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Synthetic Biology: Scientific Progress or Ethical Dilemma?

Authors: Dr. Penny Moody-Corbett, Ph.D.[1], Dr. Theophile Godfraind, M.D., Ph.D.[2] and Dr. Ashima Ananda, Ph.D.[3]

Synthetic Biology is described as "the engineering of biology: the deliberate (re)design and construction of novel biological and biologically based systems to perform new functions for useful purposes, that draws on principles elucidated from biology and engineering."[1]. The most spectacular progresses are in the synthesis of artificial and novel DNA. This emerging field is paying particular attention on engineering biomolecular systems and cellular functions for a variety of applications namely synthetic circuits and endogenous networks included in regulatory processes. This shall create immense possibilities for physiological research. The field brings both opportunity and challenges and this year at the 37th Congress of the International Union of Physiological Sciences (IUPS) in Birmingham, UK, the IUPS Ethics Committee brought together science and philosophy to talk about this fascinating new field.

Dr. François Kepes, a cell and systems biologist, who models and engineers genome architecture in microorganisms, opened the symposium. He provided information on the science behind synthetic biology and how it has arisen during a century in which we saw many innovative technologies, such as the advancements in computer science, engineering and biotechnology. Dr. Kepes used the analogy with synthetic chemistry and its emergence in the mid-19th century to describe his expectation for the emergence of synthetic biology in the 21st century. Synthetic Biology, which connects a number of disciplines, including mathematics, biology, engineering, chemistry, physics and computer science, is the basis for novel approaches to advance biotechnology. Dr. Kepes gave several examples of how this field has and will be able to tackle challenging medical problems; using techniques that are more specific and less expensive than previously available for applications in diagnostics, therapeutics, vaccines, biomaterials, biofuels, etc. He described a number of examples of applications that have health and economic benefits; such as, the

[1] Adjunct Professor Division of BioMedical Sciences, Memorial University, St. John's NL, Current address: Ottawa, ON K1H 6C2 Canada, Chair, Ethics Committee, IUPS
[2] Emeritus Professor of Physiology and Pharmacology, President of the Belgian College of Pharmaceutical Medicine, Editor-in-Chief of Frontiers in Pharmacology Université Catholique de Louvain, Current address: Avenue Mounier 50-PHAR B1.50.15, B-1200 Brussels- Belgium, Member, Ethics Committee, IUPS
[3] Exertional Breathlessness Studies Laboratory (DST), Current address: Vallbhbhai Patel Chest Institute, Delhi University, Delhi 110007 India, Member, Ethics Committee, IUPS

synthetic biological approach that has allowed the anti-malaria drug artemisinin to be produced at one-tenth the cost and at production levels more in line with current needs. In the field of physiology, he reported experiments with mammalian cells engineered for uric acid homeostasis *in vivo*. A synthetic device built by Fussenegger and Colleagues in Zurich, which senses uric acid using an engineered repressor that can be operated by uric acid, allowing expression of urate oxidase that eliminated uric acid. Cells equipped with this device were injected in transgenic mice deficient in urate oxidase and reduced uric acid body levels. Dr. Kepes concluded his lecture by presenting a future in which gene sequencing would be routine, synthetic biology would be used as a rational approach for engineering tissues and nano-technology and would be the basis for constructing non-invasive or permanently implanted biomolecular sensors coupled to biomolecular calculators and curative technologies that will be able to synthesize desired remedies on the spot. Clearly an exciting vision; however, scientists and the public struggle with how these new technologies will be regulated and managed as we move forward and the focus of the next three talks was to draw attention to current practices and new considerations that may be required in oversight.

