EMBO reports

viewpoint

Managing the unimaginable

Regulatory responses to the challenges posed by synthetic biology and synthetic genomics

Gabrielle N. Samuel, Michael J. Selgelid & Ian Kerridge

The past few years have seen a growing academic and commercial interest in synthetic genomics and synthetic biology. We refer collectively to these technologies as synthetic life sciences. They involve several distinct engineering strategies drawn from the convergence of molecular genetics, chemistry, nanotechnology and electronic engineering. Synthetic genomics can be defined as the creation of either new or already existing individual genes, chromosomes and even whole genomes through the assembly of DNA molecules. Synthetic biology encompasses the design and construction of new biological parts, devices and systems—as well as the re-design of existing, natural biological systems—for practical purposes (EC, 2005). It often uses the technologies and tools of synthetic genomics, but this is not a prerequisite.

...progress in science and technology often outpaces the relevant ethical, legal and moral discourse, and regulation...

The considerable interest in the synthetic life sciences from scientists and the public alike is due to the enormous potential of these technologies for the development of pharmaceuticals, renewable fuel production, the detoxification of chemicals, the repair of defective genes in biomedicine, and environmental control. As beneficiaries of considerable support from both the public and private sectors, these technologies are advancing rapidly. However, progress in science and technology often outpaces the relevant ethical, legal and moral discourse and regulation, which can create suspicion and cause backlashes from the public. To avoid this situation in the synthetic life sciences, it is imperative that the ethical and regulatory issues surrounding synthetic genomics and synthetic biology are identified, analysed and addressed sooner rather than later.

The potential of synthetic genomics was shown as early as 2002, when researchers at the State University of New York at Stony Brook (NY, USA) published the synthesis of the poliovirus in *Science* (Cello *et al*, 2002). In 2005, US scientists recreated the 1918 'Spanish Flu' virus (Tumpey *et al*, 2005) and, last year, biologists at the J Craig Venter Institute (Bethesda, MD, USA) synthesized the genome of the small bacterium *Mycoplasma genitalium* (Gibson *et al*, 2008). It is likely to be a matter of only a few years, or even less, until scientists are able to synthesize the genomes of other, larger bacteria and even eukaryotes (ETC Group, 2007).

Much research, however, encompasses both synthetic genomics and synthetic biology, and researchers are making rapid progress. This includes creating a 'minimal microbe'—an artificial organism that will contain the minimum number of genes required for existence—as a platform from which to create artificial bacteria with tailor-made functions (Zimmer, 2003); a BioBrick database of DNA strands that reliably perform a specific function—for example, turning genes 'on' and 'off'—that synthetic biologists can use to 'program' living organisms in the same way a computer scientist programs a computer (http://www.biobricks.org/); and engineered bacteria to synthesize drug precursors or other complex chemicals. The research group of Jay Keasling at the University of California, Berkeley, USA, has already created bacteria that produce a precursor of the anti-malarial drug artemisinin (Ro *et al*, 2006) and synthetic biofuels (Kirby & Keasling, 2008).

Both synthetic genomics and synthetic biology seem to have beneficial environmental, biomedical and commercial potential; however, these are also potentially 'high-risk' sciences. Given the excitement surrounding their emergence, it is easy to lose sight of the socio-economic, justice, human rights, intellectual property, safety, security, governance and philosophical issues raised by the creation of artificial life. Although many of these issues have already been discussed in relation to other technologies, such as genetic engineering, stem-cell research, nuclear research and nanotechnology, many questions remain unresolved. Synthetic genomics and synthetic biology arguably offer greater promise and pose greater perils than any of the sciences or technologies from which they are derived. It is crucial, therefore, that we consider carefully the broad range of ethical concerns raised by these technologies and the various ways in which they could be regulated. Although the level of risk and the appropriate regulatory response might vary between the two technologies, here, we raise issues that apply, for the most part, to both synthetic genomics and synthetic biology. Thus, we will use the term 'synthetic life science' to refer to both, except in the limited instances when we are referring specifically to one or the other. Indeed, the main ethical issues raised by the synthetic life sciences—which relate to biosecurity, biosafety and justice—apply to both technologies, although their importance might vary; for example, synthetic genomics and its associated technologies might pose more serious biosecurity risks.

