Institute on Science for Global Policy

Safeguarding the Genetic Firewall with Xenobiology**

Markus Schmidt, Ph.D.
Founder
Biofaction KG, Vienna, Austria

Summary

While progress is being made in synthetic biology to make biology easier to engineer, the safety regulations and risk assessment practices will soon be rendered outdated and inadequate to handle upcoming developments of synthetic biology functions, organisms, and products. Xenobiology, the science of biological systems made out of alternative biochemical structures, may provide a new set of tools to establish an innovative solution, a genetic firewall, to future biosafety challenges. This genetic firewall will provide a stronger safety framework than would a series of small ad hoc fixes to a set of regulations designed for genetic engineering. Decisive and collaborative action by scientists, policy makers, and other stakeholders is needed to face the medium- to long-term biosafety risks of synthetic biology.

Current realities

The potential future release of deeply engineered or novel synthetic microorganisms raises the issue of their intentional or accidental interaction with the environment. Containment systems, risk assessment, and safety regulations designed for genetic engineering in the 1980s and ’90s, for the purpose of limiting the spread of genetically engineered organisms and their recombinant traits, are still largely viewed by regulators and scientists as sufficient for contemporary synthetic biology products.

Progress in synthetic biology is expected to yield a staggering growth in the number of new biological functions and modified organisms with useful purposes. These developments will sooner or later pose a significant problem for established biosafety and risk assessment practices. A technological development that is outpacing its safety regulation is going to end up in (i) a series of unintended consequences and unforeseen accidents, (ii) a legal bottleneck for further product development because of a lack of a clear legal and regulatory framework, and/or (iii) increasing, and well justified, public resistance toward synthetic organisms if they are not considered to be “safe enough.” So far, no safety mechanism is available to provide a sustainable solution to this dilemma. Past suggestions such as so-called “suicide circuits” (that would kill the cell once it escapes into the environment) have failed to provide a sufficient degree of safety for industrial, medical, or environmental use. No strategy beyond the decades-old approach to biological containment is currently envisaged, despite significant investments and first successes in synthetic biology that have made biology easier to engineer.

Scientific opportunities and challenges

Most synthetic biologists try to convert biology into an engineering discipline by redesigning *existing*, natural biological systems for useful purposes. This means that synthetic biologists are using genes found in nature or designing new ones that closely resemble natural genes. Some bioengineers, however, are not satisfied with the biochemical substrates found in nature and try to construct new forms of life, called xenobiology, that have no counterpart in the extant world.

The synthesis of alternative biological structures focuses mostly on the three universal molecules: DNA, RNA and proteins. Recent research shows, for example, that all subunits of the DNA (base, deoxyribose, and phosphate group) can be replaced by alternative chemical structures. A DNA with three instead of only two base pairs has been made, and other carbon ring structures such as hexose or cyclohexenyl were incorporated to give rise to HNA and CeNA respectively (for all non-DNA, non-RNA molecules the term XNA is used, which stands for xeno nucleic acids). It was even possible to incorporate non-natural amino acids into proteins, so they are made up of 21 or 22 instead of 20 amino acid building blocks. First attempts have been made to come up with a biochemistry that has the opposite chirality of natural building blocks. So, instead of using left-handed proteins, future "mirror life forms" might use right-handed proteins. These experiments have mainly been carried out *in vitro* and very few if any (depending on the definition) living organisms exist with an altered biochemistry. However, sooner or later we will see the construction of new-to-nature or xenobiological systems that are increasingly farther away from their natural counterparts.

Xenobiology provides three main opportunities

1. <u>Better understanding of the origin of life.</u> Looking at all the possible alternatives to "life as we know it," the different variants of XNA, the hundreds of amino acids not used in proteins, the universal genetic code, or the selection of one type of chirality, the questions are: Why was this basic chemical make-up evolutionarily successful while others were not? Were these chemistries more robust, more likely to emerge under the conditions of early Earth or was it by chance? And, is there room for an artificial biodiversity?
2. <u>More efficient industrial biotechnology production systems.</u> Although Earth has experienced billions of years of evolutionary trial and error, nature has (by far) not "tested" all possible biological systems. This means that it is likely possible to find new and more efficient biological functions than those provided by nature. This approach constitutes a promising way to design a new class of chemically diversified biocatalysts for industrial, medical, and environmental biotechnology. Industrial strains with a fundamentally different genetic code would suddenly be immune to natural phages or viruses.
3. <u>A solution to the upcoming biosafety challenges.</u> Xenobiological systems could be used as a fundamentally new biosafety system, since they are not capable of horizontal gene transfer between the natural and new-to-nature organisms, the separation from the extant biology acts like a "genetic firewall" (see Figure 1).

