Can synthetic biology bring sustainable development to China?

New life in the laboratory

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Synthetic biology (SB) is an emerging research field in China with growing interest from the scientific community and (to a much lesser extent) from the public. This interest is not only in the research itself, but also in the societal issues. This article presents the results of interviews with 20 Chinese scholars and looks at the current research activities of SB and the related ethical, legal and social implication (ELSI) studies.

National sustainable development has been set as a priority strategy by many countries including China[1]. SB is an emerging research field that has been widely considered to have the potential to fulfil the promise of sustainable development. As part of the Austrian–Chinese project, 'Investigating the biosafety and risk assessment needs of synthetic biology in Austria and China', we aim to provide the scientific insight into the challenges of SB by analysing the current developments in the field, reviewing the current regulations, investigating biosafety and biosecurity, and initiating scientific communication. Interviews have been used to collect information on the definition of SB, research regulations, biosafety, biosecurity and SB-related ELSI. The 20 scholars interviewed represented a wide variety of the experts from research institutions and educational institutes (Figure 1). The current research activities of SB in China have been summarized on the basis of analysis of PubMed literature, online published information, and information provided by the interviewees. The current regulation on SB is analysed on the basis of information from the interviews while referring to the government documents and reports.

Scientists' perception of SB in China

SB has been used to cover so wide a range of cutting-edge research that it is difficult to provide a precise definition. The majority of the scholars we interviewed defined SB as the research on design or redesign of pathways or organisms (15 out of 20). Two of them considered that there was no clear definition; another two considered that SB was no different from bioengineering; and one thought that there were just too many definitions. More than half of them considered that SB was quite different from bioengineering (14 out of 20), whereas some thought that SB was a continuous development of bioengineering (6 out of 20). The difference between SB and bioengineering was mainly due to the interdisciplinary nature of SB, a combination of life science and engineering science involving a whole system, whereas bioengineering was more about the manipulation on a couple of genes.

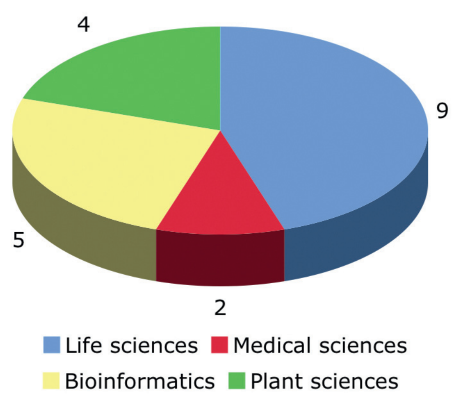

Figure 1. Background of the interviewees

Current research activities of SB in China

As an emerging interdisciplinary research field, SB promises to revolutionize biotechnology for the industrial, medical and agricultural sectors. One goal of SB is to enable the engineering of the architecture of genetic network and design new circuits for useful purposes. The research emphasis in China has apparently been placed on developing SB approaches to harness biomass. On the basis of the roadmap of scientific development strategies from the Chinese Academy of Sciences (CAS) 'Innovation 2050: Technology Renovation and the Future of China', 30% of the fuel should be biofuel derived from biomass in the year 2050. In general, the current SB research activities can be classified into five subfields: genetic circuits, minimal genomes, protocells, chemical SB (xenobiology), and DNA synthesis (for more detail, refer to Pei et al.[2]). Current research in China is focused more on the first two subfields. To date, most of the projects of SB have been supported by the government via funding from the

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Table 1. Examples of SB related research projects in China. 863 Program, National High-tech Research and Development Program of China; 973 Program, National Basic Research Program of China; MOST, Ministry of Science and Technology of China; MOE, Ministry of Education of China; NSFC, National Natural Science Foundation of China.

