stakeholders. In the United States, the Presidential Commission for the Study of Bioethical Issues suggested such a strategy when it recommended 'prudent vigilance' to oversee synthetic biology.<sup>48</sup> This is a 'middle way' between having a moratorium, which was proposed and then rejected at the outset of synthetic biology research, and unfettered freedom of self-regulation. Self-regulation overlaps with the above discussion of professionalisation and 'ethics of knowledge'. At the outset of a field that has the potential for controversy, complete self-regulation may not appease all stakeholders.

Within the above governance approaches, questions will also arise as to how possible risks should be managed. Two broad principles relevant to synthetic biology are the precautionary and proactionary principles.<sup>49</sup> The proactionary principle commences with a 'pro' perspective on research, encouraging freedom to innovate on a strong evidence base. Proponents of this perspective aim to protect innovation and avoid costs arising from restrictions on research.

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<sup>45</sup> David H Guston, 'Understanding "Anticipatory Governance"' (2014) 44 *Social Studies of Science* 218, 219.

<sup>46</sup> René von Schomberg, 'Prospects for Technology Assessment in a Framework of Responsible Research and Innovation' in Marc Dusseldorp and Richard Beecroft (eds), *Technikfolgen Abschätzen Lehren: Bildungspotenziale Transdisziplinärer Methoden* (Springer, 2012) 39, quoted in Richard Owen, Phil Macnaghten and Jack Stilgoe, 'Responsible Research and Innovation: From Science in Society to Science for Society, with Society' (2012) 39 *Science and Public Policy* 751, 753.

<sup>47</sup> See, eg, Engineering and Physical Sciences Research Council, *Anticipate, Reflect, Engage and Act (AREA)* (2015) <<http://www.epsrc.ac.uk/research/framework/area/>>.

<sup>48</sup> Presidential Commission for the Study of Bioethical Issues (US), above n 10, 25–27, 123–140.

<sup>49</sup> Christopher Wareham and Cecilia Nardini, 'Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox' (2015) 29(2) *Bioethics* 118; Parens et al, above n 10, 18–22.

The precautionary principle (PP) is widely applied in policy-making. In contrast to approaches more overtly favouring innovation, adopting the PP means that a technology or other innovation should not be widely applied until there is good evidence that it will be safe, or that the risks of its use will not outweigh its benefits. The PP is controversial in bioethics. Critiques of the principle include that it prioritises the current status quo, and that it stymies innovation due to inaction arising from any risk calculation that is inherent to applying the PP. In response, Wareham and Nardini present a modified PP<sup>49F</sup> that may mitigate these concerns.<sup>50</sup> They describe a deliberative method for collectively arriving at a measure of probability of a harmful event, with a risk being able to be discarded if it falls below that level. They also describe a particular method of determining those risks.<sup>51</sup>

Whatever approach to risk is taken in synthetic biology, there needs to be consideration of cooperative risk management to ensure the beneficial uses of synthetic biology will outweigh its possible misuse.

### III DOES SYNTHETIC BIOLOGY GIVE RISE TO NEW ETHICAL ISSUES, WARRANTING AN EXCEPTIONALIST APPROACH TO ETHICAL ANALYSIS?

Having described and briefly analysed some of the ethical and regulatory issues that have arisen, or will likely arise, in synthetic biology research, this paper will now examine and critique approaches to the analysis of synthetic biology within bioethics generally. Two interrelated questions arise: (i) Does synthetic biology raise new ethical issues? (ii) Can and should there be a distinctive 'ethics of synthetic biology'?<sup>52</sup>

The emergence of a new technology or disciplinary area in bioscience, medicine or health often brings with it a distinct ethical discussion and a slew of dedicated papers. For example, the literature is dotted with papers incorporating terms such as nanoethics, neuroethics and genethics. This kind of practice is subject to critique.<sup>53</sup> It may lead to a repetition of previous debates, it could stymie creative reflection on emerging technologies, and it could fragment bioethics as a field of inquiry.

This section is premised on a claim that there *is* a role for bioethics in discussions about synthetic biology. While this presumption is not uniformly accepted by all scientists working in synthetic biology,<sup>54</sup> the over-arching consensus in the field is that the approaches and applications of synthetic biology have, and will continue to give rise to, ethical implications.<sup>55</sup> What will be apparent from the synthesis of ethical issues in synthetic biology presented above is that the types of issues, questions and approaches to which synthetic biology gives rise are already familiar to scholars in bioethics.

This is not to say that there are no ethical issues arising from synthetic biology, or that the issues are settled. Synthetic biology will clearly have ethical implications in a number of domains. In one of the first reports written on the social and ethical implications of synthetic biology, Balmer and Martin recognised some of the novel aspects of the field of synthetic biology, stating that something 'new and important' is happening.<sup>56</sup> Heyd claims that

<sup>50</sup> Wareham and Nardini, above n 49, 121–123.

<sup>51</sup> *Ibid.*, 123.

<sup>52</sup> Erik Parens, Josephine Johnston and Jacob Moses, 'Do We Need "Synthetic Bioethics"?' (2009) 321 *Science* 1449.

<sup>53</sup> See, eg, Benjamin Wilfond and Vardit Ravitsky, 'On the Proliferation of Bioethics Sub-Disciplines: Do We Really Need "Genethics" and "Neuroethics"?' (2005) 5 *American Journal of Bioethics* 20, 20.

<sup>54</sup> Personal experience of author.

<sup>55</sup> Link, above n 4.

<sup>56</sup> Balmer and Martin, above n 10, 4, 29.

'synthetic biology does not create any ethical dilemmas that have not already been raised' but that 'the issue is, nevertheless, ethically serious.'<sup>57</sup> Likewise, Brassington has claimed that it 'seems plain that synthetic biology is something that ought to be taken seriously by policymakers.'<sup>58</sup>

However, Brassington also claims 'that there is nothing lacking from the philosophers' toolkit that would be required to address [synthetic biology].'<sup>59</sup> Synthetic biology is unlikely to give rise to *novel* ethical theory. That said, there is nothing wrong with applying known ethical concepts to new research domains, so long as scholars then also 'dig deeper',<sup>60</sup> testing claims that have been made in previous debates (such as in relation to nanotechnology) and any consensus that has arisen, and assessing validity in the new field. There are also opportunities for methodological innovation in bioethics, including novel work on the role of visions and speculation when applied to emerging technologies.<sup>61</sup>

It seems clear that synthetic biology does not present any completely new ethical issues, and that ethical analysis within synthetic biology should not be described as a discrete field of inquiry within bioethics. However, ethical questions, such as the best governance strategy or the appropriateness of an 'ethics of knowledge', have not yet been settled for synthetic biology, or indeed for other emergent and emerging technologies. There are several ethical issues and concepts relevant for synthetic biology, whether or not they have been initially raised elsewhere. There is much scope for rich analysis, and the open-endedness and capacity for creativity within synthetic biology offers opportunities for novelty. As Rogers writes, there is scope for reflecting on aspects of synthetic biology such as agenda setting, the partnership between ethics and science, and the attributes of researchers that ought to be encouraged.<sup>62</sup> This will be a multi-dimensional process. Synthetic biology can draw on, and in turn influence, wider ethical and socio-political analyses of the place of technology in society.

#### IV MOVING FORWARD: HOW MIGHT ETHICAL ANALYSIS IN SYNTHETIC BIOLOGY BE EXTENDED?

A concern with ethical analysis of emerging technologies like synthetic biology is that analyses often become superficial lists of general issues that might arise. Indeed, this paper is liable to such a charge, although the intention here is not to examine a particular issue in depth but to scope out the current debate and indicate how it might progress. The problem is how to best analyse an emerging technology when its application remains more speculative than tangible. In the prior section it was suggested that synthetic biology does not give rise to novel ethical issues, nor should it be treated as a discrete field of academic inquiry. Nevertheless, synthetic biology offers plenty of opportunities for ethical analysis. In this final section, some suggestions are made as to how ethical analysis in synthetic biology could be extended. Three domains for analysis are briefly outlined: the use of imagination, questions of scope, and fine-grained integration of ethical analysis into synthetic biology research.

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<sup>57</sup> Heyd, above n 18, 581.

<sup>58</sup> Iain Brassington, 'Synthetic Biology and Public Health: Problems, Politics and Policy' (2011) 1 *Theoretical and Applied Ethics* 34, 34.

<sup>59</sup> *Ibid* 39.

<sup>60</sup> Parens, Johnston and Moses, above n 52.

<sup>61</sup> This is addressed in the final section of this paper.

<sup>62</sup> Wendy Rogers, 'Ethical Issues in Synthetic Biology: A Commentary' (2015) 15 *Macquarie Law Journal* 42.

### A *The Use of Imagination, Vision and Speculation*

A criticism of bioethics scholarship on emerging topics is that when a new area of interest is identified, there is a flurry of activity to identify issues and publish papers before the next topic arises. Scholarship then moves on, yet 'bioethics remains, disappointingly, familiar'.<sup>63</sup> One way this might be addressed is through augmenting how bioethics scholarship is approached, using imagination, vision or speculation to generate detailed ideas about the future of emerging technologies.<sup>64</sup> This is not to say that imagined scenarios are going to be accurate, and there is controversy over how visions and speculation should be used in bioethics debates.<sup>65</sup> However, even if an imagined scenario is incorrect it may still be of use. For example, while the swine flu pandemic was curtailed, the ethical deliberation over aspects of care such as resource allocation and risk-taking by healthcare staff provided valuable ethical insights and contributed to policy development.

The rationale for using vision or speculation to critically reflect on synthetic biology is threefold. First, it may help prevent criticisms that bioethics is repetitive or constantly fragmenting.<sup>66</sup> Second, it may encourage ethical debate in synthetic biology unconstrained by the current practical limitations and relative lack of real-world applications. Third, it reflects the fact that imagination and speculation are inherent to bioethics research. Delineating interesting ideas about the potential of synthetic biology in the future may assist in assessing relevant moral questions and concepts.

### B *Analysing Questions of Scope in Synthetic Biology*

Related to considerations involving imagination, the open-ended potential of synthetic biology also has an ethical dimension. Synthetic biology offers unprecedented scope for innovation and application in a number of spheres ranging from health to the environment. This is both exciting and challenging. For example, synthetic biology may remove current limits on what life forms exist. This expansion in scope, as with other emerging technologies such as genome editing (a technology that has some overlap with synthetic biology), may provide a tipping point that requires us to critically reflect on the ethical implications, as well as considering whether current ethical and governance responses are satisfactory.<sup>67</sup>

### C *A Finer-Grained Ethical Integration?*

Ethical analysis within synthetic biology has been characterised by scientific engagement with implications of this research right from the field's inception. However, as might be expected, most analysis of ethical and social issues has been undertaken by those who work in these disciplines and not by synthetic biology scientists. There have been some exceptions,

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<sup>63</sup> Angus Dawson, 'The Future of Bioethics: Three Dogmas and a Cup of Hemlock' (2010) 24 *Bioethics* 218, 218.

<sup>64</sup> This section is adapted from research undertaken for the SYBHEL project. See Sybhel, *Synthetic Biology for Human Health: the Ethical and Legal Issues* (2010) <<http://sybhel.org/>>. The author obtained funding for this project from the European Union (SiS-2008-1.1.2.1-230401). Research on the role of imagination in bioethics was carried out by Research Associate A M Calladine.

<sup>65</sup> See, eg. Gareth Jones, Maja Whitaker and Michael King, 'Speculative Ethics: Valid Enterprise or Tragic Cul-de-Sac?' in Abraham Rudnick (ed), *Bioethics in the 21<sup>st</sup> Century* (InTech, 2011), 139, 147–154.

<sup>66</sup> This point has been discussed in Part III above.

<sup>67</sup> Ainsley Newson and Anthony Wrigley, 'Identifying Key Developments, Issues and Questions Relating to Techniques of Genome Editing with Engineered Nucleases' (Background Paper, Nuffield Council on Bioethics, 2015), 7, 19 <<http://nuffieldbioethics.org/wp-content/uploads/Genome-Editing-Briefing-Paper-Newson-Wrigley.pdf>>.

such as 'sandpit' funding initiatives, which have led to inter-disciplinary collaborations.<sup>68</sup> In line with critiques of the 'overview' approaches to ethics and synthetic biology already discussed, some have claimed that integration of ethics into synthetic biology can go even further. Heavey, for example, suggests that each domain of synthetic biology needs in-depth ethical analysis to better account for the 'everyday research' occurring in synthetic biology.<sup>69</sup> This could comprise activities such as encouraging researchers to train in both the scientific and ethical aspects of their field.<sup>70</sup> These individuals could then take a leading role in assessing the implications of discrete projects in synthetic biology, ensuring that analysis of ethical implications is aligned with project expectations. Heavey additionally suggests that each research paper published in synthetic biology could contain a brief ethics statement, similar to existing requirements for papers reporting research with human participants.<sup>71</sup>

While improving the integration of science and ethics in synthetic biology research is laudable, the strategies require further consideration. For example, is the claim for integration of ethics and science in synthetic biology unreasonably exceptionalising synthetic biology? Should this kind of approach be introduced to *all* science? Would requiring a 'brief ethical evaluation' on every synthetic biology manuscript (assuming what constitutes a synthetic biology manuscript can be determined) reduce ethical consideration to a box-ticking exercise?<sup>72</sup> The objective and potential for integration show promise, but need development.

## V CONCLUSION

This paper has surveyed ethical issues arising in synthetic biology, before considering the mode and methodology for engagement with these ethical issues. It has claimed that synthetic biology neither raises entirely new ethical issues, nor represents a discrete sub-field of bioethical inquiry. However, the field does give rise to issues that are of ethical interest and will offer opportunities for analysis on aspects not yet fully explored. Some suggested avenues for further investigation were then put forward. These suggestions have been made in response to some ethically interesting hallmarks of synthetic biology, including its potentially limitless scope and the creativity that may be harnessed by researchers. The field may benefit from an approach to ethical analysis that is capable of both thinking about the broad possible future scenarios of synthetic biology, and also focusing in on some of the more specific implications that are probable or actual. Ongoing critical reflection on bioethics methodology in synthetic biology will also in turn allow critical reflection on methodology in bioethics more generally. It may also give rise to some novel observations, particularly given the inter-disciplinary nature of this field. Issues familiar to academic ethicists may play out in unexpected ways in different fields of research.<sup>71F73</sup> Focus on the details of particular applications of research in synthetic biology will allow the development of a suite of thought experiments to guide further ethical analysis.

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<sup>68</sup> CollectiveIP, '*Sandpit*' to Address Grand Challenges in Synthetic Biology (2015) <<https://www.collectiveip.com/grants/NSF:0935932>>. Sandpit events are used to bring together researchers from a range of backgrounds to build collaborations and develop projects. The idea is to 'play' in the sandpit with new colleagues and see what arises. A discrete amount of funding is then allocated to selected projects following a competitive grant submission process.

<sup>69</sup> Heavey, above n 11, 122–124.

<sup>70</sup> It is worth noting that this is not necessarily new. There are many working in science or bioethics who have qualifications in more than one discipline.

<sup>71</sup> Heavey, above n 11, 122, 125.

<sup>72</sup> Ibid 125.

<sup>73</sup> Thanks to Dr Jane Calvert for this point.

Synthetic biology research is inherently inter-disciplinary. The range and scope of its potential applications, and the varied methodological approaches of those assessing it, mean that a single ethical determination of the field's acceptability is unlikely. However, ethical analysis will contribute to discussions on the research agenda and underlying values. Ethical analysis will also add a further lens with which to evaluate the implications of this research field and its applications.

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# SYNTHETIC BIOLOGY AND THE RESPONSIBLE CONDUCT OF RESEARCH

KAROLYN WHITE\* AND SUBRAMANYAM VEMULPAD\*\*

*In this paper, we suggest that synthetic biology poses no special issues for the Responsible Conduct for Research or for Institutional Biosafety Committees (IBCs). Moreover, researchers working in the area, as well as regulatory agencies, have been proactive in ensuring that research into synthetic biologicals are appropriately governed and potential risks mitigated. Regulatory frameworks for the responsible conduct for research, such as The Australian Code for the Responsible Conduct of Research,<sup>1</sup> provide such a governance framework. Institutional Biosafety Committees also provide an appropriate mechanism for mitigating risk.*

## I INTRODUCTION

Synthetic biology can be defined as the design and construction of new biological organisms not found in nature.<sup>2</sup> It has the potential to provide solutions to 'some of the challenges that the world faces in the fields of environmental protection (detecting and removing contaminants), health (diagnostics, vaccines and drugs) and energy and industry (biofuels)'.<sup>3</sup> However, the development of synthetic biology poses risks. Groups such as Friends of the Earth, International Center for Technology Assessment, and the Action Group on Erosion, Technology and Concentration ('ETC Group') argue inter alia that synthetic biology research must 'be accompanied by precautionary mechanisms to safeguard the health of workers and local communities, to preserve the biodiversity of the planet, to ensure public participation, [and] to provide for democratically decided social goals.'<sup>4</sup> Thus, there is agreement internationally that synthetic biology research should be regulated for the conduct of research, the products evolved and practical outcomes of the research.<sup>5</sup>

So, while there is recognition of the enormous potential benefits of synthetic biology research and caution about the potential risks, we maintain that synthetic biology poses no exceptional risks. In other words, risks can be managed and mitigated by current regulatory frameworks, legislation and by a public ethics approach to the research such as

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<sup>1</sup> National Health and Medical Research Council, *Australian Code for the Responsible Conduct of Research* (2007) <[https://www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/r39.pdf](https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/r39.pdf)>.

<sup>2</sup> Markus Schmidt et al, 'A Priority Paper for the Societal and Ethical Aspects of Synthetic Biology' (2009) 3 *Systems and Synthetic Biology* 3; Sune Holm and Russel Powell, 'Organism, Machine, Artefact: The Conceptual and Normative Challenges of Synthetic Biology' (2013) 44 *Studies in History and Philosophy of Biological and Biomedical Sciences* 627; Ainsley Newson, 'Current Ethical Issues in Synthetic Biology: where should we go from here?' (2011) 18 *Accountability in Research* 181.

<sup>3</sup> International Risk Governance Council, *Policy Brief: Guidelines for the Appropriate Risk Governance of Synthetic Biology* (2010) <[http://www.irgc.org/IMG/pdf/irgc\\_SB\\_final\\_07jan\\_web.pdf](http://www.irgc.org/IMG/pdf/irgc_SB_final_07jan_web.pdf)>.

<sup>4</sup> Eric Hoffman, Jaydee Hanson and Jim Thomas, *The Principles for the Oversight of Synthetic Biology*, Friends of the Earth (13 March 2012) Friends of the Earth <<http://www.foe.org/news/archives/2012-03-global-coalition-calls-oversight-synthetic-biology>>.

<sup>5</sup> International Risk Governance Council, above n 3.

recommended by the Nuffield Council of Bioethics.<sup>6</sup> Our view is consistent with the findings of the Gene Technology Ethics and Community Consultative Committee (GTECCC), the committee that provides advice to the Office of the Gene Technology Regulator (OGTR). The GTECCC met in early 2013 to consider inter alia whether synthetic biology raised new ethical or technical issues. It stated that synthetic biology did not raise new ethical or technical issues and thus should be regulated under the *Gene Technology Act 2000* (Cth). It also noted the importance of the social and ethical responsibility of scientists.<sup>7</sup>

## II RESEARCH INTEGRITY

Many countries have developed guidelines and codes to ensure the responsible conduct of research, otherwise known as research integrity. International guidelines have also been developed, including the 2010 Singapore Statement on research integrity, which was the first attempt to encourage and standardise policies, guidelines and codes of conduct by researchers, research institutions, funders of research and research publishers.<sup>8</sup> The 2013 Montreal Statement extended the scope to include cross-boundary research collaborations.<sup>9</sup>

*The Australian Code for the Responsible Conduct of Research* ('the Code') is the pre-eminent framework and guide for Australian research institutions and researchers governing responsible research practice. The Code 'promotes integrity in research... and explains what is expected of researchers by the community.'<sup>10</sup> A strong research culture is noted to demonstrate honesty and integrity; respect for human research participants, animals and the environment; good stewardship of public resources used to conduct research; appropriate acknowledgement of the role of others in research; and responsible communication of research results.<sup>11</sup>

The Code is divided into two parts: Part A, which outlines general principles of, and required policies for, responsible research; and Part B, which addresses breaches of the Code, research misconduct and provides a framework for resolving allegations. The Code requires research institutions to develop policies on the general principles of responsible research, which include the promotion of the responsible conduct of research, and the establishment of good governance and management practices. A good governance framework is one 'through which research is assessed for quality, safety, privacy, risk management, financial management and ethical acceptability.'<sup>12</sup> The general principles also include the requirement for the institution to monitor research carried out under its auspices.

The research governance framework set out in the Code mandates that research institutions adopt policies to ensure researchers and research students are appropriately trained and that they understand their responsibilities under the Code. They are also required to develop policies on authorship management of research data and primary materials; publication and dissemination of research findings; peer review; collaborative research across institutions;

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<sup>6</sup> Nuffield Council on Bioethics, *Emerging Biotechnologies: Technology, Choice and the Public Good* (2012) <[http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging\\_biotechnologies\\_full\\_report\\_web\\_0.pdf](http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging_biotechnologies_full_report_web_0.pdf)>.

<sup>7</sup> Office of the Gene Technology Regulator, 'Gene Technology Ethics and Community Consultative Committee Communique May 2013' (May 2013) <[http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/gteccc-comm-May2013-htm/\\$FILE/gteccc-comm-May2013.pdf](http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/gteccc-comm-May2013-htm/$FILE/gteccc-comm-May2013.pdf)>.

<sup>8</sup> Singapore Statement on Research Integrity, *Singapore Statement on Research Integrity* (22 September 2010) <<http://www.singaporestatement.org/statement.html>>.