While the first point addresses deep philosophical questions, the last two points deal with real world implications for society, economy, industry, policy, and the environment. The use of xenobiology in industry, however, will primarily depend on whether it will be safe to use. Therefore, it ultimately comes down to xenobiology as a way to provide a genetic firewall to improve biosafety.

Constructing a xenobiological organism and a genetic firewall is a very difficult task, and beyond the current capabilities of science and engineering. Not only is it difficult, it might provide hardly any return of investment over the short-term future, since the establishment of a xenobiological toolkit and expertise will take some time before reaching a level that is remotely comparable to bioengineering with traditional biochemistries. But over the mid- and long-term the investment will pay off, both in terms of increased efficiency of biotechnological processes and in terms of providing a safe and reliable mechanism that avoids unintended consequences, accidents, and legal uncertainties.

Policy issues

Synthetic biology, extrapolated into the near future, will result in radical increase in the number of synthetic biological functions, organisms, and products. Policy makers need to realize that these developments will render the current regulatory safety framework (designed for genetic engineering) outdated in a not-so-distant future.

- The response to this development may either be (i) inert, ad hoc, tactical adaptations of obsolete safety regulations and risk assessment without a clear strategy, or (hopefully) (ii) a collaborative approach that leads to a strategic vision of how to deal with upcoming safety challenges of synthetic biology, to avoid biological accidents, legal uncertainties, and safety-based public resistance. Adaptations may still be needed, but this time they would be based on a solid framework.

- The genetic firewall could at the same time improve industrial processes and establish safer biosystems, but only if a collaborative action among international scientists, policy makers, and other stakeholders can be established.

- Instead of resuscitating the limited concept of genetic suicide circuits, scientists, safety experts, and policy makers may discuss radical innovations as a strategic answer to upcoming biosafety challenges. The pros and cons of xenobiology and the support and deployment of the genetic firewall need to be discussed among international stakeholders.

- Decisive action to radically improve future biosafety issues is required from policy makers, concerned with the governance of biotechnology in Europe and the United States, in the form of (i) support to the technical development of a genetic firewall, and (ii) preparation of a regulatory framework that details in which circumstances the genetic firewall has to be deployed.

References

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*** A policy position paper prepared for presentation at the conference on 21st Century Borders/Synthetic Biology: Focus on Responsibility & Governance, convened by the Institute on Science for Global Policy (ISGP) December 4–7, 2012, at the Hilton El Conquistador, Tucson, Arizona.*

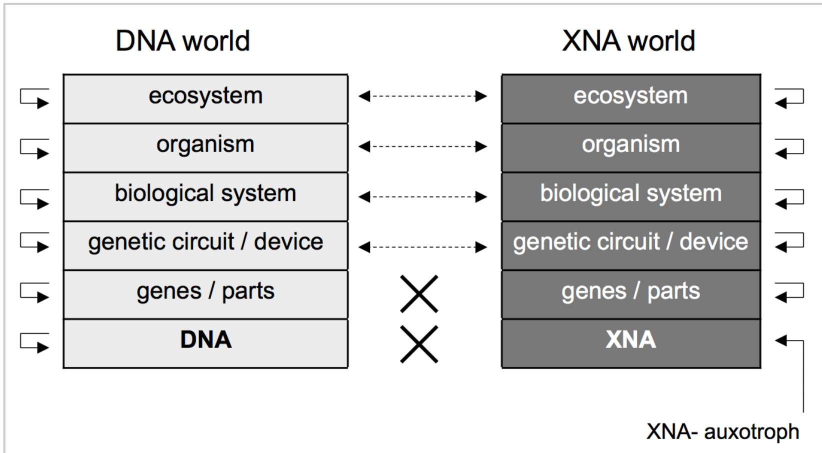

Figure 1: DNA and XNA organisms would be able to interact on the level of whole organisms but would not exchange genetic material through horizontal gene transfer or via sexual reproduction (genetic firewall). Also, the XNA world needs to be completely dependent on external supply of essential chemicals that it cannot synthesize itself (XNA-auxotrophy).