Current Synthetic and Systems Biology

Wei, et al., Curr Synthetic Sys Biol 2014, 2:3
http://dx.doi.org/10.4172/2332-0737.1000e115

Short Communication Open Access

Biosafety Considerations of Synthetic Biology: Lessons Learned from Transgenic Technology

Wei W[1*], **Pei L**[2], **Schmidt M**[2] **and Xu J**[3]

[1]*Institute of Botany, Chinese Academy of Sciences, Beijing 100093, China*

[2]*Biofaction KG, 1030 Vienna, Austria*

[3]*Chinese Research Academy of Environmental Sciences, Beijing 100012, China*

[*]**Corresponding author:** Wei Wei, Institute of Botany, Chinese Academy of Sciences, Beijing 100093, China, Tel : +861062836275; Fax: +861062836287; E-mail: weiwei@ibcas.ac.cn

Rec Date: Aug 26, 2014, **Acc Date:** Nov 5, 2014, **Pub Date:** Nov 8, 2014

Short Communication

The commercialization of transgenic crops has expanded rapidly in the past decade. However, there are still debates and concerns about the safety issues of these crops for human health and their environmental impact. Debates have also focused on the socioeconomic consequences of the monopoly of seed production of a few companies. While adhering to national and international regulations to ensure the health of people and the environment, the broad applications of this technology would be difficult without addressing the public concerns of biosafety and other related issues, including social and ethical considerations. Golden rice has been developed based on transgenic technology with aims to prevent blindness and reduce malnutrition from vitamin A deficiencies by reintroducing the biosynthesis pathway of beta-carotene into the rice. However, it is still stuck in the lab after its invention nearly 15 years ago due to public resistance and skepticism of this product [1].

Synthetic biology is a new and rapidly growing field that is building on experiences in genetic engineering, bioinformatics, system biology, and the principles of engineering science [2,3]. Its development and biosafety management should also build on the previous experiences of transgenic technology. In contrast to traditional genetic engineering, synthetic biology attempts to introduce a large number of heterogeneous genetic circuits into host cells by designing and constructing new biological parts, devices, and systems. Even synthetic forms of life can be constructed [4]. Synthetic biology brings new opportunities to life sciences research and industrial production [3]. With its successful applications in the biomass-based productions of biofuels, pharmaceuticals, and bulk chemicals, its potential contribution to sustainable development is highly expected. However, there are also concerns on its impacts on society and the environment, and these should be addressed in order to enable further development of this technology. Scientific knowledge is the determinant of attitudes toward science [5]. Thus, it is crucial to communicate with the public on the benefits and risk management of synthetic biology while trying to implement appropriate measures to eliminate, reduce, and manage the risks.

The current research activities in synthetic biology are mainly focused on microorganisms, such as bacteria, viruses, and yeasts, which leads to concerns on the creation of novel pathogens that may result in biosafety and biosecurity problems. For example, scientists have successfully synthesized several viruses that could lead to fatal diseases, such as poliovirus [6] and the 1918 Spanish influenza virus [7]. Although antibiotics and vaccines have played important roles in combating the infectious diseases caused by microorganisms, many pathogens still pose great challenges to public health. These pathogens range from multiple drug-resistant bacteria to lethal viruses (bird flu virus, HIV, Ebola virus, etc.). The situation may become worse if the revival of lethal pathogens, such as synthetic Spanish flu virus, can be achieved with the development of modern biotechnology, such as synthetic biology that can synthesize the whole genome of the virus and revive it. Currently, it is also possible to enhance the virulence of known pathogens with new traits that can contribute to their competence and resistance to existing treatments. It is believed that new pathogens can be created with technologies that have been developed for synthetic biology. For example, a novel type of avian flu virus with enhanced infectivity in mammalian animals may be created, and the H5N1 virus can be modified to evolve into a dangerous human virus [8].

The International Genetically Engineered Machines (IGEM) competition since 2004 is an event that attracts university students from around the world who represent their interest in the technology and who may become key players in the field of synthetic biology in the near future. One of the aims of the competition is to attempt to build simple biological systems from standard, interchangeable parts and operate them in living cells. In recent years, the organizers requested the participants to respond to biosafety issues and questions about their synthetic biology projects as a standard procedure in the competition. The most important issue that the participants were concerned about was laboratory biosafety [9]. The biosafety concerns raised by the IGEM teams mainly focused on physical and biological containment in routine laboratories of universities (normally below biosafety level 2). The risk assessments of DNA materials (or biobricks) and pathogens were considered the priority for safety management. There is a possibility that synthetic biology research and the products (organisms/molecules) that are derived by this technology will pose higher risks than the traditional transgenic ones because synthetic biology employs genetic elements from various sources (even completely new designs). However, concerns about risk assessment and management of synthetic biology are based on traditional transgenic organisms because they both involve DNA recombination and genetic engineering technologies [10]. Thus, the precaution principle, a case-by-case approach, and the use of other related methodologies for the risk assessment of transgenic technology may still be valid for synthetic biology. For example, biosafety containment guidance from the fifth edition of Biosafety in Microbiological and Biomedical Laboratories is applied in synthetic biology research. NIH Guidelines for Research Involving Recombinant Molecules have been slightly revised to include synthetic nucleic acid molecules [10].