<sup>9</sup> Research Integrity, *Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations* (8 May 2013) <<http://www.researchintegrity.org/Statements/Montreal%20Statement%20English.pdf>>.

<sup>10</sup> National Health and Medical Research Council, above n 1.

<sup>11</sup> *Ibid* 1.3.

<sup>12</sup> *Ibid*.

and the management of conflicts of interest. Importantly, and consistent with the recommendations of the GTECCC, the Code recognises that research integrity is a joint concern of both institutions and researchers.

### III BIOSAFETY AND SECURITY

Health and safety has been advocated for all workplaces and, resultantly, there is a duty to manage risks relating to health and safety.<sup>13</sup> The five key components of efficient management of work health and safety risks are governance; prevention; response; hazard management (biological, physical, chemical, ergonomic and psychological); and recovery.

A biohazard is any biological (plant, animal or microbial) source of potential harm. Biosafety refers to the protection of public health and environment from accidental exposure to a biological risk, usually of microbial origin. Biosecurity refers to prevention of the misuse of biohazardous material through loss, theft, diversion or, as revealed by some recent events, intentional release of toxins or pathogens.

The advent of genetic engineering opened up the potential for biological agents being used for a variety of uses. At the same time, it also brought in its wake an increased awareness of the potential hazards of manipulation of genetic material. Even way back at the first International Conference on Recombinant DNA Molecules, it was noted that recombinant DNA technology is not free from risks.<sup>14</sup> It is important to note that genes can be transferred vertically (from parents to progeny) as well as horizontally (between two individual organisms). Horizontal gene transfer ('HGT') is of particular importance in the context of microorganisms, where gene transfer can occur passively (via transformation) or actively (via transduction or conjugation). Transduction and conjugation, being active processes, are easy to monitor and hence easy to prevent. The same cannot be said of transformation. The free DNA capable of transformation can persist in the environment for long periods (months) and therefore it is not easy to monitor or control.

Luckily, the effectiveness of the common genetically modified organisms ('GMOs') has been poor, in terms of HGT as well as outcompeting native species.<sup>15</sup> However, Synthetic biology could change this, due to the creation of novel gene sequences not usually found in nature. Hence caution is warranted, for example, through measures such as the use of more fastidious hosts and non-transmissible vectors for the synthetic genes. Such measures have been embedded in the existing regulations.<sup>16</sup>

Biosafety and Biosecurity aspects for laboratories are adequately addressed by guidelines broadly based on recommendations of organisations such as the World Health Organisation,<sup>17</sup> and the Bioethics Commission.<sup>18</sup> These recommendations are based on risk assessments and include the following perspectives: code of practice (access, personal protection, procedures, laboratory work areas, and biosafety management); laboratory and facility design; laboratory equipment; health and medical surveillance; training; and waste handling.

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<sup>13</sup> *Work Health and Safety Act 2011* (Cth).

<sup>14</sup> Paul Berg et al, 'Summary Statement of the Asilomar Conference on Recombinant DNA molecules' (1975) 72 *Proceedings of the National Academy of Sciences USA* 1981.

<sup>15</sup> Markus Schmidt, 'Xenobiology: A New Form of Life as the Ultimate Biosafety Tool' (2010) 32 *BioEssays* 322.

<sup>16</sup> Office of the Gene Technology Regulator, above n 7.

<sup>17</sup> World Health Organization, *Strengthening health security by implementing the International Health Regulations* (2005) <<http://www.who.int/ihr/publications/biosafety/en/>>.

<sup>18</sup> Presidential Commission for the Study of Bioethical Issues, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (2010) <<http://bioethics.gov/synthetic-biology-report>>.

## IV RESEARCH INTEGRITY AND BIOSAFETY CHALLENGES

As described above, there are many ethical issues raised by developments in the field of synthetic biology. These include having insufficient knowledge about the potential risks inherent in the new technology; environmental concerns over the accidental or malicious release of genetically modified organisms; the creation of monopolies; exploitation of resources; and philosophical issues relating to the creation of life. Detailed discussion of these matters is beyond the scope of this paper. However, there is an inevitable tension between regulation and innovation, especially as this pertains to synthetic biology technologies as a research integrity issue. Scientific freedom is vital for innovation, defined as increased speed, efficiency, performance and cost-effectiveness in product development.<sup>19</sup> Yet the developments and discoveries made by innovative synthetic biology research must be balanced with security concerns. For Erickson et al, this means that regulators 'should support innovation and commercial development of new products while protecting the public from potential harms.'<sup>20</sup> Erickson et al suggest that this requires inculcating scientists to create a culture of safety.

The Nuffield Council on Bioethics cogently argues that emerging technologies such as synthetic biology should be governed by a public ethics approach. Essentially, consideration of the social good must be included in policy decisions via public engagement. When framing research policy through societal challenges, a public ethics approach should be taken to avoid overemphasis on technological rather than social solutions to problems with substantive social dimensions.<sup>21</sup> There is often tension between academic freedom to publish research and calls for censoring scientific details that could help terrorists develop biological warfare weaponry. This has led to the dilemma of dual use research of concern (DURC).<sup>22</sup>

The categories of research identified as DURC by the Fink report are those that render a vaccine ineffective; confer resistance to antimicrobial agents; enhance the virulence of a pathogen; increase transmissibility of a pathogen; alter a pathogen's host range; enable evasion of diagnostic tools; or enable weaponisation of a biological agent.<sup>23</sup> A direct result of this report was the establishment of the National Science Advisory Board for Biosecurity (NSABB) as a part of the National Institutes of Health (NIH). It has also prompted national authorities to draw up a specific list of biological agents (microbes and toxins), which attract strict oversight.<sup>24</sup>

It is not easy to accurately predict what future developments will bring in the area of synthetic biology. For example, we would be faced with new challenges and dilemmas if orthogonal life (biological entities with unconventional biochemical building blocks and metabolic pathways) or xeno nucleic acids (nucleic acids that do not use conventional base pairs present in DNA or RNA) become a reality through synthetic biology.<sup>25</sup>

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<sup>19</sup> Brent Erickson, Rina Singh and Paul Winters, 'Synthetic Biology: Regulating Industry Uses of New Biotechnologies' (2011) 333 *Science* 1255.

<sup>20</sup> *Ibid* 1256.

<sup>21</sup> Nuffield Council on Bioethics, above n 6.

<sup>22</sup> Bracha Rager-Zisman, 'Ethical and Regulatory Challenges Posed by Synthetic Biology' (2012) 55 *Perspectives in Biology and Medicine* 590.

<sup>23</sup> Committee on Science, Technology and Law, *Science and Security in a post-9/11 World: A Report based on Regional Discussions between the Science and Security Communities* (National Academies Press, 1<sup>st</sup> ed, 2007).

<sup>24</sup> Australian Government Department of Health, *Security Sensitive Biological Agents* (30 March 2015) <<http://www.health.gov.au/ssba>>.

<sup>25</sup> Schmidt, above n 15.

## V CONCLUSION

Authorities agree that while there is no justification for additional agencies or oversight bodies focused on synthetic biology

because of the difficulty of risk analysis in the face of uncertainty—particularly for low-probability, potentially high-impact events in an emerging field—ongoing assessments will be needed as the field progresses. Regulatory processes should be evaluated and updated, as needed, to ensure that regulators have adequate information.<sup>26</sup>

Public education and democratic deliberations between scientists, policy makers and community groups are essential to guide future policy and regulations with respect to emerging technologies, including synthetic biology.

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<sup>26</sup> Presidential Commission for the Study of Bioethical Issues, above n 17.



# REGULATORY CHALLENGES OF SYNTHETIC BIOLOGY TRIALS AND OTHER HIGHLY INNOVATIVE INVESTIGATIONAL PRODUCTS

LISA ECKSTEIN\*

*While synthetic biology remains in the early stages of innovation, achieving its posited goal of improving human health will depend on future clinical trials. This article raises questions about Australia's capacity to ensure that clinical trials involving these kinds of highly innovative investigational products have an acceptable initial and ongoing risk-benefit ratio. Particular challenges include scientific uncertainty surrounding the risks and benefits posed by highly innovative investigational products, as well as the normative nature of assessments of their likelihood and magnitude. These difficulties are compounded by a lack of substantive standards for judging the acceptability of identified trial risks in light of the trial's potential benefits. In Australia, the Office of the Gene Technology Regulator, the Therapeutic Goods Administration, and Human Research Ethics Committees will share responsibility for assessing risks and benefits for participants in future synthetic biology clinical trials. The article argues that none of these bodies — as they currently operate — are equipped to undertake such reviews and canvasses strategies for better supporting them in this role.*

## I INTRODUCTION

The past century has witnessed science fiction become reality across a gamut of medical innovations: vaccines, dialysis machines, and organ donations exemplify leaps of clinical science that have translated into remarkable health benefits. In the 1980s, attention turned to genetic sequencing and transfer, and associated 'omics' technologies, the benefits of which are starting to permeate clinical practice. Synthetic biology — the application of engineering techniques to biology to create organisms or biological systems with novel or specialised functions<sup>1</sup> — is gaining prominence for its potential to transform medicine in the future. Although most clinical applications remain some way into the future,<sup>2</sup> advances such as the creation of the world's first self-replicating synthetic genome,<sup>3</sup> and in 2014 the first eukaryotic chromosome,<sup>4</sup> highlight the rapid pace of scientific discovery. No doubt the 'century of biology'<sup>5</sup> will generate currently unimaginable technologies that further shift traditional paradigms of clinical research and practice.

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<sup>1</sup> The Presidential Commission for the Study of Bioethical Issues, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (The Presidential Commission for the study of Bioethical Issues, 2010) 2 <<http://bioethics.gov/synthetic-biology-report>>.

<sup>2</sup> *Ibid* 67.

<sup>3</sup> Daniel G Gibson et al, 'Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome' (2010) 329 *Science* 52.

<sup>4</sup> Narayana Annaluru et al, 'Total Synthesis of a Functional Designer Eukaryotic Chromosome' (2014) 344 *Science* 55.

<sup>5</sup> Craig Venter and Daniel Cohen, 'The Century of Biology' (2004) 21 *New Perspectives Quarterly* 73.

Highly innovative products and techniques provide dramatic promise for medical progress, often raising pressure to commence clinical testing speedily. Yet early uses in clinical trials can involve unforeseeable risks. The death of 18-year old Jesse Gelsinger in a 1999 gene therapy trial from an unexpected inflammatory reaction to the gene-transfer vector is well known, with news of the death and the resulting lawsuit dealing ‘a major blow for the gene therapy community’.<sup>6</sup> In the following couple of years, excitement about initially promising reports of successful gene-therapy treatments for children suffering from an immune-deficiency disease turned to alarm when two of the ten treated children developed a leukaemia-like lymphocyte proliferation.<sup>7</sup> Subsequent gene therapy studies have obtained some promising results, and the first gene therapy product has been approved for clinical use in China (albeit with some consternation about the data used to support approval); however, much remains to be learnt about the safety profile of different gene vectors.<sup>8</sup> In this and other emerging technology fields, navigating the competing demands of facilitating clinical testing and translation, while minimising risks to research participants, requires proactive regulatory attention.

This article identifies the challenges of ensuring the ethical acceptability of clinical trials involving highly innovative investigational products – most notably, determining a favourable risk-benefit ratio. Using synthetic biology as an illustrative case study, it goes on to assess the capacity of Australia’s regulatory systems to assess the risks and benefits of future clinical trials. After concluding that there are considerable gaps in protections, the article suggests options for reforming Australia’s regulatory frameworks for clinical trials with highly innovative investigational products.

## II SYNTHETIC BIOLOGY AS A HIGHLY INNOVATIVE INVESTIGATIONAL PRODUCT

The National Statement on Ethical Conduct in Human Research (‘National Statement’) – guidelines developed for researchers working with human subjects in Australia – defines a clinical trial as ‘a form of human research designed to find out the effects of an intervention, including a treatment or diagnostic procedure’.<sup>9</sup> This covers a broad spectrum of activities, ranging from the first administration of a completely novel substance to humans through to efficacy and safety comparisons of well-characterised therapeutics. To help address this diversity, clinical trials traditionally have been categorised into various ‘phases’. Phase I studies involve the first administration of an investigational product to humans to determine the product’s safety and pharmacological activity at various dose levels. In Phase II trials, an investigational product is administered to people with the health condition for which the medicine is intended to provide preliminary evidence of efficacy and safety. If Phase II studies show potential benefits, the investigational product will be tested in larger and lengthier Phase III trials to assess whether the product confers a sufficient clinical benefit to warrant marketing approval. Phase IV trials are conducted after a product has been approved for marketing to further explore the clinical use of the medicine.<sup>10</sup> More recently, drug regulators have recognised an additional trial phase: Phase 0. This encompasses exploratory, first-in-human trials conducted before traditional dose escalation and safety studies in order to establish whether the drug or agent behaves in human subjects as had been anticipated from preclinical studies.<sup>11</sup>

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<sup>6</sup> Michael L Edelstein, Mohammad R Abedi and Jo Wixon, ‘Gene Therapy Clinical Trials Worldwide to 2007 – an Update’ (2007) 9 *The Journal of Gene Medicine* 833, 834.

<sup>7</sup> Ibid.

<sup>8</sup> Edelstein, Abedi and Wixon, above n 6.

<sup>9</sup> Australian Government National Health and Medical Research Council, *National Statement on Ethical Conduct in Human Research* (2007) 3.3.

<sup>10</sup> Ibid 30–31.

<sup>11</sup> National Health and Medical Research Council, *Certification Handbook: National Certification Scheme of Institutional Processes Related to the Ethical Review of Multi-Centre Research*, 10 <[hrep.nhmrc.gov.au/\\_uploads/.../hrep\\_certification\\_handbook\\_2012.pdf](http://nhmrc.gov.au/_uploads/.../hrep_certification_handbook_2012.pdf)>.

This article focuses on the earliest part of this clinical pathway: Phase 0 and I trials involving the first administrations of an investigational product to humans. In particular, it assesses strategies to regulate the first administration of highly innovative investigational products to humans: that is, investigational products where

the biological mechanisms are not fully understood, animal models do not reliably predict human effects, adverse effects cannot be minimized by starting with a low 'dose', and the interventions have never or only rarely been previously used in humans.<sup>12</sup>

Future synthetic biology trials are likely to provide an archetypal example of highly innovative investigational products. Consider, for example, a mouse study involving implantation of a cell engineered to produce a synthetic genetic signalling cascade in response to a licensed antihypertensive drug (guanabenz). This combination of drug- and gene-based therapies allowed guanabenz to dose-dependently control hormone expression, simultaneously ameliorating the pathologies that constitute metabolic syndrome (hypertension, hyperglycaemia, obesity and dyslipidaemia).<sup>13</sup> Should such a technique be translated into clinical trials, it would involve uncertainty as to the full biological mechanisms, questions about the reliability of mouse models for predicting effects of the engineered cell in humans, and a lack of previous experience with similar interventions. It is unlikely that these uncertainties could be mitigated through reliance on a low dose. Similar challenges arise with other potential future examples of synthetic biology research, including the use of synthetic T-cells to kill targeted patient cells (such as cancer types) and the administration of genetically recoded viruses for vaccination.<sup>14</sup>

### III AUSTRALIAN REQUIREMENTS FOR ETHICAL ACCEPTABILITY OF HUMAN RESEARCH

Numerous national and international guidelines specify that trial sponsors, investigators, and institutions must ensure the ethical acceptability of clinical trials for which they are responsible.<sup>15</sup> While the scope and drafting of these guidelines differ, commentators have distilled seven requirements as the core conditions necessary for ethical acceptability: the research must have potential value; the methodology must be scientifically valid; participants must be selected fairly; the research must have a favourable risk-benefit ratio; review of the research must have been provided by an independent body; participants must have provided informed consent; and participants must be accorded respect, including the opportunity to withdraw.<sup>16</sup>

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<sup>12</sup> Bernard Lo and Deborah Grady, 'Strengthening Institutional Review Board Review of Highly Innovative Interventions in Clinical Trials' (2009) 302 *JAMA* 2697. This definition is broadly consistent with the definition of 'high risk' investigational products set out by the European Medicines Agency, which notes that concerns may be derived from the novelty of a product's mode of action, the extent of available knowledge about a product's target, and the questionable relevance of animal models: European Medicines Agency, 'Guidelines on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products'

<[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000400.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000400.jsp)>.

<sup>13</sup> Haifeng Ye et al, 'Pharmaceutically Controlled Designer Circuit for the Treatment of the Metabolic Syndrome' (2013) 110 *Proceedings of the National Academy of Sciences* 141.

<sup>14</sup> Florian Lienert et al, 'Synthetic Biology in Mammalian Cells: Next Generation Research Tools and Therapeutics' (2014) 15 *Nature Reviews Molecular Cell Biology* 95.

<sup>15</sup> Australian Government National Health and Medical Research Council, above n 9; World Medical Association, 'World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects' (2013) 310 *Journal of the American Medical Association* 2191; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 'Guideline for Good Clinical Practice E6 (R1)' <[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf)>.

<sup>16</sup> Ezekiel J Emanuel, David Wendler and Christine Grady, 'What Makes Clinical Research Ethical?' (2000) 283 *Journal of the American Medical Association* 2701.

Highly innovative investigational products test many of these ethical preconditions. The technicality of the product information can make it hard to obtain meaningful informed consent. The often-acute illness of the population being recruited can raise questions about fair subject selection. The small cohort of people with the requisite scientific knowledge can impede the potential to obtain a review by a completely unaffiliated individual. Each of these issues is worthy of dedicated consideration. For the most part, however, the strategies for promoting the ethical acceptability of trials involving highly innovative investigational products will mirror strategies developed in the context of clinical trials more generally (albeit with potentially more serious consequences). Yet, for reasons explained in following sections of this article, one ethical precondition poses particular challenges in the context of highly innovative investigational products: ensuring a favourable risk-benefit assessment.

#### IV CHALLENGES OF RISK ASSESSMENT FOR HIGHLY INNOVATIVE CLINICAL TRIALS

A favourable risk-benefit ratio for a clinical trial requires a preliminary and ongoing judgment that the trial's potential benefits to individual participants and/or society are proportionate to or outweigh its risks.<sup>17</sup> In Australia, the National Statement specifies that a trial's benefits may include 'its contribution to knowledge and understanding, to improved social welfare and individual wellbeing, and to the skill and expertise of researchers'.<sup>18</sup> The National Statement further provides, in the context of clinical trials, that:

In research without any likely benefit to participants, any known risk to participants should be lower than would be ethically acceptable where there are such likely benefits. In 'first-time-in-humans' research projects, risks are uncertain, and recruitment into the study should therefore be gradual and monitored with special care.<sup>19</sup>

Yet scholars are increasingly recognising the complexity of making any such determination, particularly when it comes to highly innovative investigational products, given the following:

- The risks and benefits are often unclear.
- Assessments of the likelihood and magnitude of risks and benefits are context-dependent and steeped in broader moral and social judgments.
- Once the relevant risks and benefits have been identified, there is no agreed framework for weighing them or substantive standards for assessing their acceptability.

##### A *Unclear Benefits and Risks*

Highly innovative investigational products, such as those likely to arise through synthetic biology, by definition involve unclear benefits and risks. Extrapolating from the gene therapy context, the likelihood of clinical benefits accruing to individual participants is low. Only a handful of the 1,340 gene therapy trials conducted since 1989 have reported positive results,<sup>20</sup> an unsurprising finding given the breadth of uncertainty about the causal pathways necessary for clinical success. The most realistic benefits therefore involve the generation of scientific knowledge. However, ascertaining such value requires considerable expertise. Gene therapy research once again poses a cautionary tale. A 1995 report commissioned to provide recommendations to the National Institute of Health ('NIH') in the US raised concerns about the limited potential to extrapolate 'useful basic information' from the majority of gene

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<sup>17</sup> Ibid.

<sup>18</sup> Australian Government National Health and Medical Research Council, above n 9, 1.1(a).

<sup>19</sup> Ibid 3.3.7.

<sup>20</sup> Edelstein, Abedi and Wixon, above n 6.

therapy studies because of experimental design deficiencies.<sup>21</sup> The authors further noted that an ‘enthusiasm to proceed to clinical trials’ meant that inadequate attention had been given to ‘basic studies of disease pathophysiology’, which were likely to be critical to the field’s future success.<sup>22</sup> These same dynamics are likely to emerge in synthetic biology and other highly innovative investigational products.

Quantifying the likelihood that an early-phase trial will harm participants (that is, the risks of an early-phase trial) is also hard. There is limited evidence quantifying harms resulting from participants in early phase research,<sup>23</sup> with some studies showing that the preponderance of such trials incur only minor adverse events.<sup>24</sup> However, fears about the potential risks associated with such trials have been raised by catastrophes such as the death of a healthy volunteer in a Phase I asthma study,<sup>25</sup> as well as the TeGenero incident in the United Kingdom, in which a Phase I trial of a monoclonal antibody led to systemic organ failure in six participants.<sup>26</sup> While the risks of early phase trials are typically estimated and minimised through research with animal models, these can have limited predictive ability – as evidenced in the TeGenero trial.<sup>27</sup> The lack of reporting requirements for early-phase trials further limits our knowledge base on adverse event rates and grades.<sup>28</sup>

Risk assessment becomes even more challenging when it comes to trials involving investigational products that pose a ‘higher level of uncertainty’ than applies with conventional biomedical interventions.<sup>29</sup> The Presidential Commission for the Study of Bioethical Issues noted one of the biggest challenges in the oversight of synthetic biology as being ‘its capacity to create novel entities that are increasingly dissimilar to known agents or organisms, making potential risks harder to assess’.<sup>30</sup> A further impediment is the potential length of time before a risk eventuates. Here, it is useful to differentiate more traditional drug treatments, which tend to be metabolised and their by-products eliminated within a limited time-period. This largely confines the risk of adverse events.<sup>31</sup> No such constraints apply with synthetic biology and most other highly innovative experimental products. Lessons here can be drawn from reports in 2014 of a research participant who developed a spinal cord mass eight years after an early-phase experimental stem cell transplantation.<sup>32</sup> Notably, the published clinical trial report for this study pronounced the procedure as

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<sup>21</sup> Stuart H Orkin and Arno G Motulsky, ‘Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy’ 2 <[osp.od.nih.gov/sites/default/files/resources/Orkin\\_Motulsky\\_Report.pdf](http://osp.od.nih.gov/sites/default/files/resources/Orkin_Motulsky_Report.pdf)>.

