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Dealing with the Outer Reaches of Synthetic Biology Biosafety, Biosecurity, IPR, and Ethical Challenges of Chemical Synthetic Biology

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Home is where one starts from. T. S. Eliot.

The chapter starts by recalling the possible analogy between astrobiology and synthetic biology, in the sense that in both cases we may be facing the encounter with new types of microorganism – with the observation that we are more likely to see "alien" species here on Earth. A brief analysis is then made on the work carried out in the field of synthetic minimal cells, and of alternative DNA forms, to then consider the societal issues in synthetic biology, with questions arising in biosafety and biosecurity, as well as ethical issues and intellectual property questions. A discussion on these challenges is presented here. Problems arising with sample return missions from outer-space objects are considered, with observations made by NASA studies. Concerning biosecurity, one problem is then recognized in preventing hostile misuse of chemical synthetic biology, and the chapter dwells on measures that are or could be taken to face this challenge. Further, the ethical aspects of chemical synthetic biology creating new forms of life are considered and discussed. This brings to the question "what is life" and to "the value of life." Finally, we discuss how chemical synthetic biology might challenge the current intellectual property rights regime.

13.1 INTRODUCTION

Many people will have heard media reports about the Search for Extra-Terrestrial Intelligence (SETI) project in the universe: the search for signals from extraterrestrial life-forms capable of sending them. Meanwhile, there is another lesser known aspect of astrobiology. In this second field of activity, called exobiology, the aim is to search the solar system for evidence of nonintelligent life-forms (such as microbes). Attention has been paid for some time to the question of what to do if intelligent life-forms are detected [1], and similar consideration is now being given to the identical question in regard to nonintelligent life-forms [2].

The Outer Space Treaty of 1967 has provisions that require space-faring nations to conduct space exploration so as to avoid harmful contamination of the Earth and celestial bodies. The Committee on Space Research (COSPAR), a permanent committee of the International Council of Scientific Unions (ICSU), provides recommendations on how these aims should be achieved. Then, for example, in the USA, NASA's Planetary Protection Office is charged with assuring that missions are planned and carried out in accord with such laws and policies.

Box 13.1 PPO

Planetary protection is the term given to the practice of protecting solar-system bodies (i.e. planets, moons, comets, and asteroids) from contamination by Earth life, and protecting Earth from possible life forms that may be returned from other solar-system bodies. Planetary protection is essential for several important reasons: to preserve our ability to study other worlds as they exist in their natural states; to avoid contamination that would obscure our ability to find life elsewhere – if it exists; and to ensure that we take prudent precautions to protect Earth's biosphere in case it does. (Source: [3]).

This it does after consultation with both international and internal bodies, such as the Space Studies Board of the National Academy of Sciences. Additionally, for the United States' planned 2014 sample return mission to Mars, NASA will have to prepare a detailed environmental impact statement and this will be subject to public scrutiny. This tight regulation clearly indicates a cautious attitude towards the appearance of novel forms of life on Earth.

Theoretically, a Mars sample might contain microbes similar in many ways to those found on Earth, and these might be dangerous to Earth life-forms. However, the samples could also be very different, and there is clearly a range of other chemical possibilities to maintain living systems [4]. The amino acids in the alien life-form's proteins, for example, could be different from those which have evolved on Earth. The structure or mechanism of operation of its information-storing molecule could be different from our DNA. On some celestial bodies, even more "alien" life-forms may have developed, say through the use of a solvent other than water or the use of very different chemical elements – say silicon rather than carbon [4]. Of course, there are other possibilities, such as variations in the tripartite DNA–RNA–protein architecture found in Earth life-forms. One such possibility would be a dual architecture with, say, just RNA and proteins. Again, some of these possibilities might be dangerous if they arrived on Earth.

Astrobiology is a science with an understanding of the principles and processes involved in the development of the universe and tools such as spacecraft and large budgets to put this understanding to use; for example, in sample return missions. But while there is every reason to avoid complacency about the possible dangers, at least there are the rudiments of an international control system in place. Such assurance cannot be given in regard to all aspects of synthetic biology, especially those working on the design of biological systems based on an alternative biochemistry. This, again, is a new science with an understanding of how life operates and the tools and money to put that understanding to use; for example, in the design and creation of new life forms.

13.1.1 Let's Give Life a Second Chance

"To understand life, it is necessary to build it from scratch," is the motto of synthetic biologists. Those who think of naturally evolved DNA as an unalterable biological axiom will be surprised by recent efforts to release life (as we know it) from its evolutionary constraints. So far, perceptions of synthetic biology are often dominated by the idea that engineers have taken over this part of biology and are busy working on the production of a library of standardized biological parts of natural systems (biobricks) which they will then be able to combine in different ways for various design purposes [5]. Such work is certainly being carried out by engineers, but synthetic biology is a diverse field of activity and also includes biologists and chemists who are trying to produce unnatural molecules and architectures [6] in order, eventually, to create artificial microbes of the kind of concern in the exobiology field of astrobiology. The most prominent research areas dealing with the creation of unnatural (alien) biological systems are protocells and xenobiology [7] (see Table 13.1).

