Regulation and management of the biosecurity for synthetic biology

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Abstract

Synthetic biology (SynBio) is a high-profile interdiscipline combining engineering with science. As a dual-purpose discipline, SynBio is bringing large changes to many fields and providing great benefits to humans. However, due to its characteristic of complexity and uncertainty, SynBio also presents potential biosafety and biosecurity risks. Biosecurity risks refer to unauthorized access, loss, theft, misuse, diversion or intentional release. If a biosecurity accident happens, it would pose a huge threat to humans and nature. Therefore, it is crucial to establish a set of regulations and management practices for the biosecurity risks of SynBio. In this paper, we summarized the sources of the biosecurity risks of SynBio, from its research materials, products, technologies, information to Do-it-yourself synthetic biology. We reviewed and analyzed the current situation of regulation and management of biosecurity for SynBio in the international community and in China. We found that in most countries and regions, SynBio risks commonly follow the regulation and management of Genetically Modified Organisms which has loopholes if applied to the regulation for SynBio without any amendments. Here, we proposed suggestions for the Chinese-featured regulation and management of biosecurity for SynBio, including a top-to-bottom governing framework, a think-tank implementation mechanism, a Synthetic Biology Laboratory Biosecurity Manual safeguarding system, and strengthening biosecurity education on synthetic biology and self-regulation awareness among relevant personnel. Through this work, we aim to improve the standardized process of biosecurity regulation and management for SynBio in China and thereby map out a peaceful, profitable, and practical development path for synthetic biology.

1. Introduction

Synthetic biology (SynBio) is usually regarded as the artificial biology or engineering biology to create novel biological system rationally and systematically. SynBio is a high-profile interdiscipline in recent decades [1,2], but to date, has no unanimously agreed definition. However, the definition of SynBio as “the application of science, technology, and engineering to facilitate and accelerate the design, manufacture and/or modification of genetics” is commonly accepted [3]. Compared to Genetic Modification (GM), SynBio features a wider range and scope and emphasizes mixed processes and technologies [4]. SynBio involves process of modifying existing biological components, including DNA bases, codons, genes, gene segments and amino acids, as well as creating non-existent engineering biological components based on modern tools for faster and easier Genetic Modification Organism (GMO) design, manufacture, and exploitation [5–7]. The scientists involved in SynBio play a designer role, making the modification and creation process more feasible, effective, and objective-oriented. However, SynBio also entails risks because of its complexity and uncertainty [8–10].

SynBio has potential biosafety and biosecurity risks [11,12]. These two kinds of risks are distinguished from each other by their different focuses [13]. Biosafety risks are biorisks that arise from human actions that are not deliberate or intentional, which may be caused by inappropriate contact with hazardous components and/or accidental release in biological laboratories [13–15]. On the other hand, biosecurity risks refer to unauthorized access, loss, theft, misuse, diversion or intentional release based on the definition given by the World Health Organization.
Biosecurity risks are more closely related to human intention and control [13,16]. If biosafety or biosecurity accident occur, they can present hazards to humans and nature. The biosafety risks and biosecurity risks of SynBio have been recognized since the field’s inception and should have been regulated and managed in a sound way [17–19]. However, in most countries and regions, SynBio risks currently follow the regulation and management for GMO which has loopholes for the regulation of SynBio [20]. Thus, it is crucial to build a suite of regulations and management practices for SynBio risks to patch the holes. With the advent of synthetic viruses and Do-it-yourself SynBio, the issue of regulating the biosecurity of SynBio is critical. In this review, we summarized the sources of biosecurity risks of SynBio, as well as reviewed and analyzed the current situation of regulation and management of the biosecurity for SynBio in the international community and in China. Furthermore, according to the characteristic of SynBio and the international and national situation, we proposed the suggestions for the Chinese-featured regulation and management on biosecurity for SynBio. In this work, we aim to map out a peaceful, profitable and practical development path for synthetic biology.