Synthetic life science is a typical 'dual-use' technology: it can be used for the greater good, but also for nefarious goals to cause considerable harm. Many critics are particularly worried about the possibility of synthesizing pathogens and using these as biological weapons. These risks are not far-fetched, as was shown by the successful synthesis of a 'live' poliovirus through the on-line ordering of oligonucleotides (Cello *et al*, 2002) and the reconstruction of the 1918 'Spanish Flu' virus—one of the deadliest pathogens humankind has ever encountered (Tumpey *et al*, 2005).

When the polio study was published in 2002, most doubted that the same technique could be used to synthesize smallpox, which is one of the most feared bioweapons. The reason was that the smallpox genome, which is nearly 190,000 bp long, is much larger than the 7,500 bp-long genome of the poliovirus. But, technology has progressed so rapidly that the synthesis of smallpox is now possible, meaning that would-be bioterrorists no longer need to gain access to the wild-type virus—officially stored under tight security at two facilities in the USA and Russia—they need only follow the recipe. The use of smallpox as a weapon could be devastating; the virus killed between 300 and 500 million people during the twentieth century—three-times more than all the wars of that period combined—and the global population is now highly susceptible to it as vaccinations ended after its eradication in 1980.

It is likely to be a matter of only a few years, or even less, until scientists are able to synthesize the genomes of other, larger bacteria and even eukaryotes...

Synthetic genomics might similarly allow the synthesis of other hard-to-get-hold-of pathogens—such as the Ebola virus—whereas synthetic biology might enable the design and creation of new pathogens particularly suited to biological warfare. Although some suggest that this latter risk is low because it would require a wide range of biological and technological factors and expertize to optimize virulence, infectivity, specificity, hardiness, resistance, delivery system and dispersal methods (NSABB, 2006; Zilinskas, 2006), others are less confident. Such concerns led to the establishment of the US National Science Advisory Board for Biosecurity (NSABB; Bethesda, MD, USA) in 2004 to advise the government about how to deal with dual-use research. One of its five working groups is focusing on both synthetic genomics and synthetic biology.

In addition to its attendant security risks, synthetic life science raises several biosafety concerns for researchers, the community and the environment. Bhutkar (2005) identifies three types of safety risk: negative environmental impact; contamination of the genome pool by genetic exchange between synthetic and wild-type organisms; and unintended consequences of the synthetic organisms' release into the environment. The latter fear has also been expressed with regard to nanotechnology in a proposed scenario in which an uncontrollable technology degrades all living matter to 'grey-goo'.

In response to these concerns, proponents of synthetic life science argue that it poses no greater or different safety risks than does genetic engineering, and that these risks have been shown to be largely insignificant. Proponents argue that organisms created in the laboratory, including synthetic ones, can be genetically compromised and, as such, would fare badly in the wild. For example, organisms could be manipulated to require an essential nutrient for survival that does not occur naturally. Proponents of synthetic genomics and synthetic biology substantiate their arguments by pointing to the lack of evidence that genetically modified organisms have caused environmental catastrophes. The matter remains controversial, however, and several international research projects aim to evaluate safety issues specific to synthetic life science and to establish precautionary guidelines to protect against any impending dangers (Garfinkel *et al*, 2007).

As with any emerging technology that has a commercial application, synthetic life science also poses several concerns regarding justice. So far, it is unclear how far-reaching patents on new engineering methods will be, or how patents on individual genes will be reconciled if many genes are used in the synthesis of an entire genome (Rai & Boyle, 2007; De Vriend, 2006). Synthetic life science, even more than other 'new' sciences and technologies—for example, stem-cell research, genomics and molecular genetic technologies—challenges the definition of what should qualify as a patentable product and how one can establish a logical patent framework to encourage investment without stifling research (Rai & Boyle, 2007).

Synthetic genomics and synthetic biology arguably offer greater promise and pose greater perils than any of the sciences or technologies from which they are derived

Furthermore, as is the case with most other commercially driven technologies, synthetic life science is more likely to benefit the wealthy and the industrialized West, rather than the poor and the developing world. Even where research aims to benefit the poor—as is the case with the synthesis of the anti-malaria drug precursor—the resultant production of synthetic artemisinic acid is likely to displace livelihoods in the poorer economies of Asia and Africa; some communities rely heavily on wormwood farming as a main source of artemisinic acid and income. Synthetic artemisinin will ultimately make these communities dependent on wealthy countries to provide sufficient quantities of the drug, rather than being able to gain from its production themselves (Heemskerk *et al*, 2006).