Scientists working on protocells try to create life from the bottom up, by assembling relevant and necessary biochemical subunits. Many dif-

Table 13.1 Characteristics of the main research fields in chemical synthetic biology [6, 7, 8, 59]

	Protocells	Xenobiology
Aims	To construct viable approximations of cells; to understand biology and the origin of life	Using atypical biochemical systems for biological processes, creating a parallel form of life
Method	Theoretical modeling and experimental construction	Changing structurally conservative molecules such as the DNA
Techniques	Chemical production of cellular containers, insertion of metabolic components	Searching for alternative chemical systems with similar biological functions
Examples	Containers such as micelles and vesicles are filled up with genetic and metabolic components	DNA with different set of base pairs, nucleotides with different structural molecules

ficulties accompany this endeavor, but step-by-step small successes have been achieved (e.g. see Ref. [9]). These protocells show some but not all of the characteristics of life, and they can be considered as “limping cells” (Luisi, 2006, personal communication).

Once life is built from scratch, why not try something new? Based on the idea that life could have evolved differently scientists are now trying to design xenobiological systems. The focus of their efforts has been to come up with alternative biomolecules to sustain living processes. Areas of research include the chemical modification of DNA, polymerases, amino acids and proteins. One area of research is the identification of amino acid sequences (proteins) that have a stable architecture but do not occur in nature. Actually, there is only a tiny fraction of theoretical possible proteins occurring naturally, with many more theoretically possible but not-yet-assembled proteins. These so-called never-born proteins could provide a lot of useful novel functions for molecular biology [8, 10, 11]. Changing the translational mechanism from mRNA to proteins via tRNA and the ribosome is another focus of interest. A mutant *Escherichia coli* aminoacyl-tRNA synthetase was evolved to selectively aminoacylate its tRNA with an unnatural amino acid and site-specifically incorporate the unnatural amino acid into a protein in mammalian cells in response to an amber nonsense codon [7, 12].

Yet another area of work consists of modifying DNA by replacing its chemical building blocks, the (desoxy) ribose molecules, and the base pairs. The attempt to come up with an unnatural nucleic acd consisting of a different backbone was the more difficult one, but resulted in novel informational biopolymers such as:

TNA:	threose nucleic acid [13, 14];
GNA:	glycol nucleic acid [15];
HNA:	hexitol nucleic acid [16, 17];
PNA:	peptide nucleic acid [18, 19]; and
LNA:	locked nucleic acid[1] [20, 21].

On the other hand, experiments replacing or enlarging the genetic alphabet of DNA with unnatural base pairs lead to a genetic code that instead of four bases ATGC had six bases ATGCPZ [22, 23, 58]. In a recent study, 60 candidate bases (resulting in 3600 base pairs) were tested for possible incorporation in the DNA [24].

In respect to these recent efforts and further possibilities, the activities of some in the outer reaches of synthetic biology need careful examination. It is early days, perhaps, but the literature on chemical synthetic biology contains examples with obvious signs of success and promise of further constructive developments. Indeed, it is not unreasonable to suggest that we are much more likely to see “alien” species produced here on Earth before we have to deal with those brought from outer space!

13.2 SOCIETAL ISSUES IN CHEMICAL SYNTHETIC BIOLOGY

The successful design of unnatural biological systems or even “alien” species will definitely not go unnoticed outside the scientific community, and a number of societal issues might be triggered. On the one hand, the scientific results will be well received as a further important step towards understanding what life is and how it could have begun on Earth almost 4 billion years ago. It will also be seen as a powerful way to design new beneficial tools for molecular biology. The design of

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[1] The LNA is a nucleic acid analogue containing one or more LNA nucleotide monomers with a bicyclic furanose unit locked in an RNA-mimicking sugar conformation.

unnatural biochemical systems or even life forms, however, also raises several critical questions in the areas of:

- biosafety – concerns regarding the prevention of unintended consequences;
- biosecurity – dealing with potentially harmful misuse of unnatural biological systems;
- ethical, philosophical and religious questions – reflecting the moral implications of creating life; and
- intellectual property rights – whether this new form of life can be owned by someone.

A first discussion of these challenges is presented here.

13.2.1 Biosafety: Avoiding Unintended Consequences

The handling of (potentially dangerous) biological agents is regulated through existing guidelines and laws covering microorganisms and viruses (including those which have been genetically modified). The biological material is classified into four risk groups, and the risk assessment that provides the basis for the classification depends on factors such as pathogenicity, severity of disease, individual worker and community risk, host range, availability of treatment or prophylaxis, and endemicity[2] [25–29]. The challenge of risk assessment, however, lies in those cases where a serious health risk is suspected and full information on these factors is not available. In such a case the material should be treated as potentially hazardous (application of standard universal precautions).

13.2.1.1 Dealing with Extraterrestrial/Unnatural Biological Agents

Precautions are also advised when sample-return missions from outer-space objects (e.g. Mars, Titan, asteroids) are carried out. As quoted in Rummel *et al.* [30], the Space Studies Board (SSB) of US National Research Council concluded that:

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[2] Endemicity means if the biological agent is already present in the environment.

> samples returned from Mars by spacecraft should be contained and treated as potentially hazardous until proven otherwise

and further on:

> rigorous physical, chemical, and biological analyses (should) confirm that there is no indication of the presence of any exogenous biological entity.