Subfield	Project description	Major funding resource
Genetic circuit	An environment-sensitive synthetic microbial ecosystem	NSFC (No. 20425620) 973 Program (No. 2007CB714301)
	Comparative proteomic analysis of tolerance and adaptation of ethanologenic *Saccharomyces cerevisiae* to Furfural, a lignocellulosic inhibitory compound	973 Program (No. 2007CB714301)
	Stochastic synchronization of genetic oscillator networks	NSFC (No. 60502009)
	Artificial synthetic cell factory	New approved by 973 Program
Minimal genome	Potential landscape and probabilistic flux of a predator prey network	NSFC (No. 90713022 and 20735003) 973 Program (No. 2009CB930100 and 2010CB833600)
	Reverse engineering of bacterial chemotaxis pathway via frequency domain analysis	863 Program (No. 2006AA02003) 973 Program (No. 2009CB918801) NSFC (No. 30770498)
	DEG 5.0, a database of essential genes in both prokaryotes and eukaryotes	NSFC (No. 90408028)
	Minimal genome of *E. coli* and its synthesis	New approved by 973 Program
Protocell	Gating of single synthetic nanopores by proton-driven DNA molecular motors	NSFC (No. 10634010, 10675009, 10675011, 50703020, 20125102, 90306011 and 20421101) MOE (No. 306018)
Chemical SB	Folding simulations of a *de novo* designed protein with a βαβ fold	NSFC (No. 20228306, 90103029 and 10721403) MOST (No. 2009CB918500)
DNA synthesis	MISSA is a highly efficient *in vivo* DNA assembly method for plant multiple-gene transformation	973 Program (No. 2006CB100100)
	PCR-based two-step synthesis for long DNA fragments	Key Project Fund of Science and Technology Commission Foundation of Shanghai (No. 993913002) Key Project Fund of the Shanghai Municipal Committee of Agriculture (No. 99-1-8)

Natural Science Foundation of China (NSFC), the 873 Program, and the 973 Program (Table 1).

Designing genetic circuits is a unique approach of SB to produce useful products from biomass. Several research institutes have been founded focusing on the research and development of biofuels and associated biological processes, such as the Qingdao Institute of Bioenergy and Bioprocess Technology (QIBEBT) and the Key Laboratory of Synthetic Biology (KLSB), CAS. Both institutes are active in using SB approaches to develop genetic circuits to produce biofuels (biodiesel and butanol).

Chemicals derived from biomass are also key research topics in China. A research group of Tsinghua University has worked on genetic circuits to enhance the production of polyhydroxyalkanoate (PHA) in engineered micro-organisms such as *Escherichia coli*, *Pseudomonas putida* and *Aeromonas hydrophila*. The research groups in Tianjin University have worked on genetic circuits designed by metabolic engineering to improve the production of chemicals from biomass, focusing on the production of riboflavin and succinate.

There are several groups currently working on minimal genomes. For instance, researchers from Tsinghua University are carrying out work to reduce the *P. putida*

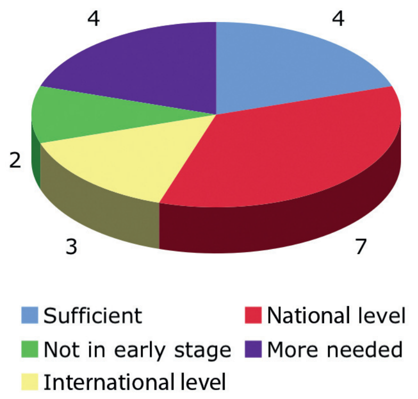

Figure 2. Opinions of the current regulation of SB

genome as a chassis for better production of PHAs. A group from Tianjin University has built a database of essential genes (DEG) on the currently available genes regarded as indispensable for the survival of an organism. Recently, a new project on minimal genome of *E. coli* has been funded by the 973 Program, which is expected to provide more insights for better engineering.

Chemical SB (xenobiology) aims to create biological systems that are different from natural ones, at both the genetic and metabolic level. Instead of working with an enlarged DNA 'alphabet', or so-called xeno-nucleic acids[3], the more popular research topic in China is to build unnatural proteins by using non-canonical amino acids or proteins with unnatural structures. Some of these unnatural proteins are believed to have novel functionalities, permitting development into novel medical applications, such as new medicines, new vaccines and new diagnosis agents.

The goal of protocell research is to construct synthetic cell-like vesicles assembled from non-living chemical components. Protocells could provide the safe and versatile chassis to study cell physiology such as energy conversion in cells, or toxicological studies[3]. The basic type of protocell is composed of a lipid bilayer membrane and membrane-associated molecules that can be used to study the interactions of membrane receptors with the molecules of interests. Researchers from Peking University and Institute of Chemistry, CAS reported a synthetic DNA-based nanopore system where the gates of single solid-state conical ion channel-like nanopores could be controlled by DNA switches immobilized inside the nanopores providing an artificial oscillatory counterpart of protein-based channels[4]. These DNA-based nanopores can function as the membrane-bound ion channels to engineer cells with more precise control in the near term.