Although there is broad public and professional support for scientific research, it is also generally accepted that research should operate within acceptable social norms and should not unreasonably threaten public safety or impose unacceptable social burdens. The challenge for regulators in relation to synthetic life science is to devise a legislative and regulatory system that balances security and safety risks to facilitate research without imposing unreasonable bureaucratic burdens on scientists and academic freedom.

There is little disagreement that synthetic life science needs some form of regulatory control. However, the questions of exactly what should be regulated, which regulatory structures should be implemented and the type of governance structures needed all remain a matter of debate. For the most part, scientists tend to support self-governance, or at least

bottom-up governance and non-binding legislative frameworks. In support of self-governance, it is worth noting that scientists at the Second International Conference on Synthetic Biology in 2006, held at the University of California, Berkeley, USA, proposed the organization of a working group to promote a range of safety measures. These include software tools to identify DNA sequences that encode hazardous biological systems or parts thereof; the control of oligonucleotide synthesis and trade using such sequence-checking technology; promulgation of new specific codes of conduct; and discussions within the science and engineering research communities and stakeholders (SB 2.0, 2006). This stance is consistent with the generally held belief within the research community that self-governance is effective for regulating biological research, including recombinant DNA technology, and that it represents the only means by which research can be regulated across national borders and between governments. Many scientists also believe that science should be politically autonomous and that self-governance is essential to the nature and progress of science.

The challenge […] is to devise a legislative and regulatory system that balances security and safety […] without imposing unreasonable bureaucratic burdens...

Critics of self-governance dismiss such proposals as inadequate. They argue that the risks of synthetic life science are profound and have an impact on both society and the environment, and that research and researchers should be tightly regulated. They believe that it would be inappropriate for scientists and engineers, who might benefit from the investigation and application of synthetic life science, to regulate themselves. Instead, they support governmental control—top-down governance of research and publication practices.

Miller & Selgelid (2007) have tried to clarify some of these issues by outlining and evaluating a range of options to manage dual-use technologies. These include governmental control, control by an independent authority, a hybrid of institutional and government control, institutional control, or control by individual scientists. Given the importance of balancing scientific freedom with biosecurity and biosafety concerns, they argue that neither self-governance nor centralized governmental control would be appropriate. The authors concluded that either an independent authority or a hybrid of institutional and government regulatory processes would provide the most ethically robust form of governance, while being able to respond to scientific and technological progress and achieve the best balance between academic freedom and public safety.

The NSABB recently mapped out 'experiments of concern' that could pose significant risks to biosecurity and biosafety (NSABB, 2007). These include experiments that might create knowledge, products or technologies that could enhance the harmful consequences of a biological agent or toxin; disrupt immunity or the effectiveness of an immunization without clinical and/or agricultural justification; introduce resistance of a biological agent against useful prophylactic or therapeutic interventions, or facilitate their ability to evade detection methodologies; increase the stability, transmissibility or the ability to disseminate a biological agent or toxin; alter the host range or tropism of a biological agent or toxin; enhance the susceptibility of a host population; generate a new pathogenic agent or toxin; or reconstitute an eradicated or extinct biological agent (NSABB, 2007).

The idea behind the establishment of the NSABB is that such experiments warrant special scrutiny given their potentially problematic nature. Any decisions about whether or not experiments that fall under any of these categories should be pursued could be made either by assessment committees within the government, the scientific community and/or an independent authority, or through the expansion of existing committees such as institutional biosafety committees (IBCs). Whichever mechanism is adopted, it will be important that this regulatory solution extends to the private sector, that regulation is harmonized on a global scale and that strict guidelines are established to protect the scientist's right to intellectual inquiry.

'Dual-purpose' research can also be regulated at the point of publication and dissemination. Several scientific journals, including *Science* and *Nature*, have already introduced editorial processes to scrutinize manuscripts that might pose security threats. Although some commentators have argued for a much more rigorous restriction of publication and dissemination (ETC Group, 2007), many scientists have responded by asserting that this represents unjustifiable censorship, restricts freedom of speech, and fails to recognize the importance of academic publications for the scientific community and intellectual progress.

Existing codes of conduct for scientific research generally fail to address the concept of dual-use research. Many scientists therefore believe that newer, more comprehensive codes of conduct are needed to address new biosecurity, biosafety and bioethical concerns. To this end, several international working groups and organizations, most notably the NSABB, have been developing codes of conduct that explicitly address dual-use research. The primary purposes of such codes of conduct include raising the awareness of the 1972 Biological and Toxins Weapons Convention and educating scientists about the dangers of dual-use research (NSABB, 2007; Bokan, 2006). Some critics dispute the effectiveness or necessity of codes of conduct, however, and argue that they either serve no purpose unless they incorporate meaningful sanctions (Rappert, 2004), or that they might inappropriately restrict justifiable research (Shea, 2007). Further questions also remain as to who will monitor adherence to a code—the scientific community, the government or independent bodies—whether codes should be legally enforceable and whether harmonization of codes can be achieved on a global scale.