In the recommendations by NASA a distinction is made between life detection and biohazard testing, as nonliving samples could also pose a hazard to Earth-life. According to the SSB, the initial evaluation of samples returned (from Mars) will focus on whether they pose any threat to the Earth's biosphere. The only potential threat posed by returned samples is the possibility of introducing a replicating biological entity of nonterrestrial origin into the biosphere. Only replicating entities (but not necessary living entities) pose a potential widespread threat, especially if they defy the natural, evolved defense mechanisms of Earth organisms. Nonreplicating entities can be considered a toxin and represent "only" a real threat to scientists or people who may be directly exposed to them, as the toxin would be diluted below a toxic concentration when released from the sample.

Similar considerations should be made with respect to unnatural biological systems (see Table 13.2). Non-self-replicating, rather simple agents can be considered and treated as new toxins (or pharmaceuticals); for example, third-type nucleic acids (e.g. HNA, LNA) that can act as steric blockers by duplex formation with mRNA [16, 20]. Greater caution, however, is necessary for self-replicating agents.

A (utopian?) worst-case scenario, for example, would be the design of a novel type of virus based on a different nucleic acid and using an unnatural reverse transcriptase. So far, however, unnatural nucleic acids

Table 13.2 Attempt to classify unnatural biochemical systems with respect to biosafety

Ability to self-replicate Complexity	No	Yes
Low	Novel toxins; e.g. steric blocker	Unnatural virus
High	Unnatural biological system, protocells	Unnatural life forms

cannot be recognized by natural polymerases, and one of the challenges is to find/create novel types of polymerase that will be able to read the unnatural constructs. At least on one occasion a mutated variant of the HIV-reverse transcriptase was found to be able to PCR-amplify an oligonucleotide containing a third-type base pair. Only two amino acids must be substituted in this natural polymerase optimized for the four standard nucleotides to create one that supports repeated PCR cycles for the amplification of an expanded genetic system. It is without doubt surprising to find a useful polymerase to be so close in "sequence space" to that of the wild-type polymerase [22]. Finding such altered but working polymerases in the evolutionary neighborhood clearly raises the necessity to ask what should be done once an unnatural replicating system has been created in the laboratory.

Sample return missions from non-Earth space objects must place their samples in special sample receiving facilities (SRFs) that can manage to prevent contamination of terrestrial material from the sample and that can maintain a strict biological containment for the sample. Requirements for such an SRF are even higher than that for high-risk biosafety Level 3 and 4 facilities, representing the strictest forms of biological containment. NASA concluded that a facility that meets the strict requirements of such an SRF is not available anywhere in the world [30]. In other words, a sample-return mission with potential biological material would not have an adequate place to deposit and investigate its samples. But while the strictest containment rules are foreseen for extraterrestrial unnatural biological agents, this is not the case for terrestrial unnatural biological agents. "Sample-return missions from Earth," such as synthesis of third-type nucleic acid, for example, are carried out in BSL 1 or 2 laboratories as current regulations do not foresee a stricter handling of this material. After all, unnatural biological systems are not mentioned by the approved list of biological agents/select agent list (e.g. see Refs [26, 31]).

13.2.2 Biosecurity: Preventing Hostile Misuse of Chemical Synthetic Biology

A major difference between astrobiology and chemical synthetic biology is that it is very unlikely that anyone involved in astrobiology would yet have in mind the hostile use of any life-forms found in space, but there is a long history of major state-level offensive biological weapons programs ever since the microbial nature of infectious diseases was discovered by scientists like Koch and Pasteur towards the end of the nineteenth century [32, 33], and it is probable that some such programs persist today [34]. In looking forward to a malign future in which there is an offensive–defensive arms race based on the new biotechnology, US military analysts envisaged three overlapping phases [35]. The first would involve the classical agents, such as anthrax, used in previous programs. However, there are few such agents with ideal properties for biological warfare; thus, the defense would eventually be able to cope. For that reason, the offense would move to modify the agents; for example, by using genetic engineering to make them resistant to antibiotics or difficult to detect in standard tests. Again, however, there are only a limited number of modifications that can be made; so, theoretically, the defense would again catch up.

As this century progresses, however, more and more of life's fundamental processes will become understood and then, these analysts suggest, the offense will turn its attention not to the agent but to the target that they wish to attack. The analysts envisage "an entirely new class of fully engineered agents ... advanced biological warfare (ABW) agents" and suggest that:

> ... Emerging biotechnologies likely will lead to a paradigm shift in BW agent development; future biological agents could be rationally engineered to target specific human biological systems at the molecular level ...

As there are a very large number of physiological processes that could be targeted to cause incapacitation or death, and many ways in which each could be attacked, it seems probable that, if we allow such an arms race to proceed, there will be a long period of offensive supremacy.

Synthetic biologists involved in efforts to bring engineering disciplines into biology have not been ignorant of such dangers [36] and have suggested a range of possible new controls, such as the systematic checking of orders for DNA sequences by manufacturing companies. It is also clear that the States Parties to the Biological and Toxin Weapons Convention (BTWC) have agreed that all biological entities, whatever their mode of production, are covered by the prohibitions in the convention [37]. However, the situation may not be so clear if synthetic biologists create alien species that some might not regard as biological entities.