2. Biosecurity risks of synthetic biology

Biosecurity risk is defined as unauthorized access, loss, theft, misuse, diversion or intentional release, etc. Over the years, biosecurity risks of SynBio has mainly focused on the theft and misuse of fixed, current, and intangible assets in SynBio laboratories, including SynBio components (Minimal genome, Orthogonal biosystems/xenobiology, protocells, etc.), SynBio products, and SynBio technologies [21,22]. In some cases, SynBio might present bioweapon risk, as it might be used to re-create known pathogens, make existing pathogens more dangerous, or create new pathogens for some purposes [2,23]. Once being stolen, transported illegally, or abused, they might cause biosecurity risks to various parties including people, community, and environment. To ameliorate these concerns related to biosecurity risks, one measure is to design the engineering components of SynBio to live only on specific nutrients in the SynBio laboratory, making such components unable to survive outside the laboratory. This measure could also mitigate biosecurity risks due to unintended/unassessed release or interactions between the man-made and biological worlds [24–26]. Although this measure for addressing such risks is commonly taken, the use of auxotroph engineering components does not provide the necessary or sufficient conditions to eliminate the biosecurity risks of SynBio due to deliberate and malicious human intentions [27]. Thus, this measure should be enhanced by improving the regulations for SynBio biosecurity risks.

More broadly, biosecurity risks can be linked to bioweapons and biothreats. In recent years, the increasing availability of technologies, cyberbiosecurity and DIY (Do-It-Yourself) SynBio can also lead to the biosecurity risks of SynBio [28–31]. Notably, cyberbiosecurity is a significant emerging biosecurity issue. As biological laboratory equipment is controlled and operated by the internet, with the increasing reliance on digital information and the calculation of SynBio on servers and networks, the operations are becoming increasingly vulnerable to cyberthreats, such as unauthorized access, theft and misuse. This creates an unprecedented cyberbiosecurity problems of SynBio [23,29,32]. These biosecurity risk factors, in turn, illustrate the significance of managing and mitigating the biosecurity risks of SynBio [33,34].

3. Situation of the regulation and management of biosecurity for synthetic biology in the international community

SynBio has attracted great attention from the scientific community and governments of all countries since its inception, and the past decade witnessed its soaring development [7,35]. In 2006, the National Academy of Sciences of the United States funded the establishment of the Synthetic Biology Engineering Research Center. The British government also gave SynBio priority for funding research in 2007. Since 2010, European and American countries have invested significantly in the field of SynBio. In 2014, the European Regional Network for Synthetic Biology Research published the report “Strategic Vision for the Next Actions of Synthetic Biology in Europe”, which described the good prospects for the future development of SynBio in Europe. However, due to the dual-use nature of SynBio, the technology’s potential biosafety and biosecurity risks, and issues related to the regulation of these risks, have also attracted significant attention from the international community. In 2010, the US National Advisory Committee on Biosafety issued a report entitled “Adjust Biosafety Issues Related to Synthetic Biology”, which noted that SynBio is a field with great potential and should be encouraged to develop, but that this field also has potential biosecurity risks [36]. In 2013, the three scientific committees of the European Union drafted scientific opinions on the operational definitions, risk assessment methodologies, biosafety, environmental risks and research priorities of SynBio. In October 2014, the 12th Conference of the parties to the Convention on Biological Diversity passed a decision on SynBio, urging the parties to establish and implement an effective risk assessment and management system consistent with the Convention on Biological Diversity to monitor biosafety and biosecurity risks arisen from SynBio [37].

As mentioned earlier, synthetic biology is a dual-use discipline. Dual-use research of concerns (DURC) is a kind of research with a legitimate scientific purpose that potentially could be misused and thereby poses a biological threat to public health and/or national security. The scientific community has attached great significance to DURC since infectious virus particles were artificially generated through the use of chemically synthesized poliovirus cDNA in 2002 [38]. Two United States policies on DURC were formulated. One is the United States Government Policy for Oversight of Life Sciences DURC released in 2012, and the other is the United States Government Policy for Institutional Oversight of Life Sciences DURC released in 2014. These two DURC policies aim to strengthen the oversight of life sciences research to identify potential DURC and implement risk mitigation [20]. Meanwhile, gain-of-function (GOF) research has also been focused on since a report was released on the creation of new viruses via genetically manipulated H5N1 highly pathogenic avian influenza (H5N1) viruses; and these new viruses were found to be transmissible among mammals via respiratory droplets [39]. GOF research is an essential component of DURC and a matter of serious concern. The particular concern is GOF research resulting in the creation of a ‘potential pandemic pathogen (PPP)’ (GOF/PPP research) where the host range, virulence or transmissibility of a pathogen is enhanced. To manage the risks and benefits of GOF/PPP research, in 2017, the Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) was formulated, which contains a set of principles that any GOF/PPP research ought to satisfy, and contains associated guidance for managing the risks of GOF/PPP [40]. All these highlight the great concerns of the biosafety and biosecurity issues of DURC, including synthetic biology.