<sup>22</sup> Ibid 1.

<sup>23</sup> N E Kass et al, ‘Balancing Justice and Autonomy in Clinical Research With Healthy Volunteers’ (2007) 82 *Clinical Pharmacology & Therapeutics* 219.

<sup>24</sup> M Sibille et al, ‘Adverse Events in Phase-I Studies: A Report in 1015 Healthy Volunteers’ (1998) 54 *European Journal of Clinical Pharmacology* 13; M Orme et al, ‘Healthy Volunteer Studies in Great Britain: The Results of a Survey into 12 Months Activity in This Field’ (1989) 27 *British Journal of Clinical Pharmacology* 125.

<sup>25</sup> J Savulescu, ‘Two Deaths and Two Lessons: Is It Time to Review the Structure and Function of Research Ethics Committees?’ (2002) 28 *Journal of Medical Ethics* 1.

<sup>26</sup> Peter Mitchell, ‘Critics Pan Timid European Response to TeGenero Disaster’ (2007) 25 *Nature Biotechnology* 485; Ezekiel J Emanuel and Franklin G Miller, ‘Money and Distorted Ethical Judgments about Research: Ethical Assessment of the TeGenero TGN1412 Trial’ (2007) 7 *The American Journal of Bioethics* 76.

<sup>27</sup> Cormac Sheridan, ‘TeGenero Fiasco Prompts Regulatory Rethink’ (2006) 24 *Nature Biotechnology* 475.

<sup>28</sup> Tony Tse, Rebecca J Williams and Deborah A Zarin, ‘Reporting “Basic Results” in ClinicalTrials.gov’ (2009) 136 *Chest* 295.

<sup>29</sup> Rebecca Dresser, ‘Building an Ethical Foundation for First-in-Human Nanotrials’ (2012) 40 *The Journal of Law, Medicine & Ethics* 802, 802.

<sup>30</sup> The Presidential Commission for the Study of Bioethical Issues, above n 1, 83.

<sup>31</sup> Pascale G Hess, ‘Risk of Tumorigenesis in First-in-Human Trials of Embryonic Stem Cell Neural Derivatives: Ethics in the Face of Long-Term Uncertainty’ (2009) 16 *Accountability in Research* 175, 183.

<sup>32</sup> Brian J Dlouhy et al, ‘Autograft-Derived Spinal Cord Mass Following Olfactory Mucosal Cell Transplantation in a Spinal Cord Injury Patient’ (2014) 21 *Journal of Neurosurgery: Spine* 618.

'feasible, relatively safe, and potentially beneficial' based on a follow-up period of up to 42 months.<sup>33</sup>

## B Normative Nature of Risk-Benefit Assessments

Risk is often conceptualised as a technical formulation, capable of precise measurement and weighing. Yet estimates of the magnitude of risk also are context-dependent and require moral and social judgments. In other words, we make normative judgments about the magnitude of respective harms and benefits, should they occur, as well as how much value the research data would have for society at large.<sup>34</sup> Members of the public (lay persons), for example, have been shown to perceive risk as higher whenever 'potential harms are dreaded, unobservable, or have delayed manifestations'.<sup>35</sup> People also tend to perceive common and unspectacular events, such as asthma and stroke, as less risky than they really are.<sup>36</sup> Additionally, the more an activity is thought to yield large benefits, the lower its risks are perceived to be. Persons who hold a high opinion about the benefits of a given technology (often scientists in the field) are therefore likely to regard research risks as lower than those without such an opinion (often lay persons).<sup>37</sup> This has clear implications for the constitution of any oversight body.

## C No Agreed Framework for Assessing the Acceptability of a Risk Level

Risk assessments are complicated further by the lack of a commonly agreed risk framework for assessing and weighing study risks and benefits. Two schools of thought on weighing trial risks have gained traction but neither provides ready answers on the acceptability of a given risk level for non-therapeutic trial interventions. The component analysis test justifies the risks of therapeutic interventions based on a participant's clinical interests: that is, whether the intervention is in 'clinical equipoise'.<sup>38</sup> For non-therapeutic interventions — which will include most, if not all, early phase trials<sup>39</sup> — risks must be minimised to the greatest extent possible and be reasonable in relation to the knowledge the study may generate. In comparison, the net risks test evaluates all research interventions based on the principle of non-exploitation: that research participants are not exposed to excessive risks of harm for the benefit of others.<sup>40</sup> However, neither of these tests specifies a substantive standard for acceptable levels of research risks,<sup>41</sup> in relation to potential benefits of research.<sup>42</sup> Determining what is a 'reasonable' or 'not excessive' risk therefore becomes an essentially

<sup>33</sup> Carlos Lima et al, 'Olfactory Mucosa Autografts in Human Spinal Cord Injury: A Pilot Clinical Study' (2006) 29 *Journal of Spinal Cord Medicine* 191.

<sup>34</sup> Annette Rid, 'Risk and Risk-Benefit Evaluations in Biomedical Research' in Sabine Roeser et al (eds), *Handbook of Risk Theory: Epistemology, Decision Theory, Ethics, and Social Implications of Risk* (Springer Science & Business Media, 2011) 180, 184.

<sup>35</sup> Jonathan Kimmelman, 'Valuing Risk: The Ethical Review of Clinical Trial Safety' (2004) 14 *Kennedy Institute of Ethics Journal* 369, 377.

<sup>36</sup> Paul Slovic, Baruch Fischhoff and Sarah Lichtenstein, 'Facts and Fears: Understanding Perceived Risk' in Richard C Schwing and Walter A Albers (eds), *Societal Risk Assessment* (Springer Science & Business Media, 1980) 181.

<sup>37</sup> Kimmelman, above n 35, 377.

<sup>38</sup> Benjamin Freedman, 'Equipoise and the Ethics of Clinical Research' (1987) 317 *New England Journal of Medicine* 141.

<sup>39</sup> James A Anderson and Jonathan Kimmelman, 'Extending Clinical Equipoise to Phase 1 Trials Involving Patients: Unresolved Problems' (2010) 20 *Kennedy Institute of Ethics Journal* 75, 83.

<sup>40</sup> For a more complete account of the non-exploitation framework, see: Franklin G Miller and Howard Brody, 'A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials' (2003) 33 *Hastings Center Report* 19; Franklin G Miller and Howard Brody, 'Clinical Equipoise and the Incoherence of Research Ethics' (2007) 32 *Journal of Medicine and Philosophy* 151.

<sup>41</sup> In the context of component analysis, for non-therapeutic research risks.

<sup>42</sup> Rid, above n 34, 199.

individual and intuitive judgment based on values that take into account other factors, such as the nature of potential benefits.<sup>43</sup>

In the absence of ready substantive answers, some commentators have proposed reliance on procedural solutions for ascertaining the acceptability of trial risks. Rid and Wendler suggest that those reviewing the acceptable upper limit of trial risks should ask whether an ‘informed and impartial social arbiter’ would recommend the trial based on a comparison of trial interventions with other activities involving an equivalent risk level, and a weighing of those risks against the value of the trial information.<sup>44</sup> For example, the risk of a serious haemorrhage from a liver biopsy could be compared with the risk of serious injury from a charity soccer game.<sup>45</sup> The authors note, however, that as the net risks to participants increase, reasonable people are likely to disagree about risk-benefit judgments. This raises the need for an adequate process, including sufficient representativeness and transparency for the reviewing body to serve as ‘legitimate arbiters of reasonable disagreement’.<sup>46</sup> The higher the cumulative net risks of a trial, the higher the requisite level of scrutiny and accountability is needed to perform this role.

## V OVERSIGHT MECHANISMS IN AUSTRALIA

How then can Australia deal with the uncertainty and normativity of judgments about the acceptability of clinical trials with highly innovative experimental products, as would be the case with any future synthetic biology trials? Various regulatory strategies are in place, but — at least as presently operating — none of these are sufficient to satisfy the trifold challenges of risk-benefit assessments for highly innovative clinical trials.

### A Office of the Gene Technology Regulator

The Office of the Gene Technology Regulator (‘OGTR’) is a Commonwealth Government regulator responsible for reviewing product dealings that contain genetically modified organisms. To fall within the OGTR’s scope, as defined in s 10 of the *Gene Technology Act 2000* (Cth) (‘*Gene Technology Act*’), an investigational product must be a live organism that has been modified by gene technology or has inherited modified traits. The product must be capable of reproduction or of transferring genetic material.

Product dealings that fall within the scope of OGTR’s review are subject to a systematic scientific risk assessment process through the preparation of a Risk Assessment and Risk Management Plan. This plan identifies any risks to human health and safety and to the environment that the product dealing would pose. The required procedures for developing this plan differ depending on whether the release of the genetically modified product into the environment is intentional or unintentional. For intentional releases,<sup>47</sup> the Regulator must seek input from the Gene Technology Technical Advisory Committee (‘GTTAC’), comprised of experts in relevant scientific fields including stem cell therapy, molecular biology, immunology, and plant science. The Regulator also must seek comment on the risk management plan from the States and Territories, prescribed Commonwealth authorities,

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<sup>43</sup> Institute of Medicine (US) et al, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* (2014) 26 <<http://www.ncbi.nlm.nih.gov/books/NBK174837/>>.

<sup>44</sup> Annette Rid and David Wendler, ‘A Framework for Risk-Benefit Evaluations in Biomedical Research’ (2011) 21 *Kennedy Institute of Ethics Journal* 141.

<sup>45</sup> *Ibid* 166.

<sup>46</sup> *Ibid* 167.

<sup>47</sup> Under s 11 of the *Gene Technology Act 2000* (Cth), an intentional occurs if the GMO is ‘intentionally released into the open environment, whether or not it is released with provision for limiting the dissemination or persistence of the GMO or its genetic material in the environment’.

local councils, and the public.<sup>48</sup> For unintentional releases (which relates to products that are not intentionally released into the open environment and has included the vast majority of clinical trial products),<sup>49</sup> the Regulator is permitted, but not required, to consult such persons and bodies.<sup>50</sup> Notably, the legislation does not provide for the Regulator to consult with members of the public on licences for unintentional releases.

To date, Phase III clinical trials of a genetically modified cholera vaccine provide the only example of a review of an 'intentional release' of a genetically modified clinical trial product under the *Gene Technology Act*.<sup>51</sup> The OGTR adopted a relatively constrained role, expressly deferring to the Therapeutic Goods Administration ('TGA'), investigator, sponsor, and role of Human Research Ethics Committees ('HREC') in ensuring participant safety. The Regulator explained that:

In order to avoid duplication of regulatory oversight, as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment.<sup>52</sup>

The OGTR approved the application contingent on a range of risk mitigation procedures.<sup>53</sup> A number of licences have been issued for clinical trial products defined as unintentional releases;<sup>54</sup> however, the limited information publicly available precludes a deeper analysis of the approval process.

The OGTR is well placed to meet most of the challenges that beset risk-benefit assessments for highly innovative investigational products, especially when intentional product release procedures are followed. The OGTR has access to excellent expertise — especially through the GTTAC — so it should have the capacity to make an assessment of scientifically complex benefits and risks.<sup>55</sup> At least for intentional releases, the Regulator's processes also address the normative nature of risk assessments through the requirement for broad expert and public consultation. A 2011 review of the *Gene Technology Act* praised the OGTR's extensive communication strategies, including advertising individual protocols in high-profile state

<sup>48</sup> *Gene Technology Act 2000* (Cth) s 52.

<sup>49</sup> For example, DNIR-536, 'Clinical study if the efficacy and safety of intra-tumoural injection of genetically modified ASN-002 in nodular basal cell carcinoma in a clinical study'; DNIR-523, 'A clinical trial to treat Hemophilia B using AAV-based gene therapy'; DNIR-501, 'A phase 1 study of autologous GD2 chimeric antigen receptor-expressing peripheral blood T cells in patients with metastatic melanoma': Office of the Gene Technology Regulator, *List of Applications and Licences for Dealings Not Involving an Intentional Release (DNIR) of a GMO into the Environment* <<http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/contained-1>>.

<sup>50</sup> *Gene Technology Act 2000* (Cth) s 47.

<sup>51</sup> Office of the Gene Technology Regulator, *Issue of Licence DIR 126 to PaxVax Australia Pty Ltd for a Clinical Trial of a Genetically Modified Vaccine against Cholera* (10 April 2014) <<http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir126notific-htm>>. The vaccine is excreted from participants into sewage and waste water, thereby constituting a release into the open environment.

<sup>52</sup> Office of the Gene Technology Regulator, 'Risk Assessment and Risk Management Plan for DIR 126: Clinical Trial of a Genetically Modified Vaccine against Cholera' 9 <<http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/65A3E9592160CA92CA257C1F007F38BA/SFile/dir126ramp.pdf>>.

<sup>53</sup> *Ibid* 39.

<sup>54</sup> For example, DNIR-536, 'Clinical study if the efficacy and safety of intra-tumoural injection of genetically modified ASN-002 in nodular basal cell carcinoma in a clinical study'; DNIR-523, 'A clinical trial to treat Hemophilia B using AAV-based gene therapy'; DNIR-501, 'A phase 1 study of autologous GD2 chimeric antigen receptor-expressing peripheral blood T cells in patients with metastatic melanoma': Office of the Gene Technology Regulator, *List of Applications and Licences for Dealings Not Involving an Intentional Release (DNIR) of a GMO into the Environment* <<http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/contained-1>>.

<sup>55</sup> The Allen Consulting Group, 'Review of the Gene Technology Act 2000' (August 2011) <<http://www.health.gov.au/internet/main/publishing.nsf/Content/gene-techact-review>> advised that the GTTAC 'appears to be working very well'.

and national newspapers and circulating advice to an email list of approximately 700 interested stakeholders.<sup>56</sup> Dedicated advice by the Gene Technology Ethics and Community Consultative Committee enhances the consultative process,<sup>57</sup> which is an important addition given theoretical and practical concerns about the efficacy of public engagement in technical decision making and risk assessment.<sup>58</sup> Finally, when reviewing intentional releases, the OGTR appears to satisfy Rid and Wendler's conditions for an 'ideal social arbiter'.<sup>59</sup> Evaluations are based on formalised risk assessment processes with input from a variety of government offices along with an expert scientific committee. The review process also allows for extensive public scrutiny and input.

Despite its clear benefits, full OGTR review only applies to a few highly innovative investigational products. For one, the definition of products that fall within the Regulator's scope is highly specific,<sup>60</sup> raising questions about its comprehensiveness for current and future synthetic biology products. The definition also excludes other kinds of highly innovative investigational products, such as nanotechnology. Moreover, many of the regulatory processes crucial for satisfying the conditions for optimal risk-benefit assessments (public consultation, mandatory expert scientific consultation, public availability of licensing information) apply only to an intentional product release, which omits the majority of early-phase trials. Finally, in the one instance in which the OGTR has reviewed the intentional release of a clinical trial product, it refrained from assessing the risks and benefits for individual participants. These were expressly deferred to the TGA and reviewing the HRECs. Everything else being equal, avoiding duplicative regulatory oversight is a worthy goal. However, this strategy warrants reassessment in light of the limited capacity for the TGA and HRECs to address the trifold challenges of reviewing the risks and benefits of synthetic biology and other highly innovative investigational products.

## B Therapeutic Goods Administration

The TGA is a Commonwealth statutory authority responsible for therapeutic goods in Australia. Before any investigational product can be used in clinical trials, the trial sponsor must satisfy the requirements of either the Clinical Trial Notification ('CTN') Scheme or the Clinical Trial Exemption ('CTX') Scheme. These pathways involve very different levels of TGA review and oversight.

The TGA plays a limited review role under the CTN Scheme. An HREC is responsible for reviewing all data relating to the clinical trial, including its scientific validity and ethical acceptability. After HREC approval, the CTN form is sent to the TGA to notify it of the trial. The TGA plays a more active role in evaluating proposed clinical trials under the CTX scheme. Under this scheme, the trial sponsor must lodge an application to conduct clinical trials with the TGA. A TGA delegate is then made responsible for reviewing product information, including any preclinical and clinical data. If no objection is raised, the trials may proceed.<sup>61</sup> The TGA has the discretion during the review process to seek input from relevant advisory committees, predominantly comprised of scientific subject-matter experts. In the synthetic biology context, this would most likely fall to the Advisory Committee on Biologicals.<sup>62</sup>

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<sup>56</sup> Ibid 33.

<sup>57</sup> *Gene Technology Act 2000* (Cth) s 107.

<sup>58</sup> Sherry Arnstein, 'A Ladder Of Citizen Participation' (1969) 35 *Journal of the American Planning Association* 216; John Gaventa and Andrea Cornwall, 'Power and Knowledge' in Peter Reason (ed), *Handbook of Action Research: Participative Inquiry and Practice* (SAGE, 2001) 70.

<sup>59</sup> Rid and Wendler, above n 44.

<sup>60</sup> *Gene Technology Act 2000* (Cth) s 10.

<sup>61</sup> Therapeutic Goods Administration, *Clinical Trials at a Glance* (18 May 2001) <<https://www.tga.gov.au/clinical-trials-glance>>.

<sup>62</sup> Established under the *Therapeutic Goods Regulations 1990* (Cth), pt 6 div 1EA.

The only investigational products for which the CTX scheme is mandatory are Class 4 biologicals. This is defined in the *Therapeutic Goods Act 1989* (Cth) as a product that 'comprises, contains or is derived from human cells or human tissues' that is processed using a method that goes beyond minimal manipulation and 'in a way that changes an inherent biochemical, physiological or immunological property'.<sup>63</sup> Under the *Therapeutic Goods (Things that are not Biologicals) Determination* of 2011 other products are specified as not constituting biologicals, including recombinant DNA products.<sup>64</sup> A product also can be declared in the regulations as a Class 4 biological.<sup>65</sup>

Except in these quite limited circumstances, a trial sponsor can choose whether to use CTN or CTX. The TGA advises that 'as a general rule', later-phase studies are most suited to the CTN scheme, and the CTX scheme may be 'more appropriate where the experimental device introduces new technology, new material or a new treatment concept which has not been evaluated previously in clinical trials in any country'.<sup>66</sup> An HREC that receives an application to review a trial under the CTN scheme may advise that it has insufficient expertise and recommend the trial's review under the CTX scheme, although it appears that such a course of action is relatively unusual. A 2005 review of access to unapproved therapeutic goods in Australia reported that, in 2000 (the most recent year for which data was available), only two clinical trials went through the CTX scheme. This is compared to the 589 trials that went through the CTN scheme during the same period.<sup>67</sup> This included most Phase I and II trials.<sup>68</sup> It is impossible from the available data to extrapolate the likelihood of a highly innovative investigational product going through the CTX scheme. Tellingly, however, the Report advised of HRECs' 'overwhelming willingness' to conduct substantial scientific reviews rather than refer trials back through the CTX process.<sup>69</sup>

In sum, the TGA regulatory framework is less suitable to meet the challenges of risk-benefit assessments for highly innovative investigational products than the OGTR. The TGA has the capacity to conduct a rigorous scientific analysis of relevant risks and benefits, particularly where the Administration receives input from a relevant advisory committee. However, the process has no clear avenue for addressing the normative aspects of risk-benefit assessments. TGA reviews are confidential and are not open to public input or submissions. The expertise available to the TGA through advisory committees is technical in nature, which limits its scope for reflection on public perceptions of risk and benefit. The TGA process also satisfies fewer of the criteria for an ideal social arbiter than the OGTR, lessening its potential to address the lack of substantive standards for judging the acceptability of risk-benefit assessments. In many circumstances, a TGA officer alone can make a CTX decision. Review by expert advisory committees is discretionary and technology-specific. Neither the TGA nor the relevant advisory committees have in place processes to make risk assessments (and the principles on which they are founded) publicly accessible, precluding the requisite level of transparency and accountability.<sup>70</sup> Moreover, in practice, only a select few investigational products will receive any TGA scrutiny of product information. Only those products that meet the complex definition of a Class 4 Biological are required to go through the CTX

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<sup>63</sup> *Therapeutic Goods Act 1989* (Cth) s 32A. See also Therapeutic Goods Administration, *Australian Regulatory Guidelines for Biologicals: Part 1* <<http://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb>>.

<sup>64</sup> Secretary of the Department of Health and Ageing, *Therapeutic Goods (Things that are not Biologicals) Determination 2011*, No 1, 31 May 2011, s 3(e) (ii).

<sup>65</sup> At the time of writing, no biological was so declared.

<sup>66</sup> Therapeutic Goods Administration, *Access to Unapproved Therapeutic Goods – Clinical Trials in Australia*, 14–15 <<http://www.tga.gov.au/publication/access-unapproved-therapeutic-goods-clinical-trials-australia>>.

<sup>67</sup> Banscott Health Consulting, *Report of the Review of Access to Unapproved Therapeutic Goods*, 38.

<sup>68</sup> *Ibid* 66.

<sup>69</sup> *Ibid* 71.

<sup>70</sup> Some information may be discoverable under freedom of information laws; however, this cannot equate to proactive publication in the context of satisfying conditions for an 'ideal social arbiter'.

Scheme. While sponsors may choose to use the CTX scheme, or a reviewing HREC may refer such trials, available data shows the rarity of these actions.