Article I of the BTWC states that:

> Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or other wise acquire or retain:
>
> (1) Microbial or other biological agents, or toxins whatever their origin or methods of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.

As Jürgen Altmann argued in his analysis of the military implications of nanotechnology, while a fully artificial toxin (not known in nature) would not be covered by Article I of the BTWC, it would be captured by the provisions of the recent Chemical Weapons Convention [38]. More seriously, he suggested that a fully or partially artificial microbe – for example, one not based on the usual biochemistry including the usual DNA coding system – might not be universally regarded as being covered by the BTWC because it was not a natural microbe. Such an artificial "microscopic" organism would also not be covered by the Chemical Weapons Convention, as it would be much more complex than a chemical. On this reading, an arms race in ABW would be unconstrained in regard to such artificial microscopic organisms.

Such differences of interpretation in regard to the prohibition of chemical and biological weapons would not be unique in the historical record. As Mark Wheelis has argued in regard to German biological sabotage in World War I [39], the German General Staff probably regarded the prohibition at that time as only covering anti-human biological warfare and their substantial anti-animal sabotage campaign as, therefore, being quite legal. Again, today, there are clearly differences of opinion as to the meaning of Article II.9(d) of the Chemical Weapons Convention and whether the peaceful exemption for "Law enforcement including domestic riot control" allows the development of new forms of incapacitating chemical weapons and, thus, provides a route by which the whole prohibition may be subverted [40].

13.2.3 New Forms of Life, Ethical Aspects of Chemical Synthetic Biology

Ethical issues in synthetic biology have been discussed at an unusually high rate, considering the early developmental stage of the technology [41]. The discussion is very often led by topics in bioengineering or synthetic genomics, resulting in debates on the methods applied, as well as different applications and distributions of the technology. However, since synthetic biology is a multi-approach technology, it is important to make clear which branch is addressed in the assessment. In this chapter we focus on ethical issues related to chemical synthetic biology as it has been defined at the outset. The protocell approach and projects on unnatural biochemical systems have been used before they have been understood as a part of synthetic biology, and certainly the integration into this emerging technology should not serve as a reason to look for ethical issues where none has been detected before. However, the context of synthetic biology does shed a new light on these approaches. The idea of designing new forms of life comes to the fore and combination with other synthetic biology approaches seems to be obvious, or at least thinkable, and might lead to the development of new types of synthetic biology products.

The aim of none of the other synthetic biology approaches is as close to the idea of "creating life from the scratch" as is the case for the chemical synthetic biology approaches. Chemical synthetic biology can result in fundamentally novel forms of life based on new types of molecular biology. Therefore, it challenges our concept of life indeed, similar to the idea of extraterrestrial life, by raising the question about the basic features of life and whether life with a completely altered biochemistry should be regarded in the same way as traditional forms of life. In this article we address in more detail what protocells or unnatural genomes can tell us about life and what consequence the establishment of these products of chemical synthetic biology might have on our ethical and philosophical understanding of life.

13.2.3.1 What is life?

Before addressing the question of what chemical synthetic biology can tell us about life, it is necessary to clarify what we mean by the term "life." Several interpretations are possible for instance from a biological, a philosophical or a religious point of view.

Even when restricted to its biological features, a definition of life is not easily established; questions such as whether the life of an individual or that of a population should be described and what features of life are the most important ones have been discussed extensively (e.g. as summarized in Ref. [42], pp. 17–23 and Ref. [43], pp. 197–205). Some authors doubt that it is possible to define life adequately because the conditions that are required to establish a definition of life, such as the necessary and sufficient features, are not available at our current state of knowledge [44]. Others point out that, on linguistic grounds, it is difficult to find a definition of life because there are different types of definitions that tend to, but should not be, mingled – for example, a lexical definition, which attempts to give the meaning of a word and an operational definition that sets out parameters to verify whether the term can be applied [45].

However, researchers working in the fields of synthetic biology or exobiology need to be able to decide under which conditions an object can be considered "alive." As suggested by Oliver and Perry [45], we start, therefore, from different "working descriptions" which do not necessarily claim to be exhaustive definitions. NASA uses a characterization of life which focuses on life as feature of a population:

> "Life is a self-sustained chemical system capable of undergoing Darwinian evolution" [46].

This description has been refined by P.L. Luisi as follows:

> "Life is a system which is self-sustaining by utilizing external energy/nutrients owing to its internal process of component production and coupled to the medium via adaptive changes which persist during the time history of the system" [47].

This understanding of life focuses on the individual organism and comprises the idea of autopoiesis, a notion that has been created by Maturana and Varela specially to describe life; it means self-production and self-organization [48].

Taken together, these working descriptions of life are based on empirically testable biological criteria that distinguish living from inert systems. However, are biological criteria sufficient to describe what we mean by the notion "life"? There is for instance a widespread notion that there are aspects of human life, such as human dignity, which cannot be explained in scientific terms [49, 50]. Human dignity asks for a special form of respect in the contact with others. Every person has certain rights with corresponding duties and responsibilities to other people. However, descending the phylogenetic tree of life, such features get more and more questionable. Does the life of a cat have meaning? Does a rose have dignity? Do we owe any kind of respect to living beings in general? And if we do, what would this respect be based on? The answers to these questions are related to our concept of life.