The risks are defined by the applications of the technology. Thus, risk assessment and management of synthetic biology depend on the nature of the applications, such as biofuel production, medical therapies, or food/feed [11]. In addition, the use of these applications, such as contained use or environmental release, should also be taken into consideration. Similar to the potential risks of engineered organisms and/or their derived products from transgenic technologies, the biosafety issues of synthetic biology are also related to three aspects--health, environment, and ethical, legal, and social implications [9]. The biosafety issues in synthetic biology have recently attracted attention from the Convention on Biological Diversity and have been extensively discussed several times at the meetings of its Subsidiary Body on Scientific, Technical, and Technological Advice [12].

Stability of the heterogeneous traits within the host cells and the expression of synthesized genes should be the prerequisite for the use of the synthesized organisms/products that are developed by synthetic biology. Actually, this stability maybe also determined by the environmental conditions and other related factors [13]. Because the synthesized product may be composed of many individual circuits/bricks/genomes, the compatibility among different parts will determine the stability of the gene expression and the designated traits. These properties of the genetic elements are the important genetic information that is needed to assess safety issues. A recently funded program by US DARPA named Biological Robustness in Complex Settings (BRICS) aims to solve the challenges regarding robustness, stability, and safety of novel synthetic biology organisms.

The substantial equivalence principle is hardly applicable in transgenic technology [14] and less suitable for biosafety assessments in synthetic biology. Once synthetic biology delivers the kind of complex genetic circuits that it aims to design and produce, we may not find a conventional comparator to assess the organisms or products, and it will be difficult to predict the possible interactions of various biological parts (genetic circuits, DNA fragments, and biobricks, etc.) within host cells and with other cells, if released into the environment. Uncertainty is another important issue that needs to be taken into consideration in risk assessment and management [14]. Thus, the risk assessment procedure should be used to identify the uncertainty, while management strategies should be developed to reduce and/or deal with the uncertainty. Information and evidence used for assessments need to be scientifically sound and updated according to the latest scientific knowledge.

Food/feed safety of the synthetic biology-derived organisms/products should be tested thoroughly before authorizing their commercial use, as was the case already for transgenic products. The transfer of synthetic genetic materials or products through the food chain will initiate debates on their safe use like the discussion on the movement of transgenes and transgenic products in traditional genetic engineering [15]. Appropriate tests, such as toxicological assays and animal models for gene transfer studies, should be conducted to evaluate food/feed safety of the products derived from synthetic biology [11]. Food safety is an area of primary concern for public. However, it is difficult to assess and control the impacts on the environment because the recovery from or remediation of causal agents in the environment is challenging. Both food safety and the environmental effects of synthetic biology are important aspects of biosafety consideration. They have the potential to significantly impact society, and these issues should be investigated further by the research community and discussed among broader stakeholders.

The interactions of engineered organisms with others in nature will affect natural organisms at certain trophic levels [15], such as microbial decomposers, plants, herbivores and their predators or parasites, and this may depend on the trophic level to which the engineered organisms belong. This interaction in the natural ecosystem will affect biodiversity and cycles of nutritional elements and biogeographical/biochemical components and, therefore, the function and stability of the ecosystem. The interactions among organisms and their environments will also be affected by environmental factors, such as climate change.

Because synthetic biology-derived organisms may have certain traits that are selectively advantageous against biotic or abiotic factors, there is a possibility of the persistence of this organism in nature to become invasive in the environment. Thus, the probability of persistence and its consequences should be evaluated as part of the risk assessment of synthetic biology-derived organisms or products. In addition, genetic materials (circuits, genetic elements, and genomes) may escape by hybridizing with sexually compatible wild species and become established in nature. The effects of this vertical gene flow as well as those of horizontal gene flow would then largely depend on the resulting fitness of the organisms [16].