### C Human Research Ethics Committees

Receipt of National Health and Medical Research Council ('NHMRC') funding is preconditioned on a research institute's compliance with the National Statement, including its requirement for an HREC to review the ethical acceptability of all research involving humans. This makes HRECs the bodies with the most broad-ranging and consistent oversight of clinical trials, including early-phase clinical trials. For trials going through the CTN scheme, an HREC may be the only review of the risk-benefit calculus for individual participants.<sup>71</sup> Even where the TGA has reviewed an experimental product under the CTX scheme, HRECs still have sole responsibility for reviewing individual trial protocols.<sup>72</sup>

Almost all Australian HRECs are established by individual research institutions,<sup>73</sup> which are responsible for ensuring that the Committee is adequately resourced and maintained,<sup>74</sup> and have procedures that promote 'good ethical review'.<sup>75</sup> To fulfil National Statement criteria, HRECs also must satisfy certain membership criteria. They must comprise a roughly equal gender balance, at least one-third of the members being from outside the institution, and membership of laypersons, persons with expertise in professional care or counselling, a person who performs a pastoral care role, a lawyer, and persons with research experience.<sup>76</sup> Moreover, 'wherever possible one or more of the members ... should be experienced in reflecting on and analysing ethical decision-making'.<sup>77</sup>

The National Statement sets out four broad values and principles on which HRECs make decisions about a trial's ethical acceptability: research merit and integrity, justice, beneficence, and respect for those involved in research. Specific rules further delineate these values and principles: most relevantly, that the value of beneficence requires an assessment of the risks of harm to research participants and others. The National Statement advises that 'risks to research participants are ethically acceptable only if they are justified by the potential benefits of the research'.<sup>78</sup> It goes on to note that

in determining the existence, likelihood and severity of risks, [HRECs] should base their assessments on the available evidence ... [and] consider whether to seek advice from others who have experience with the same methodology, population, and research domain.<sup>79</sup>

The manner in which HRECs determine whether these National Statement criteria have been satisfied varies widely, and is subject to limited transparency and oversight. To maintain their accreditation status, each HREC must file an annual report with the NHMRC advising of their composition, processes for assessing research proposals, reporting

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<sup>71</sup> Where products involve genetic manipulation, review by an Institutional Biosafety Committee ('IBC') also will be required. IBCs provide institutions with advice on the identification and management of risks associated with GMO dealings, including GMO containment: Office of the Gene Technology Regulator, 'Explanatory Information on the Guidelines for Accreditation of Organisations' <[http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/accredguideinfo-Apr2013-toc/\\$FILE/accredguideinfo-Apr2013.pdf](http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/accredguideinfo-Apr2013-toc/$FILE/accredguideinfo-Apr2013.pdf)>.

<sup>72</sup> Therapeutic Goods Administration, *Access to Unapproved Therapeutic Goods – Clinical Trials in Australia*, above n 66, 10–14.

<sup>73</sup> A notable exception is the Bellberry HRECs, which have been established by a private not-for-profit company: Bellberry Limited, *Welcome to Bellberry Limited* <<http://www.bellberry.com.au/>>.

<sup>74</sup> Australian Government National Health and Medical Research Council, above n 9, 5.1.26.

<sup>75</sup> *Ibid* 5.1.37.

<sup>76</sup> *Ibid* 5.1.30.

<sup>77</sup> *Ibid* 5.1.32.

<sup>78</sup> *Ibid* 2.1.2.

<sup>79</sup> *Ibid* 2.1.4.

arrangements, complaint handling, and processes for monitoring of approved research. However, this process relies almost exclusively on self-reporting. As Susan Dodds has noted, '[w]hile it is certain that HRECs strive to meet the requirements of the National Statement, if an HREC is not aware that its processes are inadequate, it is not going to report its lack of compliance in the annual report'.<sup>80</sup> Many HRECs are now subject to additional accountability based on their status as a Certified Reviewing HREC under the national Mutual Acceptance Scheme for single ethical and scientific review of multi-centre research.<sup>81</sup> Certification requires assessment by the NHMRC of the HREC's review processes including an on-site visit from an assessment team. HRECs are certified for specific research categories, including various phases of clinical trials (Phases 0, I, II, III, and IV).<sup>82</sup>

This raises the question of how well HRECs are placed to satisfy the challenges of risk-benefit assessments for highly innovative experimental products. The first challenge is grappling with the uncertain nature of risks associated with highly innovative clinical trials. Since HRECs differ widely in their processes and the scientific expertise they have available to them, sweeping statements are unwise in this regard. However, the task is formidable. An HREC reviewing an early phase trial must locate expertise in disciplines as broad as clinical pharmacology, toxicology, trial design and methodology, in addition to the area of specialty of the particular trial. Yet this responsibility is imposed without any transfer of resources, or even clear guidance about what constitutes a sufficient scientific review.<sup>83</sup> External experts are usually unpaid and uncompensated, with selection occurring in an uncontrolled and unevaluated way.<sup>84</sup> Given the identified challenges, there is reason to question HRECs' capacity to address the complex ratio of risks and benefits that characterise highly innovative experimental products.

Public transparency and accountability is a further issue with which HRECs struggle, limiting their potential to constitute 'ideal social arbiters' for the purpose of complex risk-benefit trade-offs. HREC meetings usually are treated as confidential,<sup>85</sup> as are meeting minutes.<sup>86</sup> While there are arguments to support such confidentiality, such as free and independent committee discussion and possible commercial implications, it also could be used to hide inadequacies in the reviewing process.<sup>87</sup> The confidential nature of HREC meetings also means that the general public is not able to access information about HREC workings and the reasoning for their decisions,<sup>88</sup> nor can members of the public contribute to these deliberations. This suggests an insufficient level of scrutiny and accountability to serve as 'legitimate arbiters of reasonable disagreement'.<sup>89</sup> Notably, Rid and Wendler use HRECs (in the US context in which they write, termed Institutional Review Boards ('IRBs'))

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<sup>80</sup> Susan Dodds, 'Is the Australian HREC System Sustainable?' (2002) 21 *Monash Bioethics Review* 43.

<sup>81</sup> National Health and Medical Research Council, *The National Approach to Single Ethical Review of Multi-Centre Research*, Human Research Ethics Portal <<https://hrep.nhmrc.gov.au/national-approach>>.

<sup>82</sup> In the October 2014 list of institutions with certified ethical review processes, 10 of the 39 clinical trial certifications expressly covered Phase 0 trials: National Health and Medical Research Council, *List of Institutions with Certified Ethical Review Processes* <<https://hrep.nhmrc.gov.au/certification/hrecs>>.

<sup>83</sup> Deborah Frew and Ainsley Martlew, 'Research Governance: New Hope for Ethics Committees?' (2007) 26 *Monash Bioethics Review* 17.

<sup>84</sup> Savulescu, above n 25, 2.

<sup>85</sup> Department of Health (NSW), *Standard Operating Procedures: Human Research Ethics Committees [GL2013\_009]*, 21 <<http://www.health.nsw.gov.au/ethics/Pages/re-and-g-policies.aspx>>; Department of Health (Qld), *Standard Operating Procedures for Queensland Health HREC Administrators*, 42 <[www.health.qld.gov.au/ohmr/documents/regu/hrec\\_sop.pdf](http://www.health.qld.gov.au/ohmr/documents/regu/hrec_sop.pdf)>.

<sup>86</sup> Department of Health (NSW), above n 85, 24; Department of Health (Qld), above n 85, 44.

<sup>87</sup> Richard Ashcroft and Naomi Pfeffer, 'Ethics behind Closed Doors: Do Research Ethics Committees Need Secrecy?' (2001) 322 *British Medical Journal* 1294.

<sup>88</sup> M Sheehan, 'Should Research Ethics Committees Meet in Public?' (2008) 34 *Journal of Medical Ethics* 631.

<sup>89</sup> Rid and Wendler, above n 44, 167.

as an example of bodies that are insufficiently representative and transparent to evaluate studies involving high cumulative net risks.<sup>90</sup>

An area in which HRECs do have an advantage over bodies such as the TGA is their capacity to deal with the normative nature of risk benefit assessments. The National Statement sets out relatively broad membership requirements, including laypersons and persons who perform a pastoral care role in the community. A robust dialogue canvassing these varying perspectives would do much to forestall a purely technical characterisation of risks and benefits. Yet this presupposes the meaningful participation of all members in discussions of the risk-benefit calculus, which there are reasons to doubt. In a 1994 publication that assessed HREC members' decision-making influence, both administrators and medical graduates were rated as significantly more active and important than the remaining members, including lawyers, ministers of religion and lay members.<sup>91</sup> The authors noted that 'the finding raises the question whether lay members can effectively balance any bias that medical, scientific, and other institutional members may bring to the committee'.<sup>92</sup> These findings are consistent with more recent empirical research in the US, reporting that lay members feel they lack influence as compared with scientific members.<sup>93</sup>

## VI DISCUSSION

The preceding discussion has highlighted the difficulties that face Australia's present regulatory bodies when assessing the risks and benefits of highly innovative investigational products, such as those likely to emerge through synthetic biology. While the OGTR is best equipped to deal with these multifold challenges, the Regulator has so far taken a relatively hands-off approach to clinical trial products, due to these products' usual classification as an 'unintentional release', as well as concerns about duplicating the oversight functions of the TGA and HRECs. Several options for reform are available, including expanding the scope of OGTR reviews of investigational products, requiring TGA review of investigational products that meet predefined risk criteria, and establishing more specialised HRECs to review early-phase clinical trials involving highly innovative products.

### A *Expanding and Integrating OGTR Review*

Given the benefits of the OGTR review procedure for satisfying the multifold challenges of complex risk-benefit assessments, consideration is warranted of extending its remit to cover a broader spectrum of clinical trials with highly innovative investigational products. The main proviso is whether this can be achieved in a practical manner and without unduly duplicating regulatory activities.

Experience from the US Recombinant DNA Advisory Committee ('RAC') suggests at least the possibility of such an endeavour, along with some lessons for how it may be achieved. The RAC has considerable similarities to the OGTR, including a purview of the scientific and ethical acceptability of novel gene therapy research protocols and scope for public participation in reviews.<sup>94</sup> The model has been credited with easing public fears about the safety and appropriateness of gene transfer research,<sup>95</sup> and generating specialist institutional

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<sup>90</sup> Ibid.

<sup>91</sup> Paul M McNeill, Catherine A Berglund and Ian W Webster, 'How Much Influence Do Various Members Have within Research Ethics Committees?' (1994) 3 *Cambridge Quarterly of Healthcare Ethics* 522.

<sup>92</sup> Ibid 526.

<sup>93</sup> Sohini Sengupta and Bernard Lo, 'The Roles and Experiences of Nonaffiliated and Non-Scientist Members of Institutional Review Boards' (2003) 78 *Academic Medicine: Journal of the Association of American Medical Colleges* 212.

<sup>94</sup> Institute of Medicine (US) et al, above n 43, 47.

<sup>95</sup> Joseph M Rainsbury, 'Biotechnology on the RAC - FDA/NIH Regulation of Human Gene Therapy' (2000) 55 *Food and Drug Law Journal* 575, 598–9; Institute of Medicine (US) et al, above n 43, 49.

knowledge about recurring gene transfer issues.<sup>96</sup> The Institute of Medicine ('IOM') has recently assessed the model as providing ongoing benefits that warrant its retention in the IOM Report.<sup>97</sup>

The procedures followed by the RAC have changed considerably since its inception to maximise its utility for the Food and Drug Administration ('FDA') and ethics committees (IRBs in the US) and to minimise undue regulatory burden. For one, RAC review has been restricted to those applications deemed as being particularly risky. Originally the RAC reviewed and approved all gene transfer research at institutions receiving related NIH research funds. As the amount of research accelerated and certain kinds of procedures became more mainstream, reviews were limited to novel protocols that presented specific safety or ethical issues, thereby ensuring that duplication is limited to those clinical trials for which robust oversight is most needed.<sup>98</sup> Reviews now are initiated by recommendations from at least three RAC members or the NIH director regarding the novelty of the research and the level of risk it poses to participants.<sup>99</sup> As a result, only about 20 per cent of protocols submitted to the RAC are selected for additional review.<sup>100</sup> The IOM Report recommended further limiting RAC review to trials that satisfy the following criteria, as identified by the Office of the Director of the NIH:

1. Protocol review could not be adequately performed by other regulatory and oversight processes (for example, institutional review boards, institutional biosafety committees, the US Food and Drug Administration);
2. One or more of the criteria below are satisfied:
  - The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.
  - The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.
  - The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.<sup>101</sup>

Constraining OGTR clinical trial reviews in a similar way could ensure that the regulatory burden is focused on those product dealings that raise the greatest need for expert and transparent risk-benefit assessments – seemingly a far more targeted criterion than the current proxy of 'intentional' as compared with 'unintentional' releases.

The RAC review process also has been finessed to better integrate RAC findings with the more general regulatory processes for clinical trials. Initially, IRBs gave gene therapy protocols a provisional approval and then deferred to the RAC before issuing a final approval.<sup>102</sup> In 2000, the timing of RAC reviews shifted to occur before, rather than after, IRB review, allowing IRBs to better incorporate into their review issues identified by the RAC.<sup>103</sup> The availability of such reviews has been credited with reassuring US ethics

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<sup>96</sup> Nancy MP King, 'RAC Oversight of Gene Transfer Research: A Model Worth Extending?' (2002) 30 *The Journal of Law, Medicine & Ethics* 381, 383–4.

<sup>97</sup> Institute of Medicine (US) et al, above n 43.

<sup>98</sup> Ibid 46; Rainsbury, above n 95, 587–92.

<sup>99</sup> Institute of Medicine (US) et al, above n 43, 51–2.

<sup>100</sup> Ibid 16.

<sup>101</sup> Institute of Medicine (US) et al, above n 43, Rec 4-1; The Director of the NIH accepted this recommendation: Francis S Collins, *Statement by the NIH Director on the IOM Report Addressing the Role of the Recombinant DNA Advisory Committee in Oversight of Clinical Gene Transfer Protocols* <[http://www.nih.gov/about/director/05222014\\_statement\\_iom\\_rac.htm](http://www.nih.gov/about/director/05222014_statement_iom_rac.htm)>.

<sup>102</sup> Nelson A Wivel, 'Historical Perspectives Pertaining to the NIH Recombinant DNA Advisory Committee' (2014) 25 *Human Gene Therapy* 19, 21.

<sup>103</sup> Institute of Medicine (US) et al, above n 43.

committee members that responsibility for entering into a new era of medicine did not rest solely on their shoulders.<sup>104</sup> The RAC findings also inform the various stages of review by the US drug regulator, the FDA.<sup>105</sup> Structuring OGTR review in this way would help to ensure that expanded OGTR oversight is most valuable for HRECs and the TGA, while minimising the regulatory burden placed on applicants.

A related question is whether the OGTR's mandate should be expanded beyond current legislative definitions of genetically modified products. While this would have the benefit of extending the benefits of a rigorous and publicly accountable review process to highly novel investigational products beyond technology-specific constraints, it raises some implementation challenges. In particular, the GTTAC is constituted on the basis of the expertise necessary to review gene transfer products.

Notably, the IOM Report recommended reforming the RAC to provide the capacity to review

the full breadth of emerging areas of research supporting human clinical intervention that may have special risks and that could not be adequately assessed under the existing regulatory processes for clinical research.<sup>106</sup>

It suggested achieving this by either expanding the Committee's purview or by retaining a broad pool of subject matter experts who could be consulted on an ad hoc basis as issues or applications emerged.<sup>107</sup> Similar choices could be considered for the OGTR.

#### B *Improving the Assessment Available Through the TGA and HRECs*

In the absence of reforms identified above, OGTR review will not be an option for many highly innovative investigational products because they fall outside the realm of genetic modification (such as, nanotechnology products). Even within the realm of genetically modified products, most clinical trials will involve an 'unintentional' product release and therefore will receive an abbreviated OGTR review. Ensuring a favourable risk-benefit ratio for these products depends on HREC and TGA review. For the reasons explained earlier in this article, neither of these processes fully encapsulate the trifold challenges of assessing risks and benefits of highly innovative investigational products. In particular, neither review process satisfies the requisite level of transparency and public participation to constitute an 'ideal social arbiter' for the purposes of trading off risks and benefits. However, in combination, HREC and TGA reviews go a long way towards addressing the scientific complexities and normative judgments involved in such judgments.

Unfortunately, Australia's present clinical trial framework fails to ensure TGA review of highly innovative products. The only explicit requirement for review under the CTX scheme applies to Class 4 Biologicals. This depends on a complex, technical definition. While it captures many current synthetic biology applications, the definition's comprehensiveness requires dedicated attention, particularly to take into account future directions of the field. The definition is limited, for example, to products that comprise, contain or are derived from human cells or tissues. Would this cover, for example, a completely synthetic cell? Many other highly innovative investigational products will fall outside the definition's scope altogether. For these, scientific review is likely to remain the sole responsibility of reviewing HRECs. Yet a scientific review conducted by an HREC is 'likely to be a significantly different review than would have been conducted by TGA (or any other regulatory agency)'.<sup>108</sup> A

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<sup>104</sup> Rainsbury, above n 95, 598.

<sup>105</sup> Institute of Medicine (US) et al, above n 43, 55.

<sup>106</sup> Ibid 89.

<sup>107</sup> Ibid 92.

<sup>108</sup> Banscott Health Consulting, above n 67, 71.

technologically neutral, risk-based assessment is warranted for referring investigational products to the CTX scheme for a robust, standardised scientific assessment.

A possible framework in this regard can be drawn from the European Medicines Agency ('EMA') Guidelines on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products.<sup>109</sup> The Guidelines explain factors that increase the riskiness of experimental products, including the novelty of the mode of action, the extent of available knowledge about the product's target, and the relevance (or lack thereof) of animal species and models.<sup>110</sup> The EMA advises that:

the higher the potential risk associated with an investigational medicinal product and its pharmacological target, the greater the precautionary measures that should be exercised in the design of the first-in-human study.<sup>111</sup>

In the Australian context, equivalent guidelines could indicate the need for review under the CTX scheme. This solution still falls short of the trifold challenges of assessing the risks and benefits of highly innovative investigational products as well as OGTR review — predominantly because of a lack of sufficient transparency and public engagement. However, at least the combination of HREC and TGA review ensures that the assessment of such products can address the scientific uncertainties of such risks and benefits and the normativity involved in weighing these risks and benefits.

A further option for facilitating a robust scientific assessment of highly innovative investigational products would be constituting a small number of specialist HRECs that would have sole authority for reviewing certain kinds of early-phase trials — termed by Julian Savulescu as 'suprainstitutional specialist committees'.<sup>112</sup> To some extent, this process has already begun through the NHMRC national certification scheme, under which some ethics committees have nominated themselves as having expertise in early phase trials. Arguably, however, reliance on specialist HRECs is less desirable for scientific review of highly innovative investigational products than referral for TGA review. At least for the foreseeable future, NHMRC certification is voluntary: there is no requirement that a certified committee review any given clinical trial. Nor are there clear guidelines or standards as to what constitutes sufficient expertise to undertake such review. More intractably, scientific review by any HREC lacks the imprimatur of Australia's therapeutic products regulator. A clear and accountable scientific assessment process is essential for promoting public trust in new, risky technologies. Whether a voluntary, institutionally dispersed ethics committee should ever be delegated complete responsibility for such a task is doubtful.

## VII CONCLUSION

Harnessing the benefits of synthetic biology and other emerging technologies, while maintaining ethical protections for clinical trial participants, requires rigorous risk-benefit assessments. Such assessments face multifold challenges: most notably, the inherent complexity of ascertaining likely risks and benefits, the normativity underpinning how those risks and benefits are weighed, and the lack of ready substantive standards for determining any acceptable level of risks to which participants could ethically be exposed. Australia's present regulatory framework is insufficiently equipped to address the challenges of risk-benefit assessments for clinical trials involving highly innovative investigational products. The OGTR provides the most promising processes in this regard, including access to high-quality scientific expertise, avenues to engage a broad spectrum of perspectives in regulatory

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<sup>109</sup> European Medicines Agency, above n 12.

<sup>110</sup> *Ibid* 4.1.

<sup>111</sup> *Ibid* 4.4.1.

<sup>112</sup> Savulescu, above n 25, 2.

decision-making, including members of the public, and transparent and accountable procedures. However, such review procedures apply to a very limited number of clinical trials, limited by technical definitions that lack a ready focus on targeting the most risky dealings. Responsibility for the overwhelming majority of risk-benefit assessments for clinical trials involving highly innovative investigational products falls to the TGA and individual HRECs. Unfortunately, both of these review processes face clear gaps in their capacity to meet the challenges of undertaking risk-benefit assessments in this context. Regulatory reforms focused on expanding the OGTR's remit, along with strengthening HREC and TGA review requirements, will place Australia in a good position for assessing future advances.