DNA synthesis is essential for the creation of synthetic genomes and to establish biosynthetic pathways by rational design. The improved capacity to generate longer sequences, with greater accuracy and lower cost, has turned DNA synthesis into a powerful tool to study gene functions of template DNAs that are difficult to obtain, or to optimize the codons of genes to be expressed in heterogeneous systems.

The current synthesis technology has created the first synthetic cells controlled by a chemically synthesized genome containing 1077947 bp of *Mycoplasma mycoides* JCVI-syn1.0[5]. However, new synthetic and assembling techniques are needed to meet the increasing demands of SB. A couple of research groups in China are currently working on this topic; a PCR-based two-step DNA synthesis (PTDS) method for synthesis of long segments of DNA (5 kb) was modified by Xiong and colleagues. The method for assembly and PCR-based accurate synthesis (PAS) of long DNA sequences was also developed based on the PTDS method with additional steps to synthesize DNA fragments up to 12 kb[6]. Lin and colleagues developed an isothermal DNA synthesis method, called isothermal unidirectional elongation method (IUEM), which is a catalysis process evolving multiple enzymes[7]. Chinese researchers also work on the codon optimization for synthesized sequences for some enzymes of industrial interests such as xylanase for the food industry and phytase for the farming industry.

Current regulation, biosafety and biosecurity of SB in China

Effective research governance should address the scientific uncertainty and concerns of society surrounding SB[8]. However, because of the novelty of the field, many potential risk implications of SB are difficult to assess properly, so it is important that an up-to-date, transparent and evolving regulation should be applied to the regulation of SB to ensure that the proper oversight is in place.

Unlike the other emerging research fields such as genetically modified organisms (GMOs), stem cells and nanotechnology, to which Chinese researchers have made significant contributions, the major breakthroughs of SB are needed from the frontline research to give the whole research field a boost. Thus the majority of the scientific community is not properly aware of the progress of SB in China yet, and this is reflected by the fact that no dedicated regulation has been established to guide the research activities of SB. Currently, as pointed out by most of the people we interviewed, national regulation and institution-based reviews of scientific activities in general are applied to SB-related research. Most researchers believed that current scientifically informed evidence-based approaches to research governance in general is sufficient to cope with the current state of SB. No common agreement was reached upon the need to develop new regulations for SB. Four interviewees out of 20 considered that the current institutional review for research regulation was sufficient. One of these four particularly appreciated the proactive open-ended regulatory style code of conduct that could cope well with possible new issues. Seven out of 20 thought that regulations at a national level would be better, whereas three preferred an international framework on regulation. Four suggested that regulation should be either targeted at risk prevention or based on research objectives. One considered that the current regulation on recombinant DNA was sufficient, and two were worried that further regulation specific for SB would hurt the development of field, taking as an example the new regulations on stem cell research (Figure 2).

Most of the scholars we interviewed were aware of biosafety issues. However, the management of biosafety was variable depending on the institutes to which they were affiliated. In those institutes that carry out research involving pathogenic microbes, human, animals and toxic substances, biosafety criteria have been well established. For those institutes focusing more on applied biotechnology, no specific biosafety regulation body exists. The existing regulations have handled many of the biosafety concerns, but it was acknowledged that there was a need to be a monitoring system.

When asked what they thought about the current risk assessment practice on SB, seven of the interviewees said there was no risk assessment for SB, six of them thought it insufficient and three of them declined to offer an opinion due to lack of experience. Only four of the interviewees considered that the current risk assessment for GMOs would be sufficient. Those who said that there was no or insufficient risk assessment, pointed out that there was a gap between the theoretical and physical foundations for living systems that makes risk assessment of SB difficult. It is therefore critical to investigate further whether the current and upcoming regulations would be sufficient to ensure that the risks associated with SB are properly assessed. In predicting the possible challenges and biosafety concerns that SB might throw up, generating virulent microbes or microbes was mentioned most frequently. It was suggested that building new organisms that could not survive outside a special environment would not be a threat to nature (Figure 3).