In Western culture, the concept of life is, for example, influenced by ideas of an immortal soul in some types of living organism (such as human beings). Furthermore, because life originally existed in parallel and not under control of human beings, it is very often directly related to "nature" and "environment." Finally, life is the feature we share with all the other organisms, which gives this property even in microorganisms a particular significance. In these meanings, the term "life" has a positive connotation; it is not purely descriptive, but comprises a normative aspect. Ethicists call such terms with a descriptive and a normative aspect "morally thick concepts";[4] "life" belongs to these concepts.

13.2.3.2 Value of life

The above-mentioned normative components are closely related to an intrinsic value in life.[3] There are many different theories of environmental ethics which argue for the assignment of intrinsic value at different phylogenetic levels of life. Many positions assign intrinsic value only to human beings (e.g. Kant) and others extend it to sentient beings (e.g. Bentham and Singer), but some do argue that all living organisms are carriers of intrinsic value (e.g. Schweitzer, Attfield, and Taylor). Interestingly, for some authors speaking of intrinsic value in lower forms of life, this value seems to be related to the naturalness of life. Paul Taylor, for example, distinguishes between life in the environment and life in bioculture. Whereas in the first category the intrinsic value[5] of living organisms is the only value that needs to be considered, in the second type this value has to be balanced against the instrumental value that living organisms have for human beings. Paul Taylor states [51], pp. 57–58:

> It becomes a major responsibility of moral agents in this domain of ethics to work out a balance between effectiveness in producing human benefits, on the one

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[3] The term "intrinsic value" is used in different meanings. In this context we understand it in a very broad sense as the claim that certain entities are morally considerable (have moral standing). This means that we cannot deal arbitrarily with any carrier of intrinsic value, but instead we should ask how we are allowed and required to treat it, because we owe moral respect to such an entity.

[4] The term "morally thick concept" was introduced by Bernhard Williams; such terms describe a certain person or fact, but at the same time imply an evaluative or normative component; Williams gives coward, lie, brutality, and gratitude as examples of morally thick concepts [57], pp. 140–143.

[5] Paul Taylor speaks of "inherent worth" when he means what we are calling intrinsic value.

> hand, and proper restraint in the control and manipulation of living things, on the other.

This constriction indicates that not even for a biocentrist[6] is the intrinsic value of microorganisms absolute.

13.2.4 Intellectual Property Rights

Little has been said about how current intellectual property rights (IPRs) will shape the development and use of unnatural biological systems, and how unnatural biological systems will shape the way IPR are applied. Articles 52 and 53 of the European Patent Convention (EPC) stipulate that European patents are granted for inventions that are new, involve an inventive step, and are susceptible of industrial application [52]. In a similar way, the US Patent and Trademark Office only grants a patent if the invention is new, not obvious (that means it cannot exist in a natural state like a plant, animal), and must be useful [53]. Different ownership regimes exist internationally when it comes to patenting fragments of DNA. While it is not possible to own random pieces of DNA, a DNA with a useful function can be owned in some countries [54]. While it is not possible to own random fragments of DNA without known function, we do not know if it would be possible to own random fragments of, let us say, TNA or HNA, or any other third-type nucleic acid. In other words, is it possible to "copy and paste" the complete genetic diversity of life from DNA onto a chemically different informational polymer and then patent it? Can artificial genetic alphabets undermine the exclusion of broad patents of life?

Going from DNA to species, the European Patent office states that plants and animal varieties are excluded from patentability; however, microbiological processes and products thereof are not excluded. It seems that a minimal life form, a bacterial chassis, can in principle be patented. In the USA the team of Craig Venter has already filed a patent application for a minimal bacterial genome (US Patent application number 20070122826). A similar treatment can be expected for simple protocells; in other words, they seem not to be excluded from patentability as long as their invention is not contrary to "ordre public" or morality.

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[6] "Biocentrism" considers all forms of life as having intrinsic value.

13.3 CONCLUSIONS

In this chapter we have attempted to review some of the societal impacts and novel aspects of synthetic biology, particularly protocells and xenobiology. We have asked whether work in these fields is sufficiently guarded by measures of biosafety and biosecurity, whether we have a sufficiently shared understanding of the ethics of the creation of life, and what IPR issues might arise as technology matures. Even this initial review leads to some interesting implications and questions for those working in the fields and those who might be affected by the work.

13.3.1 Biosafety

Currently, no living organisms based on an unnatural nucleic acid are known to exist. But the combination of an extended genetic code and an adequate novel polymerase could certainly lead to the next step towards implementing an artificial genetic system in, for example, *E. coli* [22]. The creation of such unnatural organisms will be done in increments, giving us some, but not too much, time to find out how we could assess the potential risk that these alien organisms could bring and how we should contain them until they are understood well enough to release them to BSL 1 and 2 laboratories or even beyond.

Regulators and scientists are aware that the list and classification of the biological agents must be examined regularly and revised on the basis of new scientific data [25]. The scope and impact of the ongoing research, however, would require a more proactive anticipatory approach, comparable to what NASA has done in anticipating a (possible) sample-return mission of extraterrestrial life.