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# **‘IDENTITY’ AND GOVERNANCE IN SYNTHETIC BIOLOGY: NORMS AND COUNTER NORMS IN THE ‘INTERNATIONAL GENETICALLY ENGINEERED MACHINE’ (iGEM) COMPETITION**

DAVID MERCER\*

*A number of commentaries preoccupied with the legal, social and ethical implications of synthetic biology have emphasised that an important element shaping options for its future governance will be the normative ethos that is adopted by the emerging field. One venue that has regularly been identified as central to the development of this normative ethos is the International Genetically Engineered Machine (iGEM) Competition, an annual synthetic biology competition, which attracts thousands of students from across the world. The ideal values promoted by iGEM of collaboration, interdisciplinarity, sharing of results, and overt commitment to the consideration of social and ethical implications of scientific work, are frequently interpreted as offering a model for the future development of the field. In the discussion that follows it will be noted that many of iGEM's normative aspirations appear to be difficult to convert into practice and that many of the paths which various forms of synthetic biology appear to be following deviate from the types of values iGEM publicly promotes. Policy makers are invited to make a more realistic assessment of iGEM's capacity to contribute (via generating a distinct synthetic biology normative ethos) to the future governance of the emerging field.*

## I INTRODUCTION

The International Genetically Engineered Machine (iGEM) competition is considered instrumental in the building of the discipline of synthetic biology. It was initiated at the Massachusetts Institute of Technology (MIT) in 2003 for undergraduate students, and has rapidly grown in popularity. It has played an essential role making synthetic biology an international discipline. It appeals to young minds and has captured the attention of industry academics and governments.<sup>1</sup>

In the following paper I will examine the significance of the International Genetically Engineered Machine (iGEM) Competition for the future governance and regulation of synthetic biology. iGEM's relevance to these questions is normally framed in terms of its importance as a venue for the development of the normative identity of the future synthetic biology scientist.<sup>2</sup>

Proposals for the regulation and governance of synthetic biology can be divided according to whether or not they operate within Ethical Legal and Social Implications (ELSI) traditions of policy analysis or form part of new post-ELSI approaches.<sup>3</sup> A feature of both approaches

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<sup>1</sup> Office of Economic Cooperation and Development (OECD), *Emerging Policy Issues in Synthetic Biology*, (OECD Publishing, 2014) 19, see also 3, 17, 25, 27.

<sup>2</sup> A brief history of iGEM will be provided below in Section IV. The acronym iGEM will be used in the following paper to refer to the iGEM competition.

<sup>3</sup> In this context it is also important to note the more radical position taken by various NGO's for a moratorium on synthetic biology. See for example: Friends of the Earth, CTA, ETC GROUP, *The Principles for the*

have been significant preoccupations with issues surrounding what types of norms and ethical codes of practice are appropriate for the emerging field of synthetic biology.

Funding for the study of ELSI of new genetics was formalised in 1990 as part of the Human Genome Project. ELSI research has been preoccupied with the construction of policies addressing the implications of the new genetics for areas such as privacy, clinical medicine, informed consent, intellectual property and biosecurity.<sup>4</sup> In the United States, the National Science Foundation has mandated that large Nanotech and synthetic biology research incorporate ELSI dimensions. Similar initiatives have also appeared in a variety of forms in Europe and the UK.<sup>5</sup>

Recent critiques of ELSI approaches have suggested they risk being limited to analysing the social impacts of scientific research at a distance from its sites of creation, and after the research has already begun to develop momentum. This means questions as to how the research might be being framed, and conducted to start with, are too easily back-staged. This has led to a call for post-ELSI approaches that emphasise the need for more flexible, 'reflexive', and collaborative ethical and social engagement between scientists, social scientists, regulators, and the public, as early as possible in the development of scientific projects, and in close proximity to where research is being carried out.<sup>6</sup>

ELSI and post-ELSI studies have resulted in a wealth of literature concerned with the regulation and governance of synthetic biology. One recent account notes that at least 40 major reports have been produced over the last decade, or so, since synthetic biology's emergence.<sup>7</sup> Part of the impetus for such regulatory preoccupations have been perceptions, particularly in the UK and Europe, that recent attempts for the introduction of Genetically Modified (GM) products and processes were not well managed by regulators, leading to unnecessary controversy – a situation hoped to be avoided in the future.<sup>8</sup>

Both approaches (which in practice may not always be as distinct as some proponents suggest) have evolved within a broader tradition of governance of biotechnology influenced by the Asilomar conference held in 1975.<sup>9</sup> The Asilomar Conference was initiated by Stanford

*Oversight of Synthetic Biology* (2014)

<<http://www.etcgroup.org/sites/www.etcgroup.org/files/The%20Principles%20for%20the%20Oversight%20of%20Synthetic%20Biology%20FINAL.pdf>>.

<sup>4</sup> See US National Library of Medicine, *What Are Some of the Ethical, Legal, and Social Implications Addressed by the Human Genome Project?* (8 June 2015) Genetics Home Reference

<[ghr.nlm.nih.gov/handbook/hgp/elsi](http://ghr.nlm.nih.gov/handbook/hgp/elsi)>; Michelle Garfinkel et al, *Synthetic Genomics: Options for Governance* (October 2007) J Craig Venter Institute <<http://www.jcvi.org/cms/research/projects/syngen-options/overview>>; Andrew Balmer and Paul Martin, Biotechnology and Biological Sciences Research Council, University of Nottingham, *Synthetic Biology: Social and Ethical Challenges* (May 2008) <<http://www.bbsrc.ac.uk/documents/0806-synthetic-biology-pdf/>>.

<sup>5</sup> Fillipa Lentzos, 'Synthetic Biology in the Social Context: The UK Debate to Date' (2009) 4 *Biosocieties* 303; Daniel Barben et al, 'Anticipatory Governance of Nanotechnology: Foresight, Engagement, and Integration' in E Hackett et al, *Handbook of Science and Technology Studies* (MIT Press, 3<sup>rd</sup> ed, 2007).

<sup>6</sup> See James Wilsdon and Rebecca Willis, *See-Through Science: Why Public Engagement Needs to Move Upstream* (Demos, 2004); Andy Balmer et al, *Towards a Manifesto for Experimental Collaborations between Natural and Social Scientists* (3 July 2012) Experimental Collaborations <<http://experimentalcollaborations.wordpress.com>>. For a more critical view see David Mercer, 'Human Practices and the Challenges of Upstream Engagement in Synthetic Biology' in A Bamme et al, *2011 Yearbook of the Institute of Advanced Studies on Science Technology and Society* (Profil, 2012) 67.

<sup>7</sup> Joy Zhang, Claire Marris and Nikolas Rose, 'The Transnational Governance of Synthetic Biology – Scientific Uncertainty, Cross-Borderness and the "Art" of Governance' (BIOS Working Paper No 4, London School of Economics and Political Science, May 2011) <[https://royalsociety.org/~media/Royal\\_Society\\_Content/policy/publications/2011/4294977685.pdf](https://royalsociety.org/~media/Royal_Society_Content/policy/publications/2011/4294977685.pdf)> ('BIOS report').

<sup>8</sup> Lentzos, above n 5.

<sup>9</sup> See Bjorn Kara Myskja, Rune Nydal and Anne Ingeborg Myhr 'We Have Never Been ELSI Researchers – There is No Need for a Post-ELSI Shift' (2014) 10 *Life Sciences, Society and Policy* 9.

University biologist Paul Berg to explore the issues involved in the future regulation of emerging recombinant DNA research: recombinant DNA referring to DNA that is produced from the combination of genetic materials from more than one source. Most commentators suggest an important outcome of Asilomar was the inauguration of a model for scientists in the field of biotechnology, to be pro-active in relation to issues of governance and regulation. This took the form of the development of biosafety protocols by scientists prior to external regulation, providing classifications for risk levels and appropriate commensurate safeguard strategies, and supplying advice and input into forms that national advisory bodies and oversight might take.<sup>10</sup> These traditions for scientists to have pro-active interest in regulation and promote ideals of self-governance have continued in the efforts of leading synthetic biology scientists such as J Craig Venter. Whilst he might be accused of displaying some hubris, Venter has been forward in reminding regulators of these efforts. In his testimony to a US Senate hearing in 2010, he notes for the record: 'My teams at both the JCVI and at the SGI have, as the leaders of this field, been driving these ethical and societal implications since the beginning of the research (for nearly 15 years).'<sup>11</sup>

These interests in pro-active engagement of scientists with ELSI issues and their calls for minimal external or scientific self-governance has encouraged a considerable amount of regulatory commentary to consider what types of ethical education, codes of practice and professional ethos might be required to be developed in tandem with these aspirations.<sup>12</sup> Because discussions about the development of codes of practice and professional institutions in synthetic biology involve concerns with education and the emergence of a professional ethos, iGEM, as a novel education venue unique to the field of synthetic biology, has been an obvious source of interest in terms of considering how it might contribute to these developments.<sup>13</sup>

Many post-ELSI approaches have shared these interests in the importance of the links between the development of the 'ethical' normative character of the emerging synthetic biologist and forms of scientific self-governance. In many of these approaches, these interests have been conceptualised slightly differently seeking to augment things like ethical education, codes of conduct, and professionalisation with the development of new forms of collaboration between scientists and social scientists, policy makers and the public. Ideally, these new forms of collaboration should feed back into the development and future governance of the field. These approaches also frequently suggest that the novelty of the field of synthetic biology, emerging as it is at a time of increasingly global and interdisciplinary science, demand new ways of thinking about regulatory issues.<sup>14</sup> A number of post-ELSI scholars have been attracted to iGEM as an ideal site to explore the possibilities of new forms

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<sup>10</sup> Steven Yearley, 'The Ethical Landscape: Identifying the Right way to Think About the Ethics and Societal Aspects of Synthetic Biology Research and Products' (2009) 6 *Journal of the Royal Society Interface* 559.

<sup>11</sup> J Craig Venter, *Prepared Statement of J Craig Venter, PhD – President, J Craig Venter Institute – Before the US House of Representatives Committee on Energy and Commerce* (27 May 2010) US House of Representatives – Democrats: Committee on Energy and Commerce <<http://democrats.energycommerce.house.gov/sites/default/files/documents/Testimony-Venter-HE-EC-Synthetic-Genomics-Developments-2010-5-27.pdf>>.

<sup>12</sup> Lorna Weir and Michael J Selgelid provide a good example of governance approaches which have raised the importance of the development of an appropriate synthetic biology professional ethos: 'By ethos we mean the sense of attachment and commitment that persons feel to the groups of which they form a part ... The formation of an ethos for synthetic biology would involve the emergence of a distinctive way of thinking and feeling for members of that profession. The professional ethos would also orient synthetic biologists to their work as an ongoing ethical task.' Lorna Weir and Michael J Selgelid, 'Professionalization as a Governance Strategy for Synthetic Biology' (2009) 3 *Systems Synthetic Biology* 91, 95 (citations omitted). However, it should be noted Weir and Selgelid do not single out iGEM specifically, instead drawing broader analogies with the professionalisation of Engineering and Medicine.

<sup>13</sup> For example see OECD, above n 1.

<sup>14</sup> P Rabinow and G Bennett, *Designing Human Practices: An Experiment with Synthetic Biology* (University of Chicago Press, 2012).

of collaboration between social scientists, scientists, and policy makers in synthetic biology more generally. Research has involved forms of ethnography, including participant observation in the competition as student mentors and competition judges, and producing analytical commentaries reflecting on policy implications of these engagements for the field more generally. This work provides an invaluable resource for the analysis that follows.<sup>15</sup>

A conspicuous feature of both traditional and more novel discussions of regulation of synthetic biology, then, have been preoccupations with governance options that aspire to avoid simply continuously expanding formal legal guidelines and oversight. This in turn has inspired numerous discussions about what might be involved in the development of the future identity of the synthetic biology scientist who will be exercising ethical judgement, engaging in new practices and developing new norms and professional identity.

The discussion that follows will be structured in the following way: In Section II, I will provide two brief examples where recent reports exploring regulation and governance of synthetic biology have noted the importance of normative ethical education and the iGEM. In Section III, I will provide an overview of work in the sociology of science, which has investigated the idea of professional norms. I will highlight that a feature of this work is a recognition that claims about professional norms are frequently difficult to sustain in practice. In Section IV, I will provide a brief history of the iGEM. In Section V, I will present a critical analysis of a number of rhetorical claims made by iGEM supporters about the types of normative orientations the competition is meant to be promoting. It will be suggested that iGEM may not be as well suited to the task of developing a normative identity for the future synthetic biology scientist as many commentaries suggest. It will be shown that the competition operates in a social context that encourages a variety of competing and contradictory normative orientations. In Section VI, I will suggest that whilst iGEM may well be contributing to the development of one branch of synthetic biology in general terms, many policy commentators risk overrating its significance as a venue for the development of a normative ethos that will answer the broader ethical and social concerns linked to the fields' emergence.

## II IGEM 'RESPONSIBLE STEWARDSHIP' AND THE 'ART OF GOVERNANCE'

Let me provide two examples where recent proposals for the regulation and governance of synthetic biology have highlighted the importance of initiatives to develop appropriate scientific norms and ethical education to which it is anticipated iGEM will contribute. The first example is drawn from a report primarily working within a traditional ELSI framework, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, prepared by the Presidential Commission for the Study of Bioethical Issues (PCSBI report).<sup>16</sup> The second example is drawn from a report framed by a post-ELSI approach, *The Transnational Governance of Synthetic Biology* (BIOS report). Produced by the Centre for the Study of Bioscience, Biomedicine, Biotechnology and Society, and funded by the Royal Society, it refers to the concept of the 'Art of Governance' (with iGEM as part of the process of governance in the making).<sup>17</sup>

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<sup>15</sup> Emma Frow and Jane Calvert, 'Can Simple Biological Systems be Built from Standardized Interchangeable Parts? Negotiating Biology and Engineering in a Synthetic Biology Competition' (2013) 5 *Engineering Studies* 42; Andrew Balmer and Kate Bulpin, 'Left to their Own Devices: Post-ELSI, Ethical Equipment and the International Genetically Engineered Machine (iGEM) Competition' (2013) 8 *Biosocieties* 311.

<sup>16</sup> Presidential Commission for the Study of Bioethical Issues, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (December 2010) <[http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10\\_0.pdf](http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf)> ('PCSBI report').

<sup>17</sup> See 'BIOS report', above n 7.

A *The PCSBI Report*

The PCSBI report, called by President Obama in the wake of the Venter Institute's claims to have produced the first fully synthetically generated life-form, explores the challenges faced in regulating new forms of life, environmental implications of the controlled release of genetically altered organisms into the environment, and bio-security and intellectual property (IP) implications of synthetic biology.<sup>18</sup> It also notes that these regulatory challenges have been intensified by the widening of both the locations, locally and globally, where synthetic biology research can take place and the credentials of parties who are able to engage in it. As such the report supports the need for continuing development of forms of surveillance over the sourcing of various biological materials and techniques.

The report, nevertheless, does not suggest the situation requires radical changes to existing approaches to regulatory policies involving biotechnology that have evolved since Asilomar.<sup>19</sup> A feature of the tone of the report is the adoption of a responsive and moderate, but permissive, attitude to answering questions of the regulation and governance of synthetic biology. For example, rather than pro-action or precaution, it suggests there should be a 'middle course' approach of 'prudent vigilance'.<sup>20</sup> The report also notes the importance of promoting 'intellectual freedom and responsibility' and 'regulatory parsimony', so regulation is only considered where completely necessary: 'With sufficient freedom to operate, tomorrow's achievements may render moot the risks of today. Self-regulation also promotes a moral sense of ownership within a professional culture of responsibility.'<sup>21</sup>

Underpinning these strategies, the report suggests the need to develop a culture amongst synthetic biology scientists compatible with 'responsible stewardship'. This is explained in the following terms:

Responsible conduct of synthetic biology research, like all areas of biological research, rests heavily on the behaviour of individual scientists. Federal oversight can guide the development of a culture of responsibility and accountability, but it also must be translated into practice at the laboratory level – and by the institutions that sponsor that laboratory science ... Creating a culture of responsibility in the synthetic biology could do more to promote responsible stewardship in synthetic biology than any other single strategy.<sup>22</sup>

The report goes on to emphasise the role of ethics committees, and ethics education, as key components in creating the responsible synthetic biology scientist. It notes the need to import key aspects of this culture, which are largely already present in clinical, biological, and biomedical research, into engineering research. The PCSBI report notes the significance of iGEM as a venue for the education of the next generation of synthetic biology scientists and also as a vehicle to educate the public about synthetic biology: 'Beyond building

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<sup>18</sup> Daniel G Gibson et al, 'Creation of Bacterial Cell Controlled by a Chemically Synthesized Genome' (2010) 329 *Science* 52 <<http://www.sciencemag.org/cgi/rapidpdf/science.1190719v1.pdf>>.

<sup>19</sup> Whilst there has been a mass of reports looking at policy aspects of synthetic biology over the last decade most regulatory approaches tend to have operated incrementally and avoided treating synthetic biology as exceptional. Sarah R Carter et al, 'Synthetic Biology and the US Biotechnology Regulatory System: Challenges and Options' (Report, J Craig Venter Institute, May 2014); OECD, above n 1; Yearley, above n 10.

<sup>20</sup> The avoidance of the Precautionary Approach might be envisaged as a response to the calls for its strong application to synthetic biology including a moratorium on areas of synthetic biology research by a variety of NGOs. See for example: Friends of the Earth, CTA, ETC GROUP, above n 3; Richard C Lewontin, 'The New Synthetic Biology: Who Gains?' (8 May 2014) *The New York Review of Books* <<http://www.nybooks.com/articles/archives/2014/may/08/new-synthetic-biology-who-gains/>>; Gregory Kaebnick, 'Carefully Precautionary about Synthetic Biology?' (22 March 2012) *Bioethics Forum* <<http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=5781&blogid=140>>.

<sup>21</sup> PCSBI report, above n 16, 28.

<sup>22</sup> Ibid 133.

biological systems, the broader goals of iGEM include growing and supporting a community of scientists guided by social norms.<sup>23</sup>

## B *The BIOS Report*

The BIOS report explores the implications of synthetic biology's 'borderlessness', literally in terms of geographic place, but also more abstractly, in terms of the unsettled boundaries of professional identities and scientific uncertainty. It suggests 'borderlessness' arises for the following types of reasons:

- In a rapidly globalising scientific world, numerous synthetic biology activities rely on free access to scientific information online, a domain notoriously difficult to regulate.
- Numerous scientific and social uncertainties are involved in emergent novel collaborative practices for doing research such as iGEM and DIYbio (Do it Yourself, garage or hacker biology).<sup>24</sup>
- Numerous new products and processes with currently unknowable implications, risks, and benefits are likely to emerge from the fusion of biology with engineering.

Unlike more traditional ELSI approaches which tend to treat knowledge and practices as fixed, requiring oversight and restrictions administered by independent but possibly antagonistic 'outside' actors,<sup>25</sup> the report suggests that there needs to be a re-conceptualisation of the notion of governance to one where it is seen as a flexible and responsive 'art' (involving multiple points of collaboration), not an imposition. The report singles out iGEM as one of the more important sites for the 'social engineering' of the future synthetic biology scientist.

iGEM functions as a global hub for young scientists to meet and compete (...) Undergraduate performances at iGEM contests have been treated as important indicators to assess, reflect on, and criticise national policy making. Meanwhile it generates debate about what can/should count as good 'human practices' and also facilitates global exchange and dissemination of concerns over biosafety, biosecurity, IP regimes, ethics and public engagement in the field of synthetic biology. (...) [I]n the case of synthetic biology, evolving standards, codes of conducts, collections and categorisations of BioBricks are at least as much influenced by the iGEM competition as by conventional scientific institutions. (...) [D]espite being essentially a 'scientific' competition, iGEM plays a crucial role in the 'social' engineering of the upcoming generation of young scientists. (...) [F]ew policy analyses nowadays would ignore the central role iGEM has over the formation of international research culture in this emerging area.<sup>26</sup>

iGEM, of course, only constitutes one of the many arenas where the identity of the field of synthetic biology is currently being negotiated. For example, there are mainstream professional scientific practices where chemists, biologists, and computer engineers are initiating various new interdisciplinary projects in traditional institutional settings; DIYbio which is far more experimental and speculative, both socially and epistemologically; and the entrepreneurial ventures of 'hyper-experts' such as J Craig Venter.<sup>27</sup> iGEM is still,

<sup>23</sup> Ibid 46, 157.

<sup>24</sup> I will use the term DIYbio to cover Hacker Biology, Garage Biology, Hackerspaces, Amateur Biology etc.

<sup>25</sup> M W Douglas and Dirk Stemerding, 'Challenges for the European Governance of Synthetic Biology for Human Health' (2014) 10 *Life Sciences, Society and Policy* 6  
<<http://www.lsspjournal.com/content/pdf/s40504-014-0006-7.pdf>>.

<sup>26</sup> Bios Report, above n 7, 26-27.

<sup>27</sup> Alessandro Delfanti, "What Dr Venter Did on his Holidays": Exploration, Hacking, Entrepreneurship in the Narratives of the Sorcerer II Expedition' (2009) 28(4) *New Genetics and Society* 415. For discussion of the

nevertheless, a valuable site because it sits at a junction between these other areas, involving multiple sub-cultures aside from its primarily student participants. It also represents a community that is novel and growing rapidly, and its practices are relatively transparent and have been subject to a number of ethnographic studies. By comparison, for example, DIYbio is still extremely unsettled and in its relative infancy,<sup>28</sup> and specialises in professional practices from a sociological perspective in a way that is not always transparent.<sup>29</sup>

### III NORMS AND SOCIAL ENGINEERING

If future generations of synthetic biology scientists are to be 'socially engineered' to become 'responsible stewards', one of the main vehicles for this will be through the development of various norms or dispositions, or habits of thought and practice that are reinforced by the emerging synthetic biology community. Norms operate at a deeper level than regulation and rules, although for rules and regulations to be effective, a normative ethos should ideally reinforce them by shaping expectations of appropriate behaviour in a community. Norms influence how individuals interact with each other in a community and their self-identification with that community, and how they perceive the relationship of that community with broader society. The fact that norms are in a sense tacit, and do not need to be simply codified, means that they are more likely to become topics of formal discussion when a community is reflecting on its practices, and such reflections are visible to those outside the community. These types of reflections generally become more intense during a crisis or controversy, when a new community is emerging, when there are perceptions that various individuals may be deviating from acceptable standards of behaviour, and in the induction of neophytes into a community. Norms can be analysed both in terms of the behaviour that is deemed desirable, and that which is actually typical and observable, as well as the way a community manages the relationship between these two dimensions.<sup>30</sup>

#### A *Revisiting Merton's Normative Ethos of Science*

The most influential attempt to explore the idea of norms in *the specific context of the development of scientific and technical communities* is Robert Merton's so-called norms of science.<sup>31</sup> The Mertonian image of science continues to underpin much public, media, and legal discourses surrounding science policy, especially in controversial settings where questions of the ethics of science are often measured against ideal models of conduct.<sup>32</sup> Mertonian ideals in various forms also appear in the commentaries of proponents of open

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concept of the 'hyper-expert' see David Mercer, 'Hyper-experts and the Vertical Integration of Expertise in EMF/RF Litigation' in G Edmond (ed), *Expertise in Regulation and Law* (Ashgate, 2004) 85.