As well as biosafety, biosecurity is another thorny issue in SB. The synthesis of DNA makes it hard to keep the agents of the selected organism safe using traditional security containments. It is also possible that SB approaches may enable terrorists or criminals to generate

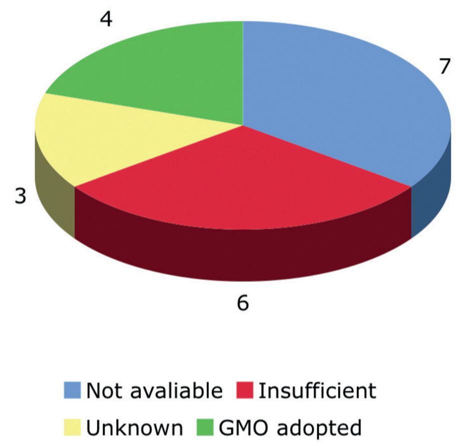

Figure 3. Opinions of the current risk assessment of SB

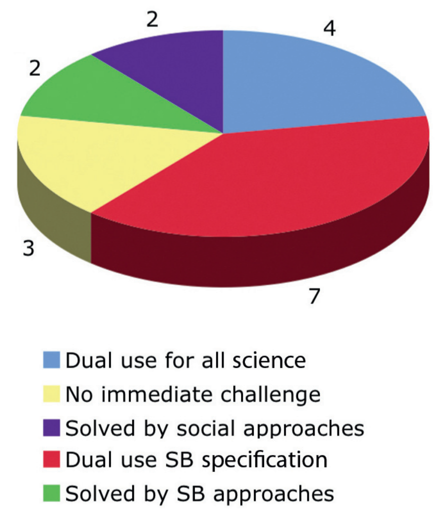

Figure 4. Opinions of biosecurity of SB

novel lethal agents. Among the scholars we interviewed, eight of them considered that such concerns were not caused by the development of SB itself, but were common to all scientific research. This opinion was supported by examples from nuclear research, which can provide benefits in energy and medical treatment, but mass-scale destruction when being used to produce weapons.

Therefore, according to these interviewees, the dual-use potential of SB applications should be fairly considered as an issue common to all scientific research activities. However, six of the interviewees thought that the dual-use potential of SB raised specific SB biosecurity concerns. These concerns were about large-scale production of lethal compounds or viruses and synthetic life turning into an environmental threat. Four of them thought that there are no immediate biosecurity challenges raised by SB as most of the work on SB is focused on designing or redesigning microbes for beneficial purposes. One thought that SB might create biosecurity issues, but it will also solve it eventually and one maintained that biosecurity was not a scientific issue, but a social one that should be left to be solved by society as whole (Figure 4).

ELSI of SB in China

There are many sociologically and philosophically interesting features of SB. The novelty and potential of SB make this emerging field attract not only public funding agencies, but also media coverage that provokes public debate on the possible benefits and potential dangers. It is notable that SB straddles a gap between social and natural science, provoking a discussion among both.

The majority of the interviewees saw no immediate ethical concerns, as long as SB research involved non-human subjects, but thought that they would encounter ethical conflict if humans and human genes were involved.

In fact, most of the SB research in China focuses on the engineering of genetic circuits for industrial-related applications, such as the generation of bioethanol[9]. Scientists in China are keen on patenting technologies that would spur science-based economic growth, although some of our interviewees remained sceptical on patents based on genetic sequences of natural origin.

Conclusion

SB has already been established in China, although is still in an early developmental stage[2,10]. The main focus of the current research activities is to develop useful applications using SB approaches as well as to learn more about biological systems. There are high expectations of SB-derived applications for biofuels, bio-based chemicals, bioremediation and novel medicine, and it is hoped that SB will help achieve the goal of sustainable development in China[11]. Currently, the Chinese government plays an important role in funding SB projects. With more expenditure on research and development in the new 5-year plan[1,12], China is likely becoming an internationally acknowledged player in the field. The Chinese scholars we interviewed acknowledged that the current research regulation on SB is sufficient to cope with the development in the field, but active monitoring is needed for an up-to-date, transparent and evolving regulation of the field.

Because of its early developing state, SB is little known to the public in China, although the media coverage of the first 'synthetic cell' of JVC in 2010, introduced the term SB to the public. Discussions on the social issues are for the moment confined to the scientific community. As for biosafety, the first workshop was held in Beijing[13] and that for ethical issues was held in Hangzhou[14]. Thus our continuing project will keep on providing detailed analysis on current research regulations on SB and better scientific insight into the challenges of SB to biosafety, resulting in a detailed analysis on the research regulation and recommendations on biosafety in the future. ■

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