More education and awareness, both within the scientific community and in the public sphere, could help to prevent a backlash of public opinion in the future...

In any case, a code of conduct would at least help to increase the awareness of the potential perils of synthetic life science. This could be further enhanced through more or ongoing mandatory education for scientific researchers about dual-use research, in addition to policies ensuring

that all life-science researchers are aware of the concerns and their own roles and responsibilities (NSABB, 2007). However, for education campaigns to be effective, public and private research institutions will need to adopt training programmes on both a national and international scale. More education and awareness, both within the scientific community and in the public sphere, could help to prevent a backlash of public opinion in the future (Tucker & Zilinskas, 2006).

Regulating the trade of DNA sequences might also ameliorate the risks associated with synthetic life science. 'DNA synthesis' companies could screen customers' orders for sequences—both short oligonucleotides and 'gene-length' DNA sequences—that could potentially be used for bioweapons (Bügl *et al*, 2007; Garfinkel *et al*, 2007). However, such companies generate a vast number of different gene sequences—most of which are not associated with biosafety or biosecurity risks—and the additional overheads would almost certainly raise the costs of DNA synthesis. Moreover, oligonucleotide sequences are short, 'non-specific' and difficult to definitively link to pathogenic sequences. The regulation of oligonucleotide synthesis might thus be inefficient, expensive and ineffective (Garfinkel *et al*, 2007). By contrast, the synthesis of long gene-length sequences—which is a relatively new technology offered by only about 50 companies worldwide—can easily be regulated to address biosafety and biosecurity concerns. But, again, bioterrorists could still circumvent such regulation by using different companies to synthesize various parts of a dangerous pathogen's sequence, or by synthesizing an entirely new pathogenic sequence.

Synthetic life science can also, in theory, be controlled through the registration and licensing of the technology for gene-length DNA synthesis. This could include commercial firms that sell synthetic DNA, owners of 'bench-top' DNA synthesizers, and the users of synthetic DNA themselves and the institutions that support their work (Bügl *et al*, 2007). Regardless of the nature of regulatory control, it will be important to establish whether licensing and/or registration generate substantial benefits, or whether such measures would impose unacceptable financial burdens on the research sector. It also raises the question of whether such regulations are sufficiently flexible to cope with scientific progress, or whether they would create additional barriers to the international harmonization of research, as it is impossible to achieve international consensus on license requirements. Moreover, bioterrorists are unlikely to operate in laboratory settings where this type of regulation would hinder their efforts.

The synthetic life sciences seem to have emerged from nowhere, and their potential uses and misuses have taken the scientific and regulatory community by surprise. This illustrates not only how quickly science can develop, particularly when propelled by funding from the private sector, but also how the direction of science can be remarkably difficult to predict. More importantly, however, it is a reminder of how scientific development might leave moral, social and legal discourse in its wake, and lead to uncertainties as to how it should be regulated and controlled.

Given the complex hybrid nature of synthetic life science, efficient regulation will have to focus on the research itself, its dissemination and on those who perform the research

In the light of the biosecurity and biosafety risks raised by synthetic life sciences, some might wonder whether it would be appropriate to prohibit this technology altogether—at least for the time being (ETC Group, 2007). Prohibition, however, would inhibit intellectual inquiry and scientific freedom, and would prevent any possible benefits from synthetic genomics and synthetic biology being realized. Regulation would therefore seem to be the most appropriate response, but the current regulatory framework would need substantial revision in order to address the specific concerns and challenges of synthetic life sciences. New regulation needs to not only accommodate risk management and scientific freedom, but also be flexible enough to accommodate rapid and unpredictable progress, and function on a global scale. This potentially requires both legislative and non-legislative regulatory responses, and the evolution of regulatory authorities as independent bodies of scientists, security experts, legislators and lay people, who will represent the interests of all stakeholders.