<sup>28</sup> Daniel Grushkin, Todd Kuiken and P Millet, 'Seven Myths & Realities about Do-It-Yourself Biology' (Report, Wilson Centre: Synthetic Biology Project, November 2013) <[http://www.synbioproject.org/process/assets/files/6673/\\_draft/7\\_myths\\_final.pdf](http://www.synbioproject.org/process/assets/files/6673/_draft/7_myths_final.pdf)>.

<sup>29</sup> Rabinow and Bennett, above n 14, 171–2.

<sup>30</sup> Melisa S Anderson et al, 'Extending the Mertonian Norms: Scientists' Subscription to Norms of Research' (2010) 81(3) *Research Journal of Higher Education* 366.

<sup>31</sup> Robert K Merton, 'The Normative Structure of Science', in Robert K Merton, *The Sociology of Science: Theoretical and Empirical Investigations* (University of Chicago Press, 1942) 221.

<sup>32</sup> David R Benson and Roger K Kjellgren, *Tacit Diplomacy in Life Sciences: A Foundation for Science Diplomacy* (31 January 2014) Science & Diplomacy <<http://www.sciencediplomacy.org/perspective/2014/tacit-diplomacy-in-life-sciences>>; Alison McLennan, 'Building with BioBricks: Constructing a Commons for Synthetic Biology Research', in Mathew Rimmer and Alison McLennan (eds), *Intellectual Property and Emerging Technologies: The New Biology* (Edward Elgar, 2012) 176; Henry Etzkowitz and Andrew Webster 'Science as Intellectual Property' in S Jasanoff et al (eds), *Handbook of Science and Technology Studies* (Sage, 1995) 488; Sheldon Krinsky, 'Science, Society and the Expanding Boundaries of Moral Discourse' in Kostas Garroglu et al (eds), *Science Politics and Social Practice: Essays on Marxism, Science, Philosophy of Culture and the Social Sciences* (Routledge, 1995) 113.

source cultures including iGEM and DIYbio.<sup>33</sup> Whilst Merton's norms have been subject to considerable critique within the field of Science and Technology Studies (STS) (more on this below), their underlying resonance in popular discourse about science makes them a useful heuristic. They assist in considering not only what sort of normative ethos may, or may not, be emerging from iGEM, but also how participants and commentators frame their descriptions and aspirations for such an ethos, and what may be some of the limits of attempting to build such a 'normative ethos' to start with.

The special character of the Mertonian norms are strongly underpinned by assumptions about what sort of standards of conduct are necessary for independent knowledge-making communities to emerge, progress, and be sustained. Consistent with objectivist philosophies of science and their Popperian variations, Merton believed in the unique cognitive and social authority of modern science.<sup>34</sup> This meant part of his sociological project was to help distinguish what made the social system of science unique, but also to identify features of that system that were exemplary for communities seeking to produce authoritative knowledge more generally. Merton derived his norms not from statistical quantitative or empirical analysis, but rather from his prior work in the history of the emergence of modern science, a wealth of anecdotal evidence, and his philosophical assumptions about the nature of science noted above. Merton believed that the very broad norms he identified were universally recognised by scientists as essential to the continuing health and progress of science. Merton noted that despite occasional non-conformity, the norms still provided, in a sense, the backbone for the survival of the ongoing social structure of science. Merton's well-known formulation was based on four interlocking norms:

- *Communalism*: Scientific work and findings should be shared.
- *Universalism*: The results of scientific work should not be interpreted on the basis of who is producing it (status and gender of the researcher for example).
- *Disinterestedness*: Scientists should avoid having too much of a personal stake in their knowledge, and their aims are ultimately to progress knowledge ahead of all else.
- *Organised Scepticism*: Scientific work should have a system of criticism embodied in practices such as peer review.

Merton was aware that things like the status afforded to scientists regarding novelty and discovery encouraged them to take a personal stake in, and adopt emotional commitment to, their work. But he suggested that these motivations for acknowledgement of priority, and rewards of eponymy, were still overwhelmed by the broader ethos that knowledge should be progressed beyond these motivations, and that various norms he identified were central to the spirit of science.<sup>35</sup>

The neatness of Merton's system has frequently been challenged by empirical work in the sociology of science, most notably that of Ivan Mitroff. Mitroff identified in his research that, depending on the context, scientists also interpreted counter-norms to be essential for science to operate: solitariness, particularism, interestedness and organised dogmatism. These are polar opposites to Merton's 'positive' norms. Accepting the existence of counter-norms compromises the neatness of the Mertonian system. If we accept Mitroff's and other

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<sup>33</sup> Alessandro Delfanti, 'Hacking Genomes: The Ethics of Open and Rebel Biology' (2011) 15 *International Review of Information Ethics* 53.

<sup>34</sup> R Albury, *The Politics of Objectivity* (Deakin University Press, 1983); D Hess, *Science Studies: An Advanced Introduction* (New York University Press, 1997).

<sup>35</sup> Robert K Merton, 'A Note on Science and Democracy' (1942) 1 *Journal of Legal and Political Sociology* 115.

critiques, we now have at best an expression of preferred norms, not always conformed to in all contexts of scientific work.<sup>36</sup>

Building on these critiques, Michael Mulkey provided a highly influential and persuasive reconceptualisation of what Merton's system seemed to 'actually' be describing.<sup>37</sup> Mulkey pointed out that there was a paucity of evidence that Merton's norms were, or have ever actually been, systematically institutionally reinforced, or that conformity to them was rewarded, or non-conformity punished. At the same time, reference to the types of norms identified by Merton is, or was, still common in popular discourse about science, and they are frequently used by scientists themselves to describe their communities. Mulkey suggested that this meant that the norms are better explained as one of the broader public cultural stereotypes about how, in an ideal world, scientific communities should work, and are drawn upon as part of the professional boundary working rhetoric of scientists.<sup>38</sup> The promotion of this idea, that science has a special normative ethos, has historically assisted scientists in building the trust and authority they require to assert functional autonomy over how they do their research and spend the funds of their sponsors. Mulkey suggests that if we are to understand the behaviour of scientists it will be through a sociologically informed contextual analysis. Neither institutional structures nor the epistemological fabric of science bind scientists in any kind of straightforward way, and an overarching normative structure for science does not exist other than as a feature of scientists' discourse and discourse about science.<sup>39</sup>

The Mertonian traditions of identifying unique scientific norms, then, are part of the ideology of science, normally serving as a form of promotional rhetoric, but also a source of ambivalence when difficulties are encountered in applying norms to practice. Studies of sociological ambivalence have been preoccupied with ways individuals maintain and manage contradictory beliefs. Merton helped develop sociological interpretations of ambivalence in part as an attempt to explain counter-norms in science. He believed that ambivalence was most likely to arise when actors occupied multiple statuses with conflicting expectations and abilities to fulfil their aspirations.<sup>40</sup> Studies of scientists have noted displays of sociological ambivalence involved in the tensions between managing questions of intrinsic versus instrumental value of work, independence versus dependency, and collegial versus legal rational modes of authority.<sup>41</sup> Given the multiple competing roles and ambiguities in status involved in iGEM, which involves the interactions of students from different academic disciplines, participant observers, and entrepreneurial visible scientists, it is an obvious arena where questions of sociological ambivalence could be expected to arise.

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<sup>36</sup> Ivan Mitroff, 'Norms and Counter Norms in a Select Group of the Apollo Moon Scientists' (1974) 39 *American Sociological Review* 579; Barry S Barnes and Robert G Dolby, 'The Scientific Ethos: A Deviant Viewpoint' (1970) 11 *European Journal of Sociology* 3.

<sup>37</sup> Michael Mulkey, 'Norms and Ideology in Science' (1976) 15 *Social Science Information* 637.

<sup>38</sup> Thomas Gieryn, 'Boundary Work and the Demarcation of Science from Non-Science: Strains and Interests in Professional Ideologies of Scientists' (1983) 48 *American Sociological Review* 781.

<sup>39</sup> Other commentators have suggested perhaps a looser, more up to date formulation of norms may still be a useful conceptual tool, adding new norms to Merton's that capture some of the changes to the way current sciences are practiced: Anderson et al, above n 30. These attempts tend to gloss over one element of Mulkey's critique (following Wittgenstein), that the contexts in which norms (like rules) are meant to operate will always offer challenges beyond the norms that are identifiable, which could lead to ongoing multiplication of norms, which can in turn limit the value of the exercise to start with: Michael Mulkey, 'Interpretation and the Uses of Rules: The Case of the Norms of Science' in T Gieryn (ed), *Science and Social Structure: A Festschrift for Robert Merton*, (New York Academy of the Sciences, 1980) 111.

<sup>40</sup> Michael Carolan, 'Sociological Ambivalence and Climate Change' 15 (2010) *Local Environment* 309.

<sup>41</sup> Michael Arribus-Ayllon and Andrew Bartlett, (2013) 'Sociological Ambivalence and the Order of Scientific Knowledge' *Sociology* 1; Edward J. Hackett (2005) 'Essential Tensions: Identity, Control and Risk in Research' (2005) 35 *Social Studies of Science* (5) 787.

In further discussion below (Section V) Mulkay's critical interpretation of the Mertonian tradition will be taken as a point of departure to analyse claims that iGEM practices will help shape the development of an ideal synthetic biology normative ethos. Before doing this, the reader needs to be provided with some background about the emergence and growth of iGEM.

#### IV IGEM: BIOBRICKS, 'GIVING AND GETTING'

Our mission is to ensure that the engineering of biology is conducted in an open and ethical manner to benefit all people and the planet. We envision a world in which scientists and engineers work together using freely available standardized biological parts that are safe, ethical and cost effective and publicly accessible to create solutions to the problems facing humanity.<sup>42</sup>

It is important to note from the outset that iGEM is most strongly linked to a 'computer engineering vision' or 'sociotechnical imaginary' for the future of synthetic biology. The idea of 'sociotechnical imaginaries' has been developed by Sheila Jasanoff (and others) to capture the way narratives about the future prospects of various scientific and technical paths also embody various broader social visions, expectations, and histories.<sup>43</sup> The 'computer engineering vision' is exemplified in the work of Drew Endy.<sup>44</sup> Other visions for the future of the field also exist, the most notable alternative being that of Steven Benner and A Michael Sismour, of synthetic biology as 'a biologically inspired extension of chemistry'.<sup>45</sup> Historian and philosopher of science Bernadette Bensaude Vincent explains that the computer engineering vision aims to re-orientate biology towards engineering by involving standardisation, decoupling of parts, abstraction, quantification, simplification, recognition of innovation in informal settings, prediction and control, responsibility and self-regulation and open IP regimes. In contrast, the biological extension of the chemistry model emphasises continuities with work over the last 20 years in organic synthesis, and biology more generally. This includes the need to follow traditional approaches to patenting and IP with a mixture of academic research, practical developments, commercial profits, and regulation, recognising that results may not be completely predictable. Bensaude Vincent's observations about the unsettled nature of the emerging disciplinary identity discourses in synthetic biology highlight that care needs to be taken in treating iGEM as a vehicle for the development of a normative ethos for the whole field of synthetic biology.

As a way to expand on the month-long short courses they had started offering at Massachusetts Institute of Technology (MIT), synthetic biology pioneers Drew Endy, Tom Knight, Randy Rettberger, and others, decided to start a competition for students to do synthetic biology projects. They drew inspiration from various student engineering

<sup>42</sup> The BioBricks Foundation, *About* (2015) <<http://biobricks.org/about-foundation/>>.

<sup>43</sup> Harvard Kennedy School, *STS Research Platform – Sociotechnical Imaginaries* (2012) <<http://sts.hks.harvard.edu/research/platforms/imaginaries>>; Nuffield Council on Bioethics, *Emerging Biotechnologies: Technology Choice and the Public Good* (2012) <<http://nuffieldbioethics.org/project/emerging-biotechnologies/>>.

<sup>44</sup> Drew Endy, 'Foundations for Engineering Biology' (2005) 438(25) *Nature* 449.

<sup>45</sup> Bernadette Bensaude Vincent, 'Discipline Building in Synthetic Biology' (2013) 44 *Studies in History and Philosophy of Biological and Biomedical Sciences* 122 <<https://hal-paris1.archives-ouvertes.fr/hoal-00931814>>; see also Susan Molyneux-Hodgson and Morgan Meyer, 'Tales of Emergence a Scientific Community in the Making' (2009) 4 *Biosocieties* 2; Drew Endy, 'Foundations for Engineering Biology' (2005) 438(25) *Nature* 449; Steven Benner and Alan Sismour, 'Synthetic Biology' (2005) 6 *Nature Reviews Genetics* 533. It should also be noted that there are also more radical DIYbio visions working beyond traditional concepts of academic or scientific communities. See Denisa Kera, 'Innovation Regimes Based on Collaborative and Global Tinkering: Synthetic Biology and Nanotechnology in the Hackerspaces' (2014) 37 *Technology in Society* 28. The relationship between DIYbio, iGEM, and the computer engineering visions of Endy will be commented on later in Section V D. It is also interesting to note, in this unsettled context of discipline building that J Craig Venter prefers the term synthetic genomics to synthetic biology.

competitions, particularly the FIRST (For Inspiration and Recognition of Science and Technology) robotics competition.<sup>46</sup> Complimentary to these relatively straightforward aims of promoting education in synthetic biology was the promotion of their concept of BioBricks. Endy and his colleagues believed that time and costs could be reduced for doing synthetic biology research if a standard for biological parts, and a registry of standardised parts to allow for their share and re-use, was created. A student competition linked to promoting the BioBricks concept could provide a stimulus for its faster growth. With help from the US National Science Foundation, they expanded their vision into the International Genetically Engineered Machine (iGEM) competition. The first competition was held in 2004 involving only a handful of US Universities (Caltech, MIT, Princeton and the University of Texas, Austin). It was held annually at MIT until 2012 and has moved more recently to a nearby venue administered by the BioBricks Foundation (BBF), now an independent non-profit organisation.<sup>47</sup> iGEM is possibly the largest single synthetic biology event in the world with 2,300 people attending its final function in 2014. iGEM has grown so much that 245 teams competed in 2014 with various regional divisions and a growing variety of prizes and judging categories.<sup>48</sup>

iGEM caters mainly for undergraduate university students, although recently there has been expansion in some areas for broader age groups to participate, such as high school divisions. Teams are still nevertheless highly reliant on academic supervisors, mentors and significant institutional support. Teams are interdisciplinary with students from backgrounds in computer science, engineering, and biology, and even budding artists and social scientists. So far, however, biologists, followed by engineers and computer scientists, have tended to form the nucleus, and drivers, of the teams.<sup>49</sup> There has also been some history of informal links between teams and amateur and DIY biologists, but organisers have generally been reluctant to allow such groups formal entry into the competition.<sup>50</sup>

The teams are asked to define a specific social or technical problem, or goal or purpose, then design and build what Endy has described as a 'DNA program' to solve it. The 'DNA program' must be designed and built according to certain rules and protocols, including safety and social implications. This also has to be done within a relatively tight time frame, during the three months of the northern hemisphere summer. Perhaps most importantly, the 'DNA program' must be built by drawing from standardised biological parts that are made available from the BioBrick repository. From 2008, projects could also include a Human Practices (now just Practices) dimension, demonstrating that the team had engaged with what could loosely be described as the social ethical aspects of their project. The majority of teams now incorporate this dimension into their projects.<sup>51</sup> I will return to discuss Human Practices in more depth at a later point.

The competition builds on the vision of facilitating biology to become an engineering discipline by building simple biological systems from standard interchangeable parts. Various metaphors from engineering and computing ('chassis' and 'wetware') blend with 'cool' images of adventure and play ('Lego blocks' and cartoon instructional magazines), and knowledge sharing ('freeware' and 'getting and giving').<sup>52</sup>

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<sup>46</sup> Christina D Smolke, 'Building Outside the Box: iGEM and the BioBricks Foundation' (2009) 27 *Nature Biotechnology* 1099.

<sup>47</sup> The BioBricks Foundation, *About* (2015) <<http://biobricks.org/about-foundation/>>.

<sup>48</sup> iGEM, *About* (2015) <<http://igem.org/About>>.

<sup>49</sup> Emma Frow and Jane Calvert, above, n 15; Andrew Balmer and Kate Bulpin, above n 15.

<sup>50</sup> Sara Aguiton, *SynthEthics: An Ethical and Sociological Analysis on Synthetic Biology*, (2009) iGEM 2009 <<http://2009.igem.org/wiki/images/archive/b/b2/20091021203514!TeamParis-SynthEthics.pdf>> 38.

<sup>51</sup> Frow and Calvert, above n 15, 53.

<sup>52</sup> Alan Liu, *The Laws of Cool: Knowledge Work and the Culture of Information* (Chicago University Press, 2004); Surfdaddy Orca, *Adventures in Synthetic Biology: An Interview with Stanford's Drew Endy* (2009) H+Magazine <<http://hplusmagazine.com/digitaledition/2009-winter/>>.

At the beginning of each competition students are sent a kit of genetic parts (getting), and at the end of the competition the teams contribute (giving) their designs back to the BioBrick repository for future use in iGEM competitions, and for use by the wider synthetic biology community. Projects are judged by a panel of scientists, biotech industry and government figures, and academics from a variety of disciplines. Medals are awarded (bronze, silver, and gold) based on the assessment of posters, oral presentations, and quality of wiki pages. There is also a Human Practices prize and the *Grand BioBrick Trophy* awarded for the best project.<sup>53</sup>

In the decade or so iGEM has operated, it can claim a number of achievements, which include:

- The continued growth of the BioBrick repository.<sup>54</sup>
- The successful development of iGEM projects in fields like bio-sensing and medical diagnostics, and projects leading to a number of external grants, patents, and prestigious publications.<sup>55</sup>
- Ex iGEMers contributing to the development of synthetic biology start-up companies, most notably Ginkgo Bioworks.<sup>56</sup>
- A number of ex iGEMers figuring prominently in the emerging DIYbio movement.<sup>57</sup>
- More intangibly, the competition has also captured the imaginations of students, universities, media, and policy makers, and has been an important tool for publicising the idea of synthetic biology.

## V NORMS AND IDEOLOGY IN iGEM

As noted in my introduction, the iGEM competition is seen by many commentators as one of the most distinctive and important features of the emerging field of synthetic biology, particularly for the development of shared norms. Frow and Calvert note: 'iGEM has proven to be important in many respects. It has been a key vehicle for training and community formation in synthetic biology, enrolling students, advisors, and laboratories across the globe into a common project with shared norms.'<sup>58</sup>

Stavrianakis, another post-ELSI ethnographer of iGEM, re-enforces the theme:

Whilst, as we will see, the question of what is made through synthetic biology varies, its practices, ends and achievements depend on different conceptualizations of biological problems, specific techniques and technologies, the question of *who* a synthetic biologist is, was at this time, to a large degree, controlled by passing through the pedagogical experience of iGEM. This experience and self-designation of a subject's position, whilst not determinative of a 'field' was constitutive of an ethos toward a practice of science and engineering.<sup>59</sup>

<sup>53</sup> Smolke, above n 46, 1100.

<sup>54</sup> Bryn Nelson, 'Cultural Divide' (2014) 509 *Nature* 152.

<sup>55</sup> Smolke, above n 46, 1102.

<sup>56</sup> Nelson, above n 54, 154.

<sup>57</sup> Catherine Jefferson, 'Governing Amateur Biology: Extending Responsible Research and Innovation in Synthetic Biology to New Actors – Research Report for the Wellcome Trust Project on "Building a Sustainable Capacity in Dual-Use Bioethics"' (Report, Wellcome Trust Project, 2013) <[http://www.brad.ac.uk/bioethics/media/ssis/bioethics/docs/Jefferson\\_Governing\\_Amateur\\_Biology.pdf](http://www.brad.ac.uk/bioethics/media/ssis/bioethics/docs/Jefferson_Governing_Amateur_Biology.pdf)>.

<sup>58</sup> Frow and Calvert, above n 15, 44.

<sup>59</sup> Anthony Stavrianakis, *Flourishing and Discordance: On Two Modes of Human Engagement with Synthetic Biology* (PhD Dissertation, University of California, Berkeley, 2012) 121–2 <<http://escholarship.org/uc/item/2b50r68z?query=Flourishing%20and%20Discordance:%20On%20Two%20Modes%20of%20Human%20Engagement%20with%20Synthetic%20Biology>> (emphasis in original); Adrian Mackenzie, 'Design in Synthetic Biology' (2009) 5(2) *Biosocieties* 180.