The probable response to such a suggestion is likely to be, first, that "alien" species are unlikely to be competitive against the highly evolved natural species here on Earth. It will also be argued that nothing should be done to restrict work that has already produced major benefits, such as the Bayer VERSANT branched DNA diagnostic assay for HIV and hepatitis viruses [6]. These are strong arguments, but they do not give enough weight to the possibility that these new species could well be able to survive on Earth, especially as very little information is available on them and scientific predictions on the fate of these organisms in the environment will hardly be possible.

13.3.2 Biosecurity

At the very least, synthetic biologists should look carefully at whether the BTWC can be strengthened with their support through, for example, an agreed understanding at the 7th Review Conference in 2011 that Article I does indeed cover all such artificially created organisms, not just natural or modified natural organisms [38].

Of course, nobody is arguing that scientists have the sole responsibility for preventing the hostile misuse of modern biology. A web of preventive policies has to be constructed by many different actors in many different dimensions [55]. Yet scientists do have a particular responsibility in regard to protecting what they are creating and need to be aware of their obligations under the BTWC and in particular the ongoing discussions among State Parties related to the generation of a culture of responsibility among scientists [37].

This will involve scientists becoming much more involved in discussions of biosafety and biosecurity, but also to be aware of the elements of a new culture of responsibility, such as oversight, codes of conduct, and a much greater focus in education and professional training on the problem of dual use – that is, hostile applications of the results of benignly intended work.

13.3.3 Bioethics

Chemical synthetic biology brings bioethics into chemistry. Bioethics in its broader sense is

> "the study of the moral, social and political problems that arise out of biology and the life sciences generally and involve, either directly or indirectly, human wellbeing" [56].

Independently of potential future applications of chemical synthetic biology in, for example, medicine, interesting bioethical discussions of this field concern the occurrence and meaning of "life" in products of chemical synthetic biology. The synthesis of living systems from scratch or the designing of fundamentally different forms of life raises questions about the meaning of the concept "life" in our society. It reveals that "life" is a multilayer concept implying descriptive, but also normative, aspects. It is an interesting question how and whether normative aspects of life, such as an intrinsic value in certain living organisms, is related to the biological criteria of life and whether or under which conditions such normative issues might apply to products of synthetic biology such as protocells.

In chemical synthetic biology, human creativity, human purposes, and human priorities are the principles deciding about the existence of living organisms. Synthetic organisms resulting from these technologies may fulfill the biological criteria of life; however, this does not necessarily mean that they also fulfill its normative criteria. Some of these features, related, for example, to an intrinsic value or the fact that life is something that exists in parallel to and not because of human beings, may not be found in synthetic organisms.

Therefore, it would be sensible to clarify what type of life ethicists, philosophers, biologists, synthetic biologists, and the public are talking about. Do they understand "life" as something related to an intrinsic value, to naturalness or to biological criteria? If these different interpretations of the term "life" are clearly separated, then a multi-stakeholder discussion of synthetic life might bypass several misunderstandings, which are currently part of the debate. On the one hand, representatives of positions arguing life was something special carrying intrinsic value that should or must *not* be "created" by humans might take into account that synthetic life may, per definition, belong to another category exactly *because* it is designed by human beings. Therefore, it may ask for evaluation based on other standards than natural life, similar to the difference between environmental ethics and the ethics of bioculture suggested by Paul Taylor. Furthermore, synthetic life at a single-cell level should be distinguished from synthetic life in higher organisms. Synthetic biology in higher organisms may raise new types of ethical issue; however, at this stage chemical synthetic biology is not attempting to design or create higher organisms. On the other hand, those scientists who argue that life can be fully explained as soon as one is able to build it may consider that there might be aspects of life that cannot be explained scientifically. In summary, the term "life" is loaded with many different meanings. New scientific developments, such as synthetic biology or exobiology, are adding additional interest and signification to this list. However, not every application of this term necessarily refers to all its different meanings, this may lead to a complicated but fascinating diversification of our concept of life.

13.3.4 Intellectual Property Rights

Chemical synthetic biology deals with biological systems and simple life forms, not (yet) with multicellular organisms. But looking into a possible future, how would plants and animals that are based on a different genetic alphabet be treated by the patent system? Would they be treated in a similar manner to natural life forms and excluded from patentability, or would they not be considered animals and plants and, therefore, not be excluded from patentability? Which definition of life will be used in order to make the decision: the biological, ethical, or philosophical definition?

Clearly, the ethical, legal, and social implications of the outer reaches of synthetic biology will require a great deal more attention before we have even the level of assurance that we now have in regard to the implications of exobiology – and the situation in regard to that field can hardly be considered to be satisfactory.