Many conventions, protocols and laws related to biosafety have been implemented prior to defining SynBio (Table 1), but none specifically focus on preventing and controlling the biosafety and biosecurity risks of SynBio. Although the experts and professionals in SynBio circle have acknowledged the potential biosafety and biosecurity risks of SynBio, few agreements, conventions or laws have targeted these risks specifically.

Some experts estimate that it is still reasonable to use existing regulations and laws to regulate the risks of SynBio at present and in the near future [41]. Additionally, to date, there have been no SynBio cases in practice outside of these regulations and laws. There are indeed some universal regulation principles among these regulations. The responsibilities of members stated in the current conventions are also applicable to the liabilities for SynBio. For example, it is decreed in the Chapter 3 of Convention on Biological Diversity that “States have in
management of SynBio. Indeed, more conventions, protocols, Biosafety Manual (4th edition) [48] are applicable to the regulation and provisions to address the risks of SynBio [43].

Development, Production and Stockpiling of Bacteriological (Biological) Conventions and the Directives of the European Union, the Acts in the U. nation. Moreover, the concepts for regulation and management in the accordance with the Charter of the United Nations and the principles of international law the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction” [42], which can be applied to SynBio regulation. Moreover, the concepts for regulation and management in the Conventions and the Directives of the European Union, the Acts in the U. S. and some related laws in other countries and regions have practical provisions to address the risks of SynBio [43–46]. For example, the Convention on Biological Diversity [42], the risk assessment strategy in Directive 2001/18/EC [47], the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxic Weapons and on their Destruction (1997)

Table 1

| Convention, Protocol and Agreement in the international level | The laws in the European Union | The laws in the United States | The laws in Singapore |
|---------------------------------------------------------------|-------------------------------|-------------------------------|----------------------|
| Convention on Biological Diversity (1992) Directive 2000/54/EC (2000) | Directive 2001/18/EC (2001) | Directive 2009/41/EC (2009) | Directive for the Safe Transport of Infectious Substances and Diagnostic Specimens, World Health Organization (1997) |
| Cartagena Protocol on Biosafety (2000) | Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition, Centers for Disease Control and Prevention (CDC) (2007) | Select Agents and Toxins, Code of Federal Regulations Title 42: Public Health, Part 73 (1977) | Workplace Safety and Health Act (2006) |
| Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety (2010) | Guide for the Care and Use of Laboratory Animals, National Research Council (2011) | | |
| Laboratory Biosafety Manual, 4th revised edition, World Health Organization (WHO) (2020) | Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, National Institutes of Health (NIH) (2013) | | |
| The International Plant Protection Convention (IPPC) (1999) | Federal Food, Drug, and Cosmetic Act (FD&C Act) (2006) | | | Health Products Act (2008) |

4. Situation of the regulation and management of biosecurity for synthetic biology in China

Compared to other developed countries, synthetic biology research in China has been rising slowly in an early time, but has developed rapidly in recent decades. The Chinese research plan on SynBio was formulated in 2011, and investment in SynBio research on the topics of material transformation, ecological and environmental protection, health and agriculture have increased over the years [51]. To date, ten National Key Basic Research and Development Programs on Synthetic Biology (973 Program), one National High Technology Research and Development Program (863 Program) on SynBio and four National Key Research and Development Programs on SynBio in China have been
launched, with the research including artificial genome synthesis and advanced chassis cell construction, artificial components and gene circuits, artificial anabolism and complex biological systems, and enabling technology systems, etc. [51].