Given the complex hybrid nature of synthetic life sciences, efficient regulation will have to focus on the research itself, its dissemination, and on those who perform it. Advisory committees could be established to offer advice to scientists and publishers who are concerned about the implications of their research; companies who synthesize DNA sequences and those institutions who use them could be subject to specific licensing requirements; codes of conduct for scientific research could be strengthened; and education of both the public as well as researchers improved. Scientists can have a significant role in the development of regulation, and must ultimately work with regulatory and security experts and with the community to ensure that research in this area provides social benefit and minimizes the dangers.

REFERENCES

Bhutkar A (2005) Synthetic biology. Navigating the challenges ahead. *J Biolaw Bus* **8:** 19–29

Bokan S (2006) Why a code of conduct for 'dual-use' research? *ASA Newsl* **115:** 06-5

Bügl H *et al* (2007) DNA synthesis and biological security. *Nat Biotechnol* **25:** 627–629

Cello J, Paul AV, Wimmer E (2002) Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science* **297:** 1016–1018

De Vriend H (2006) *Constructing Life. Early Social Reflections on the Emerging Field of Synthetic Biology*. The Hague, The Netherlands: Rathenau Institute

EC (2005) *Synbiology: An Analysis of Synthetic Biology Research in Europe and North America*. Brussels, Belgium: European Commission

ETC Group (2007) *Extreme Genetic Engineering: An Introduction to Synthetic Biology*. Ottawa, Canada: ETC Group. www.etcgroup.org

Garfinkel MS, Endy D, Epstein GL, Friedman RM (2007) *Synthetic Genomics: Options for Governance*. 2007. Rockville, MD, USA: J Craig Venter Institute. www.jcvi.org/

Gibson DG *et al* (2008) Complete chemical synthesis, assembly, and cloning of a *Mycoplasma genitalium* genome. *Science* **319:** 1215–1220

Heemskerk W, Schallig H, de Steenhuijsen Piters B (2006) *The World of Artemisia in 44 Questions*. Amsterdam, The Netherlands: The Royal Tropical Institute

Kirby J, Keasling JD (2008) Metabolic engineering of microorganisms for isoprenoid production. *Nat Prod Rep* **25:** 656–661

Miller S, Selgelid MJ (2007) Ethical and philosophical consideration of the dual-use dilemma in the biological sciences. *Sci Eng Ethics* **13:** 523–580

NSABB (2006) *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents*. Bethesda, MD, USA: National Science Advisory Board for Biosecurity. www.biosecurityboard.gov/

NSABB (2007) *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*. Bethesda, MD, USA: National Science Advisory Board for Biosecurity. www.biosecurityboard.gov/

Rai A, Boyle J (2007) Synthetic biology: caught between property rights, the public domain, and the commons. *PLoS Biol* **5:** e58

Rappert B (2004) Responsibility in the life sciences: assessing the role of professional codes. Biosecurity and bioterrorism: biodefense strategy. *Practice and Science* **2:** 164–174

Ro DK *et al* (2006) Production of the antimalarial drug precursor artemisinic acid in engineered yeast. *Nature* **440:** 940–943

SB 2.0 (2006) *Declaration of the Second International Meeting on Synthetic Biology*. Berkeley, California, USA: Second International Meeting on Synthetic Biology. http://dspace.mit.edu/handle/1721.1/32982

Shea DA (2007) *Oversight of Dual-Use Biological Research: The National Science Advisory Board for Security*. Washington, DC, USA: Congressional Research Service (CRS) Report for Congress RL33342

Tucker JB, Zilinskas RA (2006) The promise and perils of synthetic biology. *New Atlantis* **12:** 25–45

Tumpey TM *et al* (2005) Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* **310:** 77–80

Zilinskas RA (2006) Technical barriers to successful biological attacks with synthetic organisms. In *From Understanding to Action: Community-based Option for Improving Safety and Security in Synthetic Biology*, SM Mauer, KV Lucas, S Terrell (Eds). Berkeley, CA, USA: University of California, Berkeley

Zimmer C (2003) Genomics. Tinker, tailor: can Venter stitch together a genome from scratch? *Science* **299:** 1006–1007

Gabrielle N. Samuel (top left), Michael J. Selgelid (middle) & Ian Kerridge (top right) are at the Centre for Values, Ethics and the Law in Medicine, University of Sydney, Australia. Michael Selgelid is also at the Centre for Applied Philosophy and Public Ethics and The National Centre for Biosecurity at the Australian National University in Canberra, Australia.
E-mail: gsamuel@med.usyd.edu.au

doi:10.1038/embor.2008.232
Published online 12 December 2008