REFERENCES

1. Race, M.S. and Randolph, R.O. (2002) The need for operating guidelines and a decision making framework applicable to the discovery of non-intelligent extraterrestrial life. *Advances in Space Research*, **30** (6), 1583–1591.
2. Race, M.S. (2007) Societal and ethical concerns, in *Planets and Life: The Emerging Science of Astrobiology* (eds T.S. Woodruff III and J.A. Baross), Cambridge University Press, Cambridge, Chapter 24, p. 483.
3. NASA (2008) About planetary protection. http://planetaryprotection.nasa.gov/pp/about/ (last access 2 December 2008).
4. Ward, P.D. and Benner, S.A. (2007) Alien biochemistries, in *Planets and Life: The Emerging Science of Astrobiology* (eds T.S. Woodruff III and J.A. Baross), Cambridge University Press, Cambridge, Chapter 27, pp. 537–544.
5. Aldhous, P. (2006) Redesigning life: meet the bio-hackers. *New Scientist*, (2552), 43–48.
6. Benner, S.A. and Sismour, A.M. (2005) Synthetic biology. *Nature Reviews Genetics*, **6**, 533–543.
7. Schmidt, M. (2010) Xenobiology: a new form of life as the ultimate biosafety tool. *BioEssays*, **32** (4), 322–331.
8. Luisi, P.L. (2007) Chemical aspects of synthetic biology. *Chemistry & Biodiversity*, **4** (4), 603–621.
9. Szostak, J.W., Bartel, D.P., and Luisi, P.L. (2001) Synthesizing life. *Nature*, **409**, 387–390.
10. Luisi, P.L., Chiarabelli, C., and Santo, P. (2006) From never born proteins to minimal living cells: two projects in synthetic biology. *Origins of Life and Evolution of the Biosphere*, **36**, 605–616.
11. Seelig, J. and Szostak, J.W. (2007) Selection and evolution of enzymes from a partially randomized non-catalytic scaffold. *Nature*, **448**, 828–831.

12. Liu, W., Brock, A., Chen, S. *et al.* (2007) Genetic incorporation of unnatural amino acids into proteins in mammalian cells. *Nature Methods*, **4** (3), 239–244.
13. Schöning, K.-U., Scholz, P., Guntha, S. *et al.* (2000) Chemical etiology of nucleic acid structure: the α-threofuranosyl-(3′→32′) oligonucleotide system. *Science*, **290**, 1347–1351.
14. Chaput, J.C., Ichida, J.K., and Szostak, J.W. (2003) DNA polymerase-mediated DNA synthesis on a TNA template. *Journal of the American Chemical Society*, **125**, 856–857.
15. Zhang, L., Peritz, A., and Meggers, E. (2005) A simple glycol nucleic acid. *Journal of the American Chemical Society*, **127** (12), 4174–4175.
16. Vandermeeren, M., Préveral, S., Janssens, S. *et al.* (2000) Biological activity of hexitol nucleic acids targeted at Ha-ras and intracellular adhesion molecule-1 mRNA. *Biochemical Pharmacology*, **59**, 655–663.
17. Declercq, R., Van Aerschot, A., Read, R.J. *et al.* (2002) Crystal structure of double helical hexitol nucleic acids. *Journal of the American Chemical Society*, **124** (6), 928–933.
18. Wittung, P., Nielsen, P.E., Buchardt, O. *et al.* (1994) DNA-like double helix formed by peptide nucleic acid. *Nature*, **368**, 561–563.
19. Ng, P.S. and Bergstrom, D.E. (2005) Alternative nucleic acid analogues for programmable assembly: hybridization of LNA to PNA. *Nano Letters*, **5** (1), 107–111.
20. Vester, B. and Wengel, J. (2004) LNA (locked nucleic acid): high-affinity targeting of complementary RNA and DNA. *Biochemistry*, **43** (42), 13233–13241.
21. Kauppinen, S., Vester, B., and Wengel, J. (2005) Locked nucleic acid (LNA): high affinity targeting of RNA for diagnostics and therapeutics. *Drug Discovery Today: Technologies*, **2** (3), 287–290.
22. Sismour, A.M., Lutz, S., Park, J.-H. *et al.* (2004) PCR amplification of DNA containing non-standard base pairs by variants of reverse transcriptase from human immunodeficiency virus-1. *Nucleic Acids Research*, **32**, 728–735.
23. Yang, Z., Hutter, D., Sheng, P. *et al.* (2006) Artificially expanded genetic information system: a new base pair with an alternative hydrogen bonding pattern. *Nucleic Acids Research*, **34** (21), 6095–6101.
24. Leconte, A.M., Hwang, G.T., Matsuda, S. *et al.* (2008) Discovery, characterization, and optimization of an unnatural base pair for expansion of the genetic alphabet. *Journal of the American Chemical Society*, **130** (7), 2336–2343.
25. EC (2000) Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000.
26. HSE (2004) The Approved List of Biological Agents. http://www.hse.gov.uk/pubns/misc208.pdf (last access October 2010).
27. WHO (2004) Laboratory Biosafety Manual, 3rd edn. http://www.who.int/csr/resources/publications/biosafety/Biosafety7.pdf (last access October 2010).