Similar to some of the promotional rhetoric associated with DIYbio, iGEM has been lauded as one of the places where Mertonian and neo-Mertonian norms of communalism and universalism, which have arguably been compromised by excessive corporate and government interference in science, can be significantly revived. Why I suggest 'neo-Mertonian' norms is that the celebration of these traditional Mertonian normative values is also often coupled with the idea that iGEM and DIYbio are also promoting an updated ethos for synthetic biology. This allows for more individualism, experimentation with modes of practice, and diverse input into knowledge creation and authorisation, than traditionally imagined. This fosters a situation enhanced by new venues for doing science and for communicating results. Alessandro Delfanti describes these possibilities in terms of a Mertonian re-mix.<sup>60</sup>

In a sense, many of the ideal norms of iGEM do intersect quite well with aspects of a Mertonian or a neo-Mertonian image of the ideal ethos of science. For example:

- *Communalism* resonates strongly with ideals of free-ware, team wikis, giving back to the BioBrick repository and not seeking IP.
- *Universalism* appears in the wide breadth of international representation, lack of concern with status and qualifications of participants, and interdisciplinarity and collaboration – the project is more important than the promotion of any traditional disciplinary identity.
- *Disinterestedness* is exemplified in the two behaviours promoted above of sharing and aversion to IP, interdisciplinary team orientation, and in the values of promoting synthetic biology for broader human benefit ahead of individual benefit.
- *Organised Scepticism* is promoted in the processes of transparent judging of projects and awarding of prizes.

Whilst iGEM's ideal values do seem to have some congruence with Mertonian and neo-Mertonian visions, on a deeper inspection (which I will expand on below) it appears that for the competition to be sustained in practice these values operate in tandem with competing values.

There are a number of contextual features of iGEM that create challenges to sustaining its ideal norms. These can be listed under four overlapping rubrics:

- Intellectual freedom in a competition with structured rules.
- Interdisciplinarity where various disciplines are more central than others.
- Upstream reflexive ethical engagement in a culture where such concerns are routinely back-staged.
- Sharing and communalism in a context that is highly competitive and where IP laws in practice are much more complex than competitors envision them to be.

In the analysis that follows, I will expand on these rubrics drawing mainly from various post-ELSI 'ethnographic' accounts of participant observers (collaborators), who assisted iGEM teams in their preparations, visited jamborees, and functioned as judges, mentors, or informal advisors. This includes the work of Calvert and Frow, Stavrianakis, Balmer and Bulpin, and Cockerton.<sup>61</sup> Due to the nature of the competition, there are also a variety of on-line materials linked to team wikis and, where appropriate, these will also be drawn on.

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<sup>60</sup> Delfanti, above n 33.

<sup>61</sup> Caitlin Cockerton, 'Going Synthetic: How Scientists and Engineers Imagine and Build a New Biology' (PhD Thesis, London School of Economics and Political Science, 2011); Balmer and Bulpin, above n 15; Stavrianakis, above n 59; Frow and Calvert, above n 15.

Relying extensively on the analysis and interpretations provided by social science researchers engaged in 'collaborative' styled research raises some interesting methodological issues which are worthy of being flagged, although they are beyond the scope of the current paper to essay at length. The idea of collaborative research creates some interesting challenges to more traditional conceptions of the importance of maintaining critical analytical distance from the subjects of research. As noted above many of the accounts I will draw upon are from analysts who performed multiple roles in iGEM as members of multiple sub-communities. For example, researchers acted as honorary members of teacher/student communities as iGEM mentors; honorary members of the synthetic biology professional community as iGEM judges; and members of social science and social policy communities as commentators and publishers of reports and academic papers. Satisfying such multifaceted roles, and juggling sometimes competing social interests, invites questions about whether their accounts of iGEM's strengths and weaknesses might be inclined to display some sociological ambivalence. I will leave this question to the reader's judgment.

In identifying what I believe are tensions in iGEM's norms, my own position is not as a critic of iGEM per se (the literature suggests that students enjoy and personally benefit from the iGEM experience), but rather to offer an exercise in bringing to the foreground aspects of the culture of iGEM which tend to be overlooked in most accounts, which never go beyond extolling iGEM's virtues. I should also note that iGEM is something of a moving target with the capacity for rules to be modified within reasonably short time frames and in response to critics.

#### A *Intellectual Freedom and Universalism in a Competition with Structured Rules*

It is no secret that iGEM encourages a strong competitive spirit. Drew Endy describes it as 'akin to a genetic engineering Olympics for undergraduates.'<sup>62</sup> Balmer and Bulpin, and Cockerton, note the personal tensions, fear of failure, and joy of success students experience in their chase for medals, especially gold. They also note the pressures of strong expectations held by, and the superior resources and dominant success rates of, elite institutions, and the unabashed promotion of a meritocratic discourse that rather mythically implies all teams are competing on a level playing field.<sup>63</sup> The potentially narrow focus of a 'medal chase' co-exists in potential tension with other stated iGEM values – to be supportive of smaller institutions and amateur biology, and for projects to reflect on their social implications and be geared towards broader social benefit.<sup>64</sup>

Balmer and Bulpin also note that the highly structured nature of the competition creates time pressures which discourage certain projects being attempted, and continuously attenuates the capacity for participants to learn new skills and engage in interdisciplinarity and, in particular, to address the Human Practices (Practices) dimensions of their projects.<sup>65</sup>

[T]here is a major constraint on human practices work in iGEM. You have very little time to read or explore HP [Human Practices] scholarship, and – for the most part – having only studied a single subject at university, most of you will be unfamiliar with the methods and conceptual apparatus used in humanities and social sciences ... After all, there's no hope of a medal or an award if you haven't actually got an engineered microbe

<sup>62</sup> Drew Endy, *Effects of Developments in Synthetic Genomics – Hearing before the Committee on Energy and Commerce* (27 May 2010) US House of Representatives – Democrats: Committee on Energy and Commerce <<http://democrats.energycommerce.house.gov/sites/default/files/documents/Final-Transcript-FC-Developments-Synthetic-Genomics-2010-5-27.pdf>>.

<sup>63</sup> Balmer and Bulpin, above n 15. It should be noted that Merton was aware of elitism in science or the so-called 'Mathew Effect': Albury, above n 34.

<sup>64</sup> Cockerton, above n 61.

<sup>65</sup> Balmer and Bulpin, above n 15.

to present no matter how many people you've talked to about your project or how much you've learned about social science. So the priorities of iGEM teams are set-up in part by the medal criteria.<sup>66</sup>

The structured nature of the iGEM competition also places pressure on the kinds of projects teams choose in more 'technical' ways. Organisers insist on teams using the appropriate parts that are supplied to them, and that can be given back to the BioBrick repository. Teams that do not generate standardised parts do not win prizes, even if the quality of their work is exceptional. Frow and Calvert advert to tensions that teams experience in trying to get their work to fit the rules, and to judges who may face difficulties in adjudicating between projects with significant biological merit relative to projects that better fit the criteria of contributing to the BioBrick registry.<sup>67</sup> This suggests that whilst the existence of standardised rules can encourage communalism and sharing, it can also potentially compromise ideals of organised scepticism. For example, it may not be the project with the best science that wins a prize, or the most interesting project that a team would want to do, but one that they can do with the pre-approved materials that best fit the criteria of supporting the vision of developing the BioBrick repository. Chasing the competition criteria, ahead of more general scientific criteria, has extended at times to projects using the iGEM BioBrick approaches to solving problems that already have solutions using non-synthetic biology approaches.<sup>68</sup>

#### B *Interdisciplinarity where Various Disciplines are More Central than Others*

Frow and Calvert, Balmer and Bulpin, and Stavrianakis have all noted that iGEM teams often experience tensions in reconciling the roles to be played in projects of different students from different disciplines, and how these roles and contributions come to be described in final projects. This again can be seen as a drift away from values of universalism and organised scepticism. In many cases, biology students, for example, provide the greatest input at the 'hands on' messy laboratory end of projects, whereas other students, engineering and IT for example, put more effort into modelling, design, and packaging the project into a coherent polished form for final judging. So the pressures to conform to iGEM's positive innovation rhetoric, and to be viable in competition, can mean the nature of the work done by the team, and the relative contributions of team members, can come to be misrepresented. The engineering and innovation possibilities of a project may be highlighted ahead of adequate descriptions being provided of the messier laboratory work that has actually been done.<sup>69</sup>

Another challenge faced by iGEM in maintaining an inclusive, universalistic ethos surrounds its relationship with DIYbio. In many places, commentators have noted the ethos of iGEM dovetails with DIYbio.<sup>70</sup> For example there have been a number of important players in the DIYbio movement who started in iGEM, and iGEM projects that have had links with DIYbio.<sup>71</sup> Nevertheless, there are other points where the relationship has faced challenges. Most notably, in 2009 a DIYbio team applied for entry into the competition but was refused by iGEM organisers on a number of grounds, including lack of insurance and institutional oversight.<sup>72</sup> Whilst the organisers of iGEM have regularly appeared in public contexts supporting DIYbio, some DIYbio supporters have voiced concerns that the BioBricks initiative's links to business interests are not consistent with the true spirit of DIYbio.<sup>73</sup>

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<sup>66</sup> Andy Balmer, *Public Perceptions, Knowledge Deficit and Expertise* (4 September 2014) Reasonable Excuse <<https://andybalmer.wordpress.com>>.

<sup>67</sup> Frow and Calvert, above n 15, 49.

<sup>68</sup> Cockerton, above n 61, 15, 37.

<sup>69</sup> Frow and Calvert, above n 15, 50.

<sup>70</sup> Kera, above n 45; Aguiton, above n 50.

<sup>71</sup> Jefferson, above n 57, 13.

<sup>72</sup> Aguiton, above n 50, 38.

<sup>73</sup> Stavrianakis, above n 59, 135–6.

Cockerton also notes a case where tensions have (in a sense) flowed the other way, where some iGEM participants expressed the view that some DIY biologists attending various iGEM functions were not completely conforming to DIYbio ideals.<sup>74</sup> Many of these DIY biologists had full time institutional appointments and qualifications alongside their DIYbio interests, and appeared more interested in getting inspiration from iGEM for commercial start-up opportunities than building community projects.<sup>75</sup>

The dominance of various academic disciplinary perspectives, and the tensions that flow from this, have also been reported on in the way teams have dealt with the Human Practices components of projects. Stavrianakis recounts the example of an anthropology student he was mentoring, part of an iGEM team from University of California, Berkeley, being ‘told not to introduce herself [to the judges] as an anthropologist, on the grounds that “people won’t understand and it will be a distraction.”’<sup>76</sup> She was also told to only focus on narrow parts of her research which directly involved the technical steps that would be involved in patenting processes directly related to the team project, and avoid the wider theoretical discussion of the broader issues relating to open source and patenting in iGEM, which she had prepared. Stavrianakis noted that even this significantly sociologically diminished presentation elicited a response from a senior synthetic biologist from a world leading university who commented: ‘Why are you talking about patents? iGEM is supposed to be about fun. It’s meant to be a fun summer thing. I don’t think this gives the right impression, all this talk about patents, that shouldn’t be your concern.’<sup>77</sup>

This point overlaps with the discussion in the next section, and also reiterates points noted above, about how easy in practice it is for iGEM to fulfil strong universal and interdisciplinary aspirations when it is set up as a competition with strict rules, time frames, and a strong underlying focus to promote (to use Bensusan Vincent’s term) a computer engineering imaginary for synthetic biology.

### C *Upstream Reflexive Ethical Engagement in a Culture where Such Social Concerns are Routinely Backstaged*

As noted earlier, in 2008 iGEM introduced the option for teams to incorporate a so-called ‘Human Practices’ component into their project. The term Human Practices was coined by anthropologist Paul Rabinow, who initiated one of the first experiments in social science upstream engagement in synthetic biology, in the synBERC project centred on the University of California, Berkeley. Rabinow envisaged Human Practices as a radical alternative to traditional ELSI approaches to governance of synthetic biology. The approach offers an exemplary model of a policy strategy based on the idea of developing a new normative ethos amongst synthetic biology scientists. A key element of Human Practices was for social scientists, through various processes of evaluation, facilitation, engagement, and collaboration, to encourage synthetic biology scientists to become highly reflective about their practices (these processes are described under the heading of pedagogy). It would be out of this collaboration and reflection that the new ethos for practising the discipline of synthetic biology would emerge. It is through consideration of how their practices enhance ‘the good life’ that scientists and engineers (and human scientists) are enabled to ‘flourish’. Rabinow identified the goals of Human Practices as bringing:

[t]he biosciences and the human sciences into a mutually collaborative and enriching relationship, a relationship designed to facilitate a remediation of the currently existing relations between knowledge and care in terms of mutual flourishing. If successful, such

<sup>74</sup> Cockerton, above n 61, 269-270.

<sup>75</sup> Ibid.

<sup>76</sup> Stavrianakis, above n 59,135.

<sup>77</sup> Ibid 134–5.

practices should facilitate our current work in synthetic biology – understood as a Human Practices undertaking – through improved pedagogy and the invention of collaborative means of response.<sup>78</sup>

Some important themes that one would expect to be exported from Human Practices into iGEM include things like: considering users in design; incorporating insights from collaborations with non-scientists into the early phases of design and project objectives; and ongoing serious engagement with ethical and epistemological questions raised by the mutual learning taking place between scientist and non-scientist collaborators.<sup>79</sup> These preoccupations could be expected to be set against the avoidance of so-called literary deficit models towards the public understanding of science, that is, that public ignorance is the key factor explaining negative public views about new science.<sup>80</sup>

Frow and Calvert, Cokerton, Stavrianakis, and Balmer and Bulpin, have all noted that these visions for 'Human Practices' have been far from realised in the vast majority of projects. Rather than the ideal of developing ethical and social awareness (reflexivity) in budding synthetic biologists by having 'social' concerns integrated into the fabric of projects from the outset, Human Practice components tend to have become exercises that run parallel or behind the main project, with little integration into the content of the project, and with greater preoccupations with synthetic biology public relations than ethical reflection. Performing surveys of public attitudes towards synthetic biology, framed by assumptions about public ignorance, and thinking of ways to increase public awareness of the benefits of a synthetic biology future (and variations on this theme), would appear to have become standard approaches to dealing with 'Human Practices' in most projects. Andrew Balmer, who was involved as a social scientist ethnographer and mentor in iGEM, describes the way most iGEM teams retreat from more serious ethical and sociological engagements:

A related idea was that this 'public ignorance' of the science could be somehow cured if we educated people about GM technologies. In this regard, scientists assumed the main problem was a 'knowledge deficit' in public understanding of science, which meant that public perceptions of science were skewed and inappropriate but could be changed by better education and 'outreach'. So scientists set about telling people about the GM work they were doing, hoping to calm 'the public' fears by providing knowledge. In iGEM much of the work that teams do in human practices still follows this model. Most teams go out into public spaces like schools, community centres and so forth, to tell people about the work they're doing. Mostly it is a one way thing, where teams tell people the science and hope that this interests them or at least that it allays some of their fears.<sup>81</sup>

Frow and Calvert acknowledge the trajectory identified by Balmer, but retain their optimism by suggesting that iGEM judges are working to overcome it:

But there is a growing tendency for iGEM judges to reward those teams who embrace the spirit of heterogeneous engineering and incorporate an understanding of social, political, economic and human factors into the details of their technical projects ... A flexible space for interaction between ELSI and engineering ethics work may be starting to open up

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<sup>78</sup> Paul Rabinow, 'Prosperity, Amelioration, Flourishing: From a Logic of Practical Judgment to Reconstruction' (2009) 21(3) *Law and Literature* 305. It is interesting to note that the Human Practices experiment more generally has been beset with difficulties in being applied in practice. See also Gary Edmond and David Mercer, 'Norms and Irony in the Biosciences: Ameliorating Critique in Synthetic Biology' (2009) 21(3) *Law and Literature* 445; David Caudill, 'Synthetic Science: A Response to Rabinow' (2009) 21(3) *Law Literature* 431; Rabinow and Bennet, above n 14.

<sup>79</sup> Jane Calvert and Paul Martin, 'The Role of Social Scientists in Synthetic Biology: Science and Society Series on Convergent Research' (2009) 10(3) *EMBO Reports* 201.

<sup>80</sup> B Wynne, 'Public Understanding of Science' in S Jasanoff et al (eds), *Handbook of Science and Technology Studies* (Sage, 1995), 361, 361–88.

<sup>81</sup> Balmer, above n 66.

through the iGEM competition, in response to demands for training a new generation of reflexive bioengineers.<sup>82</sup>

So the original vision of Human Practices is in some form still promoted as a part of iGEM, but more as a future possibility. There are clear differences and slippages in what the initiative actually means, and how it might influence (if at all) the actual normative and ethical orientation of iGEM participants.

Following Mulkay's more critical reading of Merton's norms as important parts of the rhetoric for scientists to communicate to outsiders, which may have tenuous links with practice, the continued reference back to the novelty of Human Practices in iGEM appears to satisfy a similar role. Fairly mundane engagements with ethical and social issues by iGEM teams, which do not display much sense of them evolving new normative sensitivities, are regularly still rhetorically packaged as part of some kind of important emerging iGEM ethos.

D *Sharing and Communalism in a Context that is Competitive and Where Intellectual Property Laws in Practice Are Much More Complex Than Competitors Envision Them to Be*

One of the most highly visible ideals of iGEM surrounds appeals to the ethos of freeware and open access intellectual property regimes, which appear frequently in more formal statements made about the competition. Aspects of these ideals are embedded within its rules, and are also part of the informal culture of competitors. Frow and Calvert, for example, note: 'When one team announced at a 2009 competition that it had filed three patents as part of its projects, boos were heard in the audience.'<sup>83</sup>

Maintaining an ideal separation between iGEM, corporate, and institutional interests is not easy in practice. Participating in iGEM can be an expensive undertaking requiring considerable institutional support and expenditure on things like lab facilities, airfares, and accommodation. To secure sponsorship, iGEM teams prominently display corporate logos and other promotional advertising for their sponsors on various web sites and T-shirts. Sponsors include the very types of companies benefiting from IP regimes to which iGEM and BioBricks are in theory offering an alternative. Cockerton notes that the dissonance between the more idealistic face of iGEM, and corporate and institutional realities, is also noticeable at iGEM Jamborees. She recounts the conspicuous presence of corporate representatives and, perhaps more jarringly, extremely friendly, armed FBI agents and FBI sponsored talks on bio-security.<sup>84</sup>

Tensions can also run at a deeper level where at numerous points iGEM discourse is also openly entrepreneurial (since 2012 the competition has sported an entrepreneurial division) and aspirations of generating huge wealth from engaging in synthetic biology are widely promoted. Cockerton ironically recounts iGEM organiser Randy Rettberger's advice to iGEMers in a closing ceremony in 2009:

I think that over the next 40 years synthetic biology will grow in a similar way [as the computer revolution] and become at least as important as the Internet is now and that you will be the leaders, that you will form companies, that you will own the private jets and that you will invite me for rides.<sup>85</sup>

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<sup>82</sup> Frow and Calvert, above n 15, 54.

<sup>83</sup> Ibid 51.

<sup>84</sup> Cockerton, above n 61, 249, 270.

<sup>85</sup> Ibid 277.

What is not said is that most of the likely paths to the levels of wealth envisaged above are likely to be dependent on establishing intellectual property rights that are not inevitably, but highly likely to be, in conflict with the open-sharing ethos publicly championed as a feature of iGEM.

Debates surrounding whether a communalistic ethos is consistent with private ownership of knowledge and business success are not new and are unlikely to be easily resolved. For hackers who see seeking wealth as unproblematic, the aphorism that is frequently deployed is 'free speech not free beer' in the sense that freeware is free. For others there is a risk that a hacker or freeware ethos is at best a temporary affectation prior to the co-optation of knowledge to serve business interests.<sup>86</sup> Norms of communalism may apply when one is an iGEM student, but not when one becomes a professional scientist, or creates a start-up company, or an iGEM project offers potential commercial success in the 'outside' world. For iGEM to be an incubator of a normative ethos of communalism it could be expected that the ethos would 'travel' beyond the competition. This may be difficult.<sup>87</sup>

In many respects the tensions experienced by iGEMers in relation to IP philosophies can be seen as a microcosm of issues being negotiated across the field of synthetic biology more generally. A recent commentary in *Nature*, for instance, refers to the two cultures of synthetic biology relative to attitudes they embrace towards intellectual property.<sup>88</sup> In a thoroughgoing analysis of the discourses and practices encouraged by the BioBrick Foundation's approach to intellectual property, Stephen Hilgartner points out that the BioBrick initiative embodies a vision of open source that may deviate considerably from a straightforward defence of open science and public knowledge.<sup>89</sup> He notes that their model strongly privileges the ideal of the creative, innovative User ahead of the Contributor. Whilst Users are encouraged to contribute their creations to the foundation, it does not employ *copyleft* licences on parts (which would restrict future uses) and provides very few restrictions on how Users might wish to use the foundation's materials:

The regime is designed to allow Users to deploy parts at will, without constraints stemming from availability, fees or propriety restrictions. The User's rights to his or her creations even extend to allowing exit from the restrictions of the regime. If a User invents something of value using BioBricks parts as components, the User may file for patent or otherwise seek property rights in that invention.<sup>90</sup>

Contributors, in contrast, are subject to numerous restrictions on asserting any kind of property rights or licences in relation to their contributions. Hilgartner describes this as a 'leaky regime': 'the regime cannot prevent next generation creations assembled using BioBrick parts escaping its control'.<sup>91</sup> They are at the mercy of Users voluntarily deciding to become Contributors and donate their parts rather than simply patenting and commercialising parts as they see fit.<sup>92</sup> Hilgartner suggests that the 'leaky' ideal of freedom of the User continues into the domain of biosecurity where their extremely broad, vaguely defined agreement not to do harm with BioBricks is subject to the vagaries of community norms, and becomes a little like disciplining Users to make voluntary contributions.<sup>93</sup> It

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<sup>86</sup> Alesandro Delfanti, *BioHackers: The Politics of Open Science* (Pluto Press, 2013).

<sup>87</sup> Nelson, above n 54,153. Quotes technology policy researcher Davy van Doren who has documented a trend towards increasing patent applications in synthetic biology: 'We couldn't find any evidence that patent trends in synthetic biology might be different compared with other domains'.

<sup>88</sup> Ibid 152.