The use of synthetic biology within contained settings has served as a very important strategy in biosafety management, which includes physical, temporal, and spatial isolation. Further containment strategies of synthetic organisms have been proposed [17], but they should be validated before being applied. The so-called genetic firewall approach has also been proposed to separate novel organisms from natural ones by creating a parallel genetic world that is not compatible to any known organisms on earth. For this hypothesis, a genetic firewall is created by designing orthogonal systems (xenobiology) by replacing deoxyribose in DNA with other backbones to convert DNA into xenonucleic acids (XNA), which would result in the whole genome being written in XNA, which is not recognized by the natural world [18]. However, the stability of such incompatibility and new biosafety and biosecurity issues need to be experimentally evaluated first.

Risk assessment of new synthetic biology-derived organisms is predominantly based on the experiences with transgenic organisms. As of 2014, practically all areas of synthetic biology can still be handled with existing regulatory frameworks and risk assessment procedures. In the coming years, a number of tools and strategies to assess the risk will become less relevant, such as the use of a comparator organism to establish the risk. While the concept of risk assessment is valid to date, synthetic biology challenges risk assessments because it requires a wealth of new data that needs to be produced and evaluated to help make scientifically correct decisions. Any new technology may have both benefits and harm, and the applications of new technology should proceed with caution in order to avoid any unnecessary risks and to minimize the negative effects through appropriate assessment, management, and long-term monitoring [19]. Once the strategy for risk assessment and management is developed and validated, safe, robust, and stable applications of this new technology may be ensured.

Acknowledgement

This work was supported by a joint-project "Investigating the biosafety and risk assessment needs of synthetic biology in Austria (Europe) and China" funded by the National Natural Science Foundation of China (NSFC grant no.30811130544) and the Austrian

Science Fund (FWF grant no. I215-B17) and the Project for Implementation of the Convention on Biological Diversity funded by the Ministry of Environmental Protection of China (grant no. 20110106). MS and LP acknowledge the financial support of the European Commission's FP7 projects METACODE (289572) and ST-FLOW (289326).

References

1. Enserink M (2008) Tough lessons from golden rice. Science 320: 468-471.
2. Pei L, Schmidt M, Wei W (2011) Synthetic biology: An emerging research field in China. Biotechnol Adv 29: 804-814.
3. Schmidt M (ed) (2012). Synthetic Biology: Industrial and Environmental Applications. Wiley-VCH, Weinheim.
4. Gibson DG, Glass JI, Lartigue C, Noskov VN, Chuang RY, et al. (2010) Creation of a bacterial cell controlled by a chemically synthesized genome. Science 329: 52-56.
5. Sturgis P, Allum N (2004) Science in Society: Re-evaluating the deficit model of public attitudes. Pub Underst Sci 13: 55-74.
6. 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.
7. Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solórzano A, et al. (2005) Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science 310: 77-80.
8. Herfst S, Schrauwen EJ, Linster M, Chutinimitkul S, de Wit E, et al. (2012) Airborne transmission of influenza A/H5N1 virus between ferrets. Science 336: 1534-1541.
9. Guan Z-J, Schmidt M, Pei L, et al. (2013) Biosafety considerations of synthetic biology in the international genetically engineered machine (iGEM) competition. BioScience 63: 25-34.
10. National Institutes of Health (2013) NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.
11. EFSA (2011) Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use. EFSA Journal 9: 2193.
12. Secretariat of the Convention on Biological Diversity (2014) New and emerging issues: synthetic biology. UNEP/CBD/SBSTTA/18/L.6.
13. Canton B, Labno A, Endy D (2008) Refinement and standardization of synthetic biological parts and devices. Nat Biotechnol 26: 787-793.
14. Secretariat of the Convention on Biological Diversity (2012) Guidance on Risk Assessment of Living Modified Organisms. UNEP/CBD/BS/COP-MOP/6/13/Add.1.
15. Wei W, Schuler TH, Clark SJ et al. (2008) Movement of transgenic plant-expressed Bt Cry1Ac proteins through high trophic levels. J Appl Entomol 132: 1-11
16. Davison J (1999) Genetic exchange between bacteria in the environment. Plasmid 42: 73-91.
17. Moe-Behrens GH, Davis R, Haynes KA (2013) Preparing synthetic biology for the world. Front Microbiol 4: 5.
18. Schmidt M (2010) Xenobiology: a new form of life as the ultimate biosafety tool. Bioessays 32: 322-331.
19. Schmidt M (2009) Do I understand what I can create? Biosafety issues in synthetic biology. In: Schmidt M. Kelle A. Ganguli A, de Vriend H. (Eds.) Synthetic Biology. The Technoscience and its Societal Consequences. Springer Academic Publishing 81-100.