28. Fleming, D.O. (2006) Risk assessment of synthetic genomics: a biosafety and biosecurity perspective, in *Working Papers for Synthetic Genomics: Risks and Benefits for Science and Society* (eds M.S. Garfinkel, D. Endy, G.L. Epstein and R.M. Friedman), J. Craig Venter Institute/CSIS/MIT, pp. 105–164.
29. ABSA (2008) Risk Group Classification for Infectious Agents. American Biological Safety Association. http://www.absa.org/riskgroups/index.html (last access October 2010).
30. Rummel, J.D., Race, M.S., DeVincenzi, D.L. *et al.* (2002) A Draft Test Protocol for Detecting Possible Biohazards in Martian Samples Returned to Earth, NASA/CP-2002-211842, Washington, DC. http://spacescience.nasa.gov/admin/pubs/marssamples/draft_protocol.pdf (last access 2 December 2008).
31. CDC (2008) HHS and USDA Select Agents and Toxins. http://www.selectagents.gov/resources/List%20of%20Select%20Agents%20and%20Toxins_111708.pdf (last access October 2010).
32. Geissler, E. and Van Courtland Moon, J.E. (eds) (1999) *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945*, Oxford University Press, Oxford.
33. Wheelis, M.L., Rozsa, L., and Dando, M.R. (2006) *Deadly Culture: Bioweapons Since 1945*, Harvard University Press, Cambridge, MA.
34. Kerr, P.K. (2008) Nuclear, Biological, and Chemical Weapons and Missiles:Status and Trends. CRS Report for Congress. Congressional Research Service, United States.
35. Petro, J.B., Plasse, T.R., and McNulty, J.A. (2003) Biotechnology: Impact on biological warfare and biodefense. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, **1** (3), 161–168.
36. Garfinkel, M., Endy, D., Epstein, G.L., and Friedman, R.M. (2007) Synthetic Genomics–Options for Governance. http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf (last access October 2010).
37. United Nations (2006) Final declaration. Sixth Review Conference of the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. Geneva.
38. Altmann, J. (2006) *Military Nanotechnology: Potential Applications and Preventive Arms Control*, Routledge, London.
39. Wheelis, M.L. (1999) Biological sabotage in World War I, in *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945* (eds E. Geissler and J.E. Van Courtland Moon), Oxford University Press, Oxford, pp. 35–62 in Geissler and van Courtland Moon.
40. Pearson, A.M., Chevrier, M.I., and Wheelis, M.L. (2007) *Incapacitating Biochemical Weapons: Promise or Peril?* Lexington Books, Boulder, CO.
41. Presidential Commission for the Study of Bioethical Issues. (2010) New Directions: The Ethics of Synthetic Biology and Emerging Technologies. www.bioethics.gov

42. Luisi, P.L. (2006) *The Emergence of Life*, Cambridge University Press, Cambridge.
43. Popa, R. (2004) *Between Necessity and Probability: Searching for the Definition and Origin of Life*, Springer, Berlin.
44. Cleland, C.E. and Chyba, C.F. (2002) Defining "life". *Origins of Life and Evolution of the Biosphere*, 32 (4), 387–393.
45. Oliver, J.D. and Perry, R.S. (2006) Definitely life but not definitively. *Origins of Life and Evolution of the Biosphere*, 36 (5–6), 515–521.
46. Joyce, G.F. (1994) Foreword, in *Origins of Life: The Central Concepts* (eds D.W. Deamer and G.R. Fleischacker), Johnes and Bartlett, Boston, MA, pp. xi–xii.
47. Luisi, P.L. (1998) About various definitions of life. *Origins of Life and Evolution of the Biosphere*, 28 (4–6), 613–622.
48. Varela, F.G., Maturana, H.R., and Uribe, R. (1974) Autopoiesis: the organization of living systems, its characterization and a model. *Currents in Modern Biology*, 5 (4), 187–196.
49. Hollinger, D. (2004) Life, sanctity of, in *Encyclopedia of Bioethics*, Vol. 3 (ed. S. Post), Macmillan Reference USA, New York, pp. 1402–1406.
50. Metz, T. (2008) The meaning of life, in *The Stanford Encyclopedia of Philosophy* (ed. E.N. Zalta), Metaphysics Research Lab, Stanford, CA http://plato.stanford.edu/archives/fall2008/entries/life-meaning (last access October 2010).
51. Taylor, P. (1986) *Respect for Nature*, Princeton University Press, Princeton, NJ.
52. EPO (2008) About Patents. http://www.epo.org/patents/Grant-procedure/About-patents.html (last access October 2010).
53. USPTO (2008) General Information Concerning Patents. http://www.uspto.gov/web/offices/pac/doc/general/index.html (last access October 2010).
54. Oye, K.A. and Wellhausen, R. (2009) The intellectual commons and property in synthetic biology, in *Synthetic Biology. The Technoscience and Its Societal Implications* (eds M. Schmidt, A. Kelle, A. Ganguli-Mitra and H. de Vriend), Springer Academic Publishing, pp. 121–140.
55. International Committee of the Red Cross (2002) *Appeal of the International Committee of the Red Cross on Biotechnology, Weapons and Humanity*, ICRC, Geneva.
56. Frey, R.G. (1998) Bioethics, in *Routledge Encyclopedia of Philosophy* (ed. E. Craig), Routledge, London. http://www.rep.routledge.com/article/L008 (accessed 17 December 2008) (subscriber log in required).
57. Williams, B. (1985) *Ethics and the Limits of Philosophy*, Fontana, London.
58. Yang, Z., Sismour, A.M., and Sheng, P. *et al.* (2007) Enzymatic incorporation of a third nucleobase pair. *Nucleic Acids Research*, 35 (13), 4238–4249.
59. O'Malley, M., Powell, A., Davies, J.F., and Calvert, J. (2008). Knowledge-making distinctions in synthetic biology. *BioEssays*, 30 (1), 57.

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