Professor Thomas Baldwin, with an expertise in the central themes of contemporary philosophy, and the editor of the leading UK-based philosophy journal *Mind*, was the second speaker of the afternoon and he addressed the topic of 'humanizing' animals in the course of biomedical research, a potential consequence of new biotechnologies, such as synthetic biology. His recent work on bioethics and his experience as a member of the Nuffield Council on Bioethics, the Human Fertilisation and Embryology Agency and the Human Genetics Commission provided the background for his participation in the Academy of Medical Sciences (UK) working group commissioned to review and report on the oversight of research involving animals containing human materials (ACHM) obtained by various approaches: transgenesis or stem cell transplantation. Several examples of this occur in current research, such as, metabolic studies, which may be performed in mice transplanted with human hepatocytes or the study of the FOXP2 gene involved in language disorder in humans that can be introduced in mice under the normal or mutated form in order to characterize altered function. The working group chaired by Martin Bobrow, from Cambridge, included experts in biomedical sciences, philosophy, ethics, law and social sciences and the public participated through public dialogue. Professor Baldwin explained that research involving ACHM, like other animal research in the UK, is governed by the Home Office and is required to adhere to the 3-Rs principle of reduce, refine and replace. The particular issues raised by ACHM of the potential of humanizing animal species, he reminded the audience, is a topic that is popularized in lay literature and has been reinforced over the years by the fictionalization of human-animal mixes. Professor Baldwin described that the major problems from the public dialogue dealt with the potential for humanizing non-human primates; specifically, in neurological aspects, appearance or in ways that may result in the production of hybrid human-animal embryos. However the report also demonstrated that the techniques of synthetic biology provide a means of studying very bad diseases and disorders in less

complex organisms therefore potentially reducing the use of whole animal research by conducting studies in simpler systems. In acknowledging this he also raised the concern, from an animal welfare perspective, that the use of ACHM may increase animal suffering by transferring harmful human disorders to non-human animals. As Professor Baldwin reported this point underpins the importance of effective oversight to assess the degree to which the level of harm inflicted on animals is mitigated by significant beneficial findings.

The next two speakers, Drs. Djims Milius and Catherine Rhodes, addressed the challenges in ownership and intellectual property (IP) rights that are created in the field of synthetic biology. These topics play across international boundaries and both speakers reminded the audience of the importance of considering the two areas of biosafety and biosecurity in access and ownership of biological materials and innovation. Dr. Milius approached this topic from his transdisciplinary expertise in the law of IP, corporate science and technology policy. He described how combining the disciplines of biology, engineering and information technology have resulted in unique legal approaches as well as ethical concerns. He summarized synthetic biology into four basic categories: developing biological product from combinations of nucleotides; developing products from a metabolic engineering approach (e.g., drug production); creating fit-for-purpose materials (biological scaffolding) and creating parts, devices and systems from biologically based components. As he presented, the framework for patent law varies based on the conceptual approach taken by the science and therefore may range from a biological systems approach to one of bioengineering, novel discovery or design, depending on the perspective of the applicant. Dr. Milius described three models currently in practice, which range from IP protection to open-source approaches and fall under areas of copyright, patent and licensing. In considering copyright law synthetic biologist may regard strings of nucleotide sequences similar to software code and therefore protection could be offered using copyright. However, copyright law does not cover functionality or methods of operation. Alternatively, patent protection for a group of common users is another approach. This would provide basic patent protection on key technologies while allowing other licensee members access to patentable improvements. The challenges with this approach include defining the inventive territory, one that does not infringe on previous patents or provide information already in the public domain. At the other extreme is the approach taken by big business to provide access and reduce excessive protectionism. These approaches, such as non-assertion status, 'click-wrap' licences and 'copyleft' reduce excessive patenting in an attempt to enable technological advances. To date synthetic biology has taken more of a proprietary approach and less open-source approach, however Dr. Milius pointed out that the laws have really not clarified how synthetic biology and biotechnology should be handled. In concluding, he raised the importance of considering a new legal entity(ies) to address new concepts in biology and biotechnology as well as additional topics which will need to be considered such as trademark, trade secrets, data exchanges, one of a kind legislation, etc.

Dr. Catherine Rhodes addressed the challenging issue of who owns synthetic organisms. Her background in international actions to prevent misuse of biology provided the basis for her current interests in the international governance of genetic resources including how synthetic organisms should be regarded. Dr. Rhodes framed her talk by establishing the importance of the field of synthetic biology in being used for the benefit of humankind. She presented the importance of identifying a correct definition of what is to be owned and in this context established that organisms resulting from synthetic biology should be regarded as a form of genetic resource as defined under the terms of the International Convention of Biological Diversity. Dr. Rhodes provided a list of many of the international laws, guidelines and frameworks that apply to genetic resources (Table 1). She identified four strategies used with genetic resources: state sovereign rights (where the rights rest with national governments and national legislation), free access (tending to favour those with the financial and technological ability to access resources), common heritage of mankind approach (in which genetic resources are universally managed and economic and scientific benefits shared by all) and IP rights (based on patent law); commenting that, of these, state sovereign rights and IP rights are the dominant approaches for genetic resources. Dr. Rhodes argued that the approach used for ownership of synthetic organisms requires attention to the developmental stage of the organism and will be particularly influenced by the ability to achieve particular purposes or goals. She proposed that the approach taken for synthetic organisms (and genetic resources in general) should be towards a modified common heritage approach. In this regard she emphasized the importance of more public domain/open source approaches to enhance accessibility and affordability and to develop solutions that are adapted to local needs and conditions, avoiding a concentration of benefits in already wealthy and technologically advanced states.