With the increasing investments in SynBio research in China over the years, the regulation and management of biosafety risks and biosecurity risks were highlighted as priorities in the schedule [54,55]. In 2016, the delegations of China and Pakistan jointly proposed a Model Code of Conduct for Biological Scientists to the Eighth Review Conference of the Biological Weapons Convention. The Model Code of Conduct for Biological Scientists provides several recommendations and principles for all relevant personnel engaged in biological research, including three recommendations related to the duties and responsibilities of synthetic biologists. Meanwhile, sub-projects on the assessment and management of biosafety and biosecurity risks were established in the Key National Research and Development Programs on SynBio from 2018 to 2020. In 2019, the Center for Biological Safety Strategic Research of Tianjin University in China and the Johns Hopkins Center for Health and Safety of the United States co-sponsored the “Track II dialogue” entitled “The Challenges Facing China and the United States in the Era of Synthetic Biology”. All these developments indicate that the risks of synthetic biology are attracting significant attention. Although regulation system for SynBio are not yet integrated into relevant programs, many activities were undertaken to improve the safety of biological research, including the Regulations for the Safety Management of Biotechnology Research and Development drafted by The Ministry of Science and Technology following the gene-edited baby event in 2019; the Biosafety Law of the People’s Republic of China officially implemented in April 2021; and the Tianjin Biosafety Guidelines for Codes of Conduct for Scientists (Tianjin Biosafety Guidelines) proposed by scientists led by Tianjin University in China and Johns Hopkins University in the United States in 2021. The Tianjin Biosafety Guidelines propose ten guiding principles and standards of conduct, and outline the primary responsibilities of scientists to safeguard against the misuse and abuse of biological sciences in their research along with responsibilities of relevant institutions. The Tianjin Biosafety Guidelines were designed to promote responsible sciences and strengthen biosecurity governance at the national and institutional levels [56]. Moreover, as biologists are at the front line of biotechnology development and key to maintain biosecurity awareness and moral self-discipline, it was suggested that biologists should actively participate in the formulation and implementation of relevant biosecurity policies and measure [57]. Furthermore, Chinese scientists, ethicists, and philosophers have attached great importance to the biosafety and biosecurity risks of synthetic biology in recent years, stressing the need to regulate synthetic biology. These scientists suggest, e.g., that codes of conduct should be proposed and implemented, that prevention and control should be shifted from “passive management” to “active defense”, that “responsible innovation” in synthetic biology should be established, and that risk assessment should be improved, etc. [9,58–62].

Like the situation in the international community, the regulation and governance measures for genetically modified organisms (GMO) are relatively well-constructed in China, including the Regulations on the Safety Control of Genetically Modified Organisms in Agriculture [63], the Measures for Management of Safety Evaluation of Agricultural Genetically Modified Organisms [64], the Safety Management System for Genetically Modified Organisms Processing, and the Measures for the Administration of Import Safety of Agricultural Genetically Modified Organisms.

For biosafety in biological laboratories, there are relevant regulations including Laboratories General Requirements for Biosafety (GB19489-2008), General Biosafety Standard for Causative Bacteria Laboratories (WS233-2017), Measures for Biosafety Examination and Approval of Laboratories and Experimental Activities of Highly Pathogenic Microorganisms from Human Infections in China and Biosecurity Law of the People’s Republic of China. These regulations might be currently used for the management of SynBio biosafety in laboratories due to the lack of regulations specific to SynBio. However, due to the aforementioned complexity and uncertainty of SynBio, and the fundamental differences of SynBio from GMO, current regulations are not sufficient to regulate and manage the biosafety and biosecurity risks of SynBio. Therefore, it is urgently necessary to construct the regulation system for the biosafety and biosecurity risks of SynBio in China.

5. Suggestions on the regulation and management of biosecurity for synthetic biology in China

5.1. A top-to-bottom framework for governing the biosecurity risks of SynBio

Regulating and governing the biosecurity risks of SynBio would facilitate the development of SynBio in a peaceful and sustainable way to deliver benefits to people and environment across the planet without causing damage. The objective of regulating and governing SynBio is to strike a balance between its maximum development and minimized risks [23,34].