<sup>89</sup> Stephen Hilgartner, 'Novel Constitutions? New Regimes of Openness in Synthetic Biology' (2012) 7(2) *BioSocieties* 188.

<sup>90</sup> Ibid 201.

<sup>91</sup> Ibid 201–2.

<sup>92</sup> Ibid.

<sup>93</sup> Ibid 203.

would appear that the key stated normative values of iGEM, associated with sharing and communalism, may be the ones which are most difficult to articulate in practice, beyond the competition, or in future shaping of the field.

Aside from the tensions in different visions of Contributors and Users, it would appear that even some of the founders of the BioBrick concept are anxious about its legal viability in current IP regimes. For example, the registry holds many DNA sequences regularly used by teams that are already covered by patent claims:

If iGEM was a for-profit competition then it would undoubtedly be sued for IP infringements. As it is currently an academic venture (with teams requiring an academic affiliation to participate), the incentive for patent holders to pursue litigation is limited, but this threat continuously hovers in the background, with the potential to be fatal to the whole operation.<sup>94</sup>

Another factor in this vexing IP context, which paradoxically may be contributing to iGEM's current 'success', is that many of the student-generated parts may be untrustworthy. This limits their value to commercial enterprises that otherwise might be more interested in taking them over, which would undermine the competition.<sup>95</sup> This suggests that for the concept of BioBricks to ultimately be successful it may need to move beyond iGEM into being organised in a more industrial or technocratic mode, where there are professional skills and financial resources directed to maintain appropriate quality control, and provide legal oversight, over their development.<sup>96</sup>

## VI CONCLUSIONS: IGEM NORMS, COUNTER NORMS AND COMPETING VISIONS

Drawing upon the discussion above (in Section V), the ethos of iGEM appears to be based on matching Mitroff-like counter norms with Merton-like norms. In a succinct form these relationships could be expressed as follows:

- *(Following discussion in A):* To win a medal, a norm of double guessing judges and designing projects to match iGEM rules and benefit the BioBrick concept is encouraged. This co-exists with norms of academic curiosity for its own sake, and organised scepticism and research for community benefit.
- *(Following discussion in B):* To manage time constraints and be 'competitive', norms of privileging traditional disciplinary perspectives are encouraged. These norms co-exist with norms of universalism, interdisciplinarity, and collaboration.
- *(Following discussion in C):* To satisfy the competition's scientific and technical demands, norms of 'backstaging' concerns with Human Practices (social implications) are encouraged. These norms co-exist with norms of universalism, collaboration, and concerns with Human Practices (social implications).
- *(Following discussion in D):* To develop a career in synthetic biology and become wealthy, norms of individualism and ownership of intellectual property (interestedness) are encouraged. These co-exist alongside norms of communalism, community benefit, freeware, and teamwork.

<sup>94</sup> Jane Calvert, 'Ownership and Sharing in Synthetic Biology' (2012) 7(2) *Biosocieties* 169, 177.

<sup>95</sup> Roberta Kwok, 'Five Hard Truths for Synthetic Biology' (2010) 463 *Nature* 288.

<sup>96</sup> Rabinow and Bennett, above n 14, 66-69; Nelson, above n 54, 154.

Considering these norms and counter norms, it would appear that the culture of iGEM at present is unlikely to provide a normative ethos in synthetic biology that is coherent enough to promote (or inhibit) a new ethos for the field to address emerging issues of governance. Some values iGEM appear to be promoting in practice are consistent with its stated aspirations, while others are not.

Further, it is not clear that its stated aspirations are consistently shared by all those who are involved at a practical level, nor across the emerging field as a whole. Nor are they likely to be sustainable given current commercial realities and intricacies of intellectual property laws, and the mundane power relationships and institutional ecologies in the contemporary biosciences.<sup>97</sup> As was noted in the introduction to Section IV, iGEM fits most snugly with a 'computer engineering' vision of the future of the field. More 'conservative' visions of synthetic biology as a continuation of synthetic chemistry, and more radical visions of DIY biology, intersect with iGEM but ultimately offer different imaginaries for the field's future development.<sup>98</sup>

Following Mulkey, and his observations about the rhetorical roles played by reference to norms as part of professional field building, it is not particularly surprising that identifying simple correspondence between common images of iGEM and its practices is far from a straightforward process. The image of iGEM as a model for a future synthetic biology scientific community has an obvious appeal for promoters of the field and university educators more generally. Youthful idealism and vigour, and the fact that students can develop considerable skills, communicate with other students, and enjoy themselves in the process, are hard things to be critical of — even if they do not clearly mesh with the development of a normative ethos that might encourage Mertonian or neo-Mertonian visions.

It may be the case that iGEM will continue to be re-shaped in response to challenges, 'flourish' and help facilitate the development of scientific-technical practice in some precincts of the field of synthetic biology. But policy makers need to make sure when they address the challenges of regulation and governance of synthetic biology, and iGEM's possible contributions to it, that they keep squarely in mind iGEM's limitations: that synthetic biology is an emerging field inspiring multiple visions for its future development; that iGEM inhabits one part of one particular vision of that future; and that aspirational visions of the development of an ideal iGEM ethical normative ethos often appear to be more consistent with promotional rhetoric than the contingencies of practice.

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<sup>97</sup> Rabinow, above n 78; Edmond and Mercer, above n 78; Caudill, above n 78.

<sup>98</sup> Bensuade Vincent, above n 45; Delfanti, above n 86.



# ISOLATING THE PATENTABILITY OF GENETIC MATERIALS: THE *D'ARCY V MYRIAD GENETICS SAGA*

VALIANT WARZECHA\*

*D'Arcy v Myriad Genetics Inc (D'Arcy)*<sup>1</sup> thoroughly examined the patentability of isolated genetic sequences and laid scrutiny to the application of the 'manner of manufacture' test found in *National Research Development Corporation v Commissioner of Patents (NRDC)*.<sup>2</sup> In September 2014, a specially enlarged five member bench of the Full Federal Court ('Full Court') held that the isolated materials were patentable, with the case turning on whether those materials constituted an 'artificial state of affairs' or were the 'mere discovery' of a 'product of nature'.<sup>3</sup> Whilst the Full Court affirmed the trial judgment, the matter was granted special leave to be heard by the High Court of Australia ('High Court') in June 2015.<sup>4</sup>

It is notable that the patent expires on 11 August 2015, and as such, will have little impact on Myriad Genetics Inc ('Myriad'). More broadly, the case will have ramifications for patent examiners' guidelines and, in the long run, forms a limited precedent for litigation. In addition to the commercial significance of the decision, on-going litigation in this area highlights the judiciary's difficulty in analysing technical products to discern patentability and, similarly, the legislative void surrounding the commercialisation of human biological materials. This case note provides up to date analysis as of 22 June 2014.

## I FACTS

Myriad, an American molecular diagnostics company, obtained a standard Australian patent (Australian Patent 33212/95) in the field of human genetics for the 'methods and materials' used to locate and analyse the BRCA1 gene sequence in patient samples. These sequences can be used to determine a patient's predisposition to cancer, particularly ovarian and breast cancer.<sup>5</sup> Claims 1–3 of the patent assert protection for the isolated coding sequences of 'typical', 'mutated' and 'polymorphic' BRCA1 genes.<sup>6</sup> Myriad uses these isolated materials as comparison tools for diagnosing patient susceptibility to the respective cancers.

## II DECISIONAL HISTORY

In 2010, Cancer Voices Australia ('CVA') joined with Yvonne D'Arcy to launch action against Myriad in the Federal Court, asserting that the patent's claims did not relate to patentable subject matter. It was argued that they were a 'discovery of the laws of nature' and thereby failed to satisfy the 'manner of manufacture' test in s 18 (1)(a) of the *Patents Act 1990* (Cth) ('*Patents Act*').<sup>7</sup>

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<sup>1</sup> (2014) 224 FCR 479 (*D'Arcy*).

<sup>2</sup> (1959) 102 CLR 252.

<sup>3</sup> *D'Arcy* (2014) 224 FCR 479, 517-8.

<sup>4</sup> *Ibid*; Transcript of Proceedings, *D'Arcy v Myriad Genetics Inc and Anor* [2015] HCATrans 12 (13 February 2015).

<sup>5</sup> *D'Arcy* (2014) 224 FCR 479, 491 [66].

<sup>6</sup> *Ibid*.

<sup>7</sup> *Cancer Voices Australia v Myriad Genetics Inc* [2013] FCA 65 (*Cancer Voices*).

At first instance and subsequently upon appeal, CVA contended that the evolved product was not 'materially different' to the cellular form and, hence, is the equivalent of naturally occurring DNA, which is unpatentable.<sup>8</sup> Conversely, the respondent (Myriad) argued that the claims satisfied the *NRDC* test for a 'manner of manufacture', in that the isolated product is 'chemically, structurally and functionally different' and thereby artificial.<sup>9</sup>

Nicholas J's analysis focused on the effect of the process of isolation to ascertain if the product was altered from its natural form. He rejected CVA and D'Arcy's argument, stating that 'an artificial state of affairs' was produced by virtue of the sequence being 'extracted from cells obtained from the human body and purged of other biological materials'.<sup>10</sup> The primary judge further justified his decision with reference to the deliberately 'expansive language' used by the High Court in *NRDC* and the 'immense research and intellectual effort' involved to perform the isolation.<sup>11</sup>

### III JUDGMENT

In upholding the decision at first instance, Allsop CJ, Dowsett, Kenny, Bennet and Middleton JJ differed from the primary judge only by emphasising that the isolated BRCA1 sequence illustrated structural 'but more importantly ... functional differences because of isolation'.<sup>12</sup> The court stated that heritable information did not exist outside of the cell, which gave the 'chemical *in situ*' a distinct character from its cellular counterpart and facilitated its 'economically useful' application.<sup>13</sup>

It similarly clarified that the *NRDC* test asked whether the subject matter 'consist[ed]' of 'an artificial state of affairs' and not if it 'produc[ed]' one, thereby directing the court to focus on differences rather than similarities.<sup>14</sup> The court also reasoned that the prohibition of all natural derivatives on this basis would prevent the patentability of other biological products such as antibiotics.<sup>15</sup>

### IV HIGH COURT APPEAL

On 13 February 2015, D'Arcy (the appellant) was granted special leave to have the matter heard before the High Court.<sup>16</sup> The Institute of Patent and Trademark Attorneys of Australia ('IPTA') also obtained leave to be heard as *amicus curiae*, providing constitutional and general analysis of the case's impact.

In her written submissions, the appellant challenged the Full Court's determinations on three grounds. It was claimed that the Full Court erred by finding that the isolated and the natural sequences were different, the interpretation of the *NRDC* test encompassed products of nature, and the claims constituted a 'manner of manufacture'.

It is notable that the appellant submitted that granting the patent would result in ambiguity for medical practitioners who may infringe the patent when performing routine testing, given that a significant proportion of the population will carry mutations and other

<sup>8</sup> *D'Arcy* (2014) 224 FCR 479, 509 [162–3].

<sup>9</sup> *Ibid.*

<sup>10</sup> *Cancer Voices* [2013] FCA 65 (15 February 2013) [136].

<sup>11</sup> *Ibid* [107–9].

<sup>12</sup> *D'Arcy* (2014) 224 FCR 479, 517 [212].

<sup>13</sup> *Ibid* 513 [191].

<sup>14</sup> *Ibid* 508, 510.

<sup>15</sup> *Ibid* 514 [196].

<sup>16</sup> Please note that the following section refers to Appellant and Respondent submissions found on the High Court Website: High Court of Australia, *Case S28/2015* (7 April 2015) High Court of Australia <[http://www.hcourt.gov.au/cases/case\\_s28-2015](http://www.hcourt.gov.au/cases/case_s28-2015)>.

polymorphic variants in this gene. It was also asserted that this patent would create a monopoly over the sequences of the individuals whose information is included in the claims. These arguments are valid considerations, but they are phrased in terms of a 'general inconvenience' exception, which involves the judiciary making a policy decision. The respondent countered with this analysis and it is likely that the High Court will endorse the Full Court's reluctance to make a ruling on these grounds, explicitly stating that such considerations are a legislative matter rather than a judicial one.<sup>17</sup>

### A *Functional and Structural Differences*

The appellant's submission relied on the decision from the parallel US litigation, which found that the claim was expressed to assert protection for the genetic material itself and not the chemical change that evolved a product.<sup>18</sup> It is notable that Nicholas J, endorsed by the Full Court, clarified that the claim did not grant protection for the written or digitised forms of the genetic information, or the cellular form.<sup>19</sup> Following this line of argument, the respondent put forward that the claim seeks protection for 'a chemical compound' and on this basis the court should apply its most recent examination of the issue in *Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd*.<sup>20</sup>

In resolving this issue, the High Court case will turn on two major interpretative matters:

#### 1 'Coding For'

The parties to the matter dispute the meaning of the claim's phrase 'coding for', as a means of ascertaining the functional attributes of the isolated sequences. The appellant submitted that 'code for' is expressed to assert ownership of the information rather than a distinct product with commercial application. By contrast, the respondent submitted that the information in the product allows for the 'coding' of a specific type of nucleic acid (cDNA), which cannot occur within a cell and, on this basis, the information is altered from its natural state.

#### 2 Structure

The parties also disputed the structural distinction between the isolated product and its natural form. D'Arcy submitted that the court should consider the 'substance' of the change to the chemical structure and that the alteration of the structure does not impact on its ability to produce cellular proteins. In response, Myriad argued that this is not contentious, given the expert evidence elicited at trial, in particular that the breaking of covalent bonds constitutes sufficient evidence that a chemical change has occurred. It was also asserted that the sequences are differentiated through the removal of its beginning and end 'tails', which prevent genetic degradation and assist with other 'cellular' functions.

### B *A Product of Nature?*

The appellant's submissions were that a naturally occurring sequence is not an invention and information carried by the sequence is not changed by isolation. On the semantics of the *NRDC* principle, the appellant contended that removal from cellular processes is a negative attribute rather than a positive one, as described in *NRDC*. The respondent challenged that the High Court should not follow the US decision, given that the judgment in *NRDC*

<sup>17</sup> *D'Arcy* (2014) 224 FCR 479, 502 [125].

<sup>18</sup> *Association for Molecular Pathology v Myriad Genetics, Inc*, 596 US 12-398 (2013).

<sup>19</sup> *Ibid* 497 [103].

<sup>20</sup> (2013) 304 ALR 1.

emphasises the product's difference from the naturally occurring substance and, more broadly, that the US patent system has evolved independently of Australian jurisprudence.

## V ANALYSIS

The *D'Arcy* case highlights three main gaps in the current legislative and judicial approach to this area of law. Firstly, discerning the requisite standard for 'artificiality' is extremely difficult in the absence of solid prescriptions for what constitutes an 'artificial state of affairs'.<sup>21</sup> Secondly, the existing law does not allow the judiciary to engage in policy considerations beyond evaluating the products for economic utility. Finally, in the absence of a solid legislative determination either way, there is no policy framework to assist with judicial analysis.

### A Reform Discourse

In analysis of the issues before the court, both the trial and appeal substantially addressed the legislative 'consideration[s]' and 'refusal' to explicitly exclude isolated genetic sequences from attracting protection under the patent system.<sup>22</sup> Whilst it is a valid comment that Parliament has considered the issue, the *Patent Amendment (Human Genes and Biological Materials) Bill 2010* (Cth) failed to clear the committee stage and, hence, there has been no definitive ruling either way.<sup>23</sup> Currently, s 18(2) of the *Patents Act* prevents 'human beings, and their biological processes for the generation [of humans]' from being patentable, which clearly reflects the prohibition on human cloning and genomic ownership. However, distinct and direct drafting that excludes genetic patents would only provide a short-term solution by restricting the patentability of a single subject matter.

A more desirable legislative response would provide a more general and long-term interpretative framework that is dynamic and adaptable to unforeseen technological progress, particularly in an industry as vigorous as the life science sector.

#### 1 Policy Considerations

The development of reform in this area involves balancing numerous factors, including: protecting legitimate research and development investments; incentivising innovation and domestic investment; treating life-threatening diseases; protecting the genetic materials of individuals; and solidifying the protection of existing products. The existing *NRDC* interpretation of 'manner of manufacture' has an inherently commercial bias with the 'artificial state of affairs' being required to produce economic benefit. It can be argued that such a test fails to acknowledge the aforementioned public policy rationales that concern patentability in this area, particularly where the patent involves the ownership of a patient's isolated BRCA1, which is the motivation that underpins Ms D'Arcy's case. Failure to rectify this issue will result in on-going litigation in this area.

#### 2 International Obligations and Comparison

It is also significant that the *Agreement on Trade-Related Aspects of Intellectual Property Rights* ('TRIPS')<sup>24</sup> does not clarify whether such patents should be prohibited. Rather, the

<sup>21</sup> Tim Vines, 'Cancer Voices Australia v Myriad Genetics Inc [2013] FCA 65: Should Gene Patent Monopolies Trump Public Health?' (2013) 20 *Journal of Law and Medicine* 747, 756.

<sup>22</sup> *D'Arcy* (2014) 224 FCR 479, 508–9.

<sup>23</sup> Vines, above n 22, 754–5.

<sup>24</sup> (Annex 1C to the Marrakesh Agreement establishing the World Trade Organisation), opened for signature 15 April 1994, 1869 UNTS 299 (entered into force 1 January 1995) ('TRIPS').

lack of legislative action in this area can be attributed to restrictions in TRIPS, with signatories being precluded from discriminating between patenting biotechnological and other scientific technologies.<sup>25</sup> On this basis, it is apparent that the Australian Myriad litigation is symptomatic of the broader vacuum on this issue in international law.

In comparing the varying global approaches, the Australian determination is a more expansive acceptance of gene patentability whereas the US has definitively rejected this subject matter.<sup>26</sup> The tradeoff of this diametric outcome is between attractiveness of the jurisdiction for commercialisation, and the integration of non-economic policy considerations such as an individual's intellectual property rights. Whilst Australia becomes commercially attractive, an absolute acceptance ignores the nuances of the types of products being commercialised and the public policy repercussion of each type.<sup>27</sup> By contrast, the European Union ('EU') has implemented a more moderate approach under Article 5(2) of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions. Under this scheme, the structural similarity of the gene is immaterial (thereby addressing artificiality) and the patentability of the product is more reliant on the commercial application of the information. Similarly, EU case law has developed to limit the protection of genetic sequences to the function that it was patented.<sup>28</sup> Arguably, this provides greater clarity for balancing commercial interests and the broader neutrality of the information in line with the limitations prescribed by Nicholas J.

## B *Impact*

### 1 *Scope of the Decision*

It has been widely noted that these proceedings have been deliberately framed to focus on the core issue of patentability as a test case for genetic patents.<sup>29</sup> The patent's claims have not been disputed on other grounds such as novelty, inventiveness and the patent's economic benefit. Arguably, the claims for diagnostic and analytical methods may not satisfy the requisite inventiveness as a result of common usage in the scientific community.<sup>30</sup> Narrow framing of this case substantially limits its usefulness in developing general patent law.

### 2 *Practical Effects*

Irrespective of the outcome of the High Court challenge, patent enforcement occurs where large-scale infringement derives substantial profit. It is well known that laboratory scientists regularly infringe patents in the course of their work and are protected from sanction through the experimental usage exception in the *Patents Act*.<sup>31</sup> In a commercial context, fears have been raised that monopolising this product will severely restrict competition through the ability to charge monopoly prices and prevent entry of rival providers in refusing to grant licences. This is particularly concerning given that the patented product can be widely applied to developing diagnostic technologies and gene-based therapies.<sup>32</sup> Whilst a

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<sup>25</sup> Belinda Huang, 'Biotech Patents in Australia: Raising the Bar on the Generally Inconvenient Exception' (2013) 24 *Australian Intellectual Property Journal* 40, 51.

<sup>26</sup> Adam Denley et al, 'Intellectual Property: Isolated Nucleic Acids: Now Patentable in Australia' (2014) 6(1) *Law Society of NSW Journal* 82, 82  
<<http://search.informit.com.au/documentSummart;dn=786172139466178;res=IELHSS>>.

<sup>27</sup> *Ibid* 82–3.

<sup>28</sup> *Monsanto Technology v Cargill International* [2007] EWHC 2257 (Pat) (10 October 2007).

<sup>29</sup> *D'Arcy* (2014) 224 FCR 479, 516 [206].

<sup>30</sup> *Ibid* 504; *Patents Act* ss 18(1)(b)(i), (ii).

<sup>31</sup> *Patents Act* s 119C.

<sup>32</sup> Huang, above n 26, 43.

valid concern, this argument fails to take into account the 20-year limitation period on standard patents and the compulsory licencing and government usage provisions of the *Patents Act*.<sup>33</sup> Similarly, as a precedent, this case is unlikely to have a great impact on new patent applications with the prior art base growing due to 'second generation genome sequencing of other organisms'.<sup>34</sup>

### 3 *Finding Otherwise*

Pending the High Court challenge, an adverse determination will impact beyond the diagnostics industry. The ramifications of the US decisions have been seen with the United States Patents and Trademark Office ('USPTO') issuing guidelines for the examination of isolated genetic sequences in addition to chemicals derived from nature sources, foods and natural metallic compounds.<sup>35</sup>

## VI CONCLUSION

In the absence of any new argument advanced by either party, it is likely that the High Court will endorse the Full Court's determination and find that genetic sequences are patentable given the current limitations of Australia's patent legislation and self-imposed judicial restraint. The current Australian position remains that genetic sequence patents are patentable. However, this saga is unlikely to adduce a holistic solution especially where the aforementioned gaps in the *D'Arcy* case are yet to be tested.

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<sup>33</sup> Ibid ss 133, 163.

<sup>34</sup> Denley et al, above n 27, 83.

<sup>35</sup> Ibid.

## CONTRIBUTORS

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