The final speaker of the afternoon was Dr. Dorothée Benoit-Browaeys, the founder of the non-governmental organization VivAgora, which acts to develop public debates on technological choices. As a scientific journalist for the past 20 years her work has focused on providing the public with information on science discoveries and innovation particularly in the area of biotechnology. Dr. Browaeys highlighted the role that VivAgora has played in providing informative sessions in France to enhance public understanding and engagement in the field of synthetic biology. In her presentation, Dr. Browaeys pointed out that synthetic biology is not simply another form of genetically modified organisms (GMOs); rather, it raises the possibility of creating new life forms and as such must be considered in a new light. The issues raised by synthetic biology have an impact on the entire biomass, from single cells to biofuels and these projects have social, ecological and economic consequences. The aim of her work is to help citizens understand issues raised by technological developments and to provide venues for dialogue among all stakeholders, even with conflicting interests, in exploring responsible innovation practices. She posed several questions including the relationship of synthetic biology to GMOs and if the promises of synthetic biology are credible, what are the dangers of these new technologies and how will they be controlled? Like previous speakers, she commented on the governance of this field worldwide and whether

current regulations for other genetic modifications, such as GMOs, are sufficient or applicable to synthetic biology. Dr. Browaeys also raised the concept of how synthetic biology may revolutionize biology itself. Dr. Browaeys' presentation emphasized the importance of public engagement, in particular the important role that non-scientists play in techno-scientific decision-making bodies and that there is a collective responsibility in oversight of this field.

Overall this symposium provided a good deal of information to be considered in the interaction of physiology with the field of synthetic biology from the excitement of innovation and discovery to the concerns of new technologies and the unknown. As with other emerging fields over the generations synthetic biology has a number of challenges but it is essential in advancing the science that there is involvement at all levels of society to understand this new field and develop appropriate governance structures that will advance the benefits of this technology and provide safeguards for its impact in order to become a resource for all. In conclusion, the symposium reinforced the importance of mandatory bioethics in the evaluation of the introduction of synthetic biology techniques in a given physiological study.

Table 1 International Rules that apply in oversight of genetic resources (from C Rhodes, 2013)

- Convention on Biodiversity and its Nagoya Protocol
- Pandemic Influenza Preparedness Framework
- International Treaty on Plant Genetic Resources
- Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS)
- International Convention for the Protection of New Varieties of Plants
- Budapest Treaty on the Deposit of Microorganisms for the Purpose of Patent Procedure
- Biological Weapons Convention
- Universal Declaration on the Human Genome and Human Rights; International Declaration on Human Genetic Data; Universal Declaration on Bioethics and Human Rights
- United Nations Convention on the Law of the Sea
- Disease control regulations for human, animal and plant health
- United Nations Declaration on the Rights of Indigenous Peoples; Indigenous and Tribal Peoples Convention
- Laboratory Biosafety Manual; Laboratory Biosecurity Guidance; Guidance on Regulations for the Safe Transport of Infectious Substances

Speakers:

Dr. Francois Kepes is currently research director at CNRS and founding director of the Epigenomics Project, Genopole® Institute of Systems & Synthetic Biology, Genopole®, CNRS, Evry, France
Professor Thomas Baldwin is Professor of Philosophy, Department of Philosophy,

University of York, Heslington, York, UK
Dr. Djims Milius is currently Academic Associate, Department of Human Genetics, Faculty of Medicine, McGill University, Montreal, QC, Canada
Dr. Catherine Rhodes is a Research Fellow in Science Ethics at the Institute for Science, Ethics and Innovation, University of Manchester, Manchester, UK.
Dr. Dorothée Benoit-Browaeys is Déléguée générale de VivAgora, Paris, France

1. ERASynBio: http://www.erasynbio.eu/index.php?index=32