An effective management framework for the biosecurity risks of SynBio is required in this context. The principle of top-to-bottom administrative approval and examination represents a possible avenue to realize this goal in China since the efficiency and legitimacy of this method have been tested over time in different fields. A top-to-bottom SynBio risk regulation framework could consist of three hierarchical levels: the national level, the provincial or municipal level, and the SynBio laboratory level. A National Commission on Biosafety and Biosecurity for Synthetic Biology should be established at the national level. Each level should have its own responsibilities in this hierarchical relationship. In practical terms, this hierarchical relationship operates in two directions. The deliberations and requirements at the national level can be delivered to SynBio laboratories in a top-to-bottom direction. On the other hand, risk registration and submission would be handled at the provincial/municipal level or at the national level in a bottom-to-top direction. This process is shown in Fig. 1. Undoubtedly, all deliberations and requirements must ultimately be transmitted to SynBio.

![Fig. 1. The regulatory framework for the biosecurity risks of SynBio.](image-url)
5.2. A think tank implementing system for governing the biosecurity risks of SynBio

A regulatory framework will not work without the contribution of a think tank at each level. The regulation and management of biosecurity risks for SynBio under the top-to-bottom framework would entail different responsibilities for think tanks, including Risk Assessment and Registration, Risk Examination and Supervision, and Risk Precaution and Mitigating Measures (risk here and hereafter refers to the Biosecurity risk of SynBio).

5.2.1. Risk Assessment and Registration (RA&R)

Risk assessment and registration are shared processes of risk regulation and governance. For the risk assessment of SynBio, it is vital to grade the risk level. As the biosecurity levels in laboratories are graded into four levels in the Laboratory Biosafety and Biosecurity Risk Assessment Technical Guidance Document by Sandia National Laboratories [11], we suggest also grading the biosecurity risk of SynBio into four levels: SynBio Biosecurity Risk Level 1 (SBRL1), SBRL2, SBRL3, and SBRL4, where SBRL4 is the highest risk level.

RA&R could be completed by the SynBio Laboratory level and specialized SynBio biosecurity evaluation agencies. The SBRL could be assessed at the SynBio laboratory level first according to assessment criteria and then be approved by specialized evaluation agencies. To ensure efficiency, we recommend that SBRL1 activities in SynBio laboratories do not require approval at the provincial/municipal level or the national level. However, such activities would need registration at the corresponding affiliated unit. SBRL2 activities would need approval from the province or municipality level and need registration at the laboratory and provincial/municipal levels. SBRL3 laboratory activities would need provincial/municipal and national approval, as well as registration with the laboratory, province or municipality, and nation levels. SBRL4 laboratory activities would need the approval of provinces/municipalities and the nation, as well as registration with the laboratory, province or municipality, and nation levels. In this way, RA&R could be implemented hierarchically according to the biosecurity risk levels of the SynBio activities.

5.2.2. Risk examination and supervision (RE&S)

While some overlaps exist between RE&S and RA&R, the two activities run in different directions. RA&R occurs along the bottom-to-top line, while the process for RE&S is reversed. Managing RA&R only from bottom to top would not be sufficient for the peaceful development of SynBio. In this context, RE&S would provide another check from top to bottom. RE&S would involve think tanks at the national level visiting provincial/municipal authorities and SynBio laboratory authorities for risk examination and supervision at random dates a few times annually. The think tank at the provincial/municipal level would then visit SynBio laboratories for risk examination and supervision in the same way. RE&S plus RA&R would integrate the three levels involved in regulation and governance (i.e., the national, the provincial/municipal level, and the SynBio laboratory level) into an operating circle in practice. The think tanks at each level would play indispensable roles in the operation of this circle. Thus, it would be a complex job to select relevant experts, professionals, and scholars for the think tank based on qualifications such as expertise, loyalty, and responsibility.

5.2.3. Risk Precaution and Mitigating Measures (RP&MM)

RP&MM would be a necessity element of biosecurity risk registration when the lower level asks for approval from the higher level. It would be necessary for the lower level to provide RP&MM to the higher level for approval of SBRL2 to SBRL4 activities, which would help higher levels make decisions more efficiently and comprehensively. Importantly, higher think-tank levels should provide revisions and/or suggestions for RP&MM submitted by lower levels, regardless of approval. These revisions and/or suggestions would improve the security of the SynBio laboratory in the case of approval from the higher level. These suggestions would also help the SynBio laboratory improve their precaution and mitigation measures if approval were not granted, thus helping the laboratory seek authorization at a later time. In addition, appeals should be reserved for SynBio laboratories and provinces/municipalities, if authorities at these levels do not agree with the decision(s) of the think tank at the national level. All of the above measures would help ensure more reasonable, efficient, and transparent hierarchical relationships between the national, provincial/municipal, and SynBio laboratory levels.

5.3. A Synthetic Biology Laboratory Biosecurity Manual for safeguarding the biosecurity of SynBio laboratories

A Synthetic Biology Laboratory Biosecurity Manual (Biosecurity Manual) would help ensure safe operations at the SynBio laboratories to minimize the biosecurity risks of SynBio. The Biosecurity Manual will contain contents including physical security, personal security, information security, transport security related with synthetic biology research for laboratories with different biosecurity risk levels, so as to minimize biosecurity risks and safeguard the normal operations of SynBio laboratories. We suggest that this Biosecurity Manual should be co-drafted by think tanks from the nation, provinces/municipalities, and laboratories, and even getting suggestions and recommendations from the international community, as well as individual experts such as scientists, ethicists, and philosophers. The cooperation of experts in these circles would make the Biosecurity Manual more comprehensive, reasonable, applicable, and advanced. The Biosecurity Manual may include content in, but not limited to, General Principles, Biosecurity Guidelines, Laboratory Technology and Equipment, and Personnel Biosecurity Training. Moreover, a hierarchical feedback system from the bottom to the top should be included in the regulation and governance mechanism. Feedback provided through this mechanism could enhance the Biosecurity Manual. Under the guidance of the Biosecurity Manual and the measures mentioned above (as shown in Fig. 2), a dynamic balance could be achieved between maximum development and
minimized risks of SynBio.

5.4. Strengthening biosecurity education on synthetic biology and self-regulation awareness among relevant personnel

In addition to the supervision and management of government, it is also very important to strengthen biosecurity education and emergency training for synthetic biology researchers with different academic backgrounds and among relevant personnel in enterprises engaged in this field. These personnel should be educated about possible biosecurity risks, how to prevent biosecurity problems, and how to handle such problems if arisen, so as to improve their awareness and knowledge of biosecurity prevention. We suggest that biosecurity education and emergency training should be performed by specialized SynBio biosafety and biosecurity education agencies at the provincial/municipal level (for SBRL2 to SBRL4 risk-level activities) or at the institutional level (for SBRL1 risk-level activities). Biosecurity emergency training is required for those involved in high-risk synthetic biology activities.

The awareness of self-regulation among relevant personnel is also very important (Fig. 2). Self-regulation emphasizes that relevant personnel have a sense of responsibility and self-discipline. Scientists engaged in synthetic biology should be aware of the possible dangerous consequences associated with their research, carry out their research in accordance with the operational manuals of the corresponding facilities to prevent biosecurity risks, and take emergency treatment measures in time in case of a biosecurity emergency. The awareness of self-regulation among relevant personnel could be strengthened by related education, including education on codes of conduct for biologists. For example, the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists, proposed by scientists led by Tianjin University in China and Johns Hopkins University in the United States in 2021, provides good guideline for scientists to promote responsible science and strengthen biosecurity governance.

6. Conclusion

Due to the aggressive development of SynBio together with the risks posed by this technology, the regulation and management of SynBio biosecurity risks are urgently needed, especially considering the absence of such measures in the international community, including China. In this study, we provided some suggestions for regulating and governing SynBio biosecurity risks by combining considerations related to the national conditions in China, the overall risk management concept, the philosophy of biorisk regulation, and the acts and policies implemented before the emergence of SynBio, both at home and abroad. We hope that this paper will help drive the process of biosecurity regulation and management for synthetic biology in China to map out a peaceful, profitable, and practical development path for SynBio.

CRediT authorship contribution statement

Xiaomei Zeng: Conceptualization, Investigation, Writing – original draft, Review & editing, Supervision, Validation, Project administration, Funding acquisition. Halun Jiang: Conceptualization, Investigation, Writing – original draft, Review & editing. Guangying Yang: Investigation, Writing – original draft. Yakun Ou: Investigation, Writing – review & editing. Shan Lu: Investigation, Writing – original draft. Jia Jiang: Investigation, Writing – original draft. Ruipeng Lei: Investigation, Writing – review & editing. Li Su: Conceptualization, Validation, Writing – review & editing, Supervision.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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