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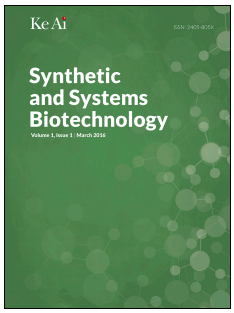

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Prudently conduct the engineering and synthesis of the SARS-CoV-2 virus

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On Feb. 21, 2020, a research group from the University of Bern published a paper titled “Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform” [1] on the pre-print platform BioRxiv, which has not been evaluated by peer review. Based on the outbreak of (Coronavirus Disease 2019, COVID-19) sweeping the world, the authors claimed to have been able to engineer and resurrect chemically-synthesized clones of the (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) with a yeast-based synthetic genomics platform. This paper presents the genetic reconstruction of diverse RNA viruses, including the novel coronavirus. The authors believe that with the use of this platform, generation of SARS-CoV-2 from chemically synthesized DNA could bypass the limited availability of virus isolates to allow genetic modifications and functional characterization of individual genes, as well as to generate serological diagnostics, to develop and assess antivirals and vaccines, and to establish appropriate *in vivo* models. During this critical period of global research and emerging combat with this epidemic disease, the present research could contribute to the development of antiviral therapeutics and that of a vaccine.

The authors of the aforementioned paper claim to have taken into consideration the “dual-use” problem. The so-called “dual-use” problem in biology denotes that “the techniques needed to engineer a bioweapon are the same as those needed to pursue legitimate research” [2]. For example, the pathogen synthesis technique can be used to rescue patients, as well as to possibly manufacture

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bioweapons. Even if the motivation for the development of this type of technology is noble, any deviation, misuse, or abuse during the research may result in calamitous consequences; for instance, an accidental leak from the laboratory, or the purposeful misuse by others.

The chemically synthesized SARS-CoV-2 virus is a part this type of technology, with the benefits mainly including the acceleration of therapeutics and vaccine development, and the protection of human life and health from the virus. However, the risks include the following: (1) Owing to the fact that SARS-CoV-2 is a virus with high transmissibility and susceptibility, there exists a biosecurity risk wherein bioterrorists could exploit this characteristic, with potentially hazardous consequences. (2) By publishing the technology roadmap, it is possible for scientists and terrorists to be able to apply the same technique to synthesize more complex viruses [3]27, or to develop a "super virus" with extremely high infectivity, virulence, or vaccine-resistant. Currently, internet has made it easier to order the related biological materials that could potentially be used to synthesize bioweapons. (3) Accidental leakage of synthesized virus particles from the laboratory increases biosafety risks, threatening the safety of humans as well as that of the ecological environment.

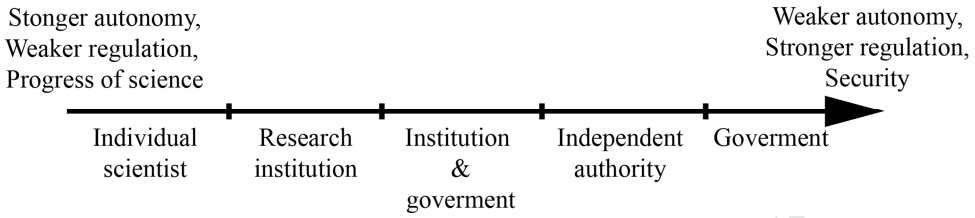
In view of these risks, the international scientific community had previously reached an agreement on the development of dual-use techniques. First, based on the "Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction" (better known as "The Biological Weapons Convention" (BWC) effective since March 1975) and the existing international laws and regulations[1], the research and development of dual-use biotechnology must guarantee safety and security, and never, in any circumstance, be used to harm the safety of individuals and the society at large. The convention and the relevant laws and regulations draw a red line for dual-use biotechnology research, to ensure "morality of duty"[2][4], and also to serve as the bottom line for the development of biological science. Second, dual-use biotechnology must promote scientific independent innovation while ensuring the protection of social safety. The two basic values of safety/security and intellectual freedom of research must be considered evenly. Therefore, countries all over the world are promoting biotechnological innovation while stressing equally on the importance of biosafety and biosecurity legislation. To reduce the predictable risks caused by the dual-use of biotechnology as much as possible, it is necessary to take the following into consideration before development of any high-risk technology: (1) Whether it is essential to undertake the research and to undertake it now? Whether there exist other alternative technologies, as in, whether it is necessary and urgent? (2) Whether and how to undertake the implemention of mandatory safety/security measures? (3) Whether and how to compulsorily certify the technology? (4) Whether and how to educate and train researchers? (5) Whether and how to investigate the reliability of the researchers? (6) Whether and how to oversee the publication and propagation of the research results? How to answer the above questions on the basis of balancing the value of

[1] For example, "Regulation of Research into Biological Disease Agents Act" of Israel, "Public Health Security and bioterrorism preparedness response act" of the U.S., "Safety management measures for biotechnology research and development" of China, etc.

[2] The so-called "morality of duty" lays down the basic rules without which an ordered society is impossible or without which an orderly society fails to achieve certain essential goals. Such moral norms can be regarded as a synonym of state law. The violation of such rules will lead to the punishment of the state's coercive power.

safety/security and intellectual freedom, and risk assessment, depends on which subjects own the biosafety/biosecurity regulation rights, and depends on which standard technique and behavioral norm to carry out.

According to previous research, from the perspective of the rights distribution on biosafety/biosecurity regulation, there are five theoretical and practical decision-making models, ranging from an individual researcher to a complete government agency [3]63-64:



There would exist some problems when the allocation of regulation rights is located too far on the left or right side of the above axis. Individual scientists and research institutions (located on the left) may emphasize too much on the value of technological development during the determination of the value tradeoff, and they may also lack the professional ability to assess the economic, political, and ethical issues arising from the development of a specific biotechnological innovation. On the right side of the axis, government agencies often lack professional judgment on rapidly changing biotechnology; they may overemphasize the value of social safety/security and their strict adherence to formal norms is not beneficial for flexible case-by-case decision-making. However, in the case of the independent regulatory agencies, consisting of scientists, ethicists, jurists, and government regulators, due to the diversity of their decision-making members, they are able to undertake a comprehensive review of the process of knowledge acquisition from the perspectives of science, economy, politics, and law, and balance the value between social safety/security and technological development.

With respect to the norms of biosafety/biosecurity regulation, owing to the rapid progress of biological research, it is difficult for regulators and researchers to design or construct clear and specific systems for the measurement or ranking of the variable values of science, economics, politics, and ethics involved in research. Therefore, even if a particular research action complies with the law, it does not mean that it is ethically responsible. To achieve responsible research[3], it is necessary to supplement the deficiencies of the "hard law" with the more flexible, voluntary, and ethical "soft law," so as to promote the voluntary participation of diverse groups and the action of the safety committee within the research institution, and to encourage the relevant personnel to comply with the "morality of aspiration" or the "challenge of excellence"[4][4].

As observed in the ethical statement from the research group of the University of Bern, there was

[3] Responsible research includes, but is not limited to, research with irreplaceable necessity, research behaviors with sufficient goodness, and research value with an optimal balance between risks and benefits.

[4] The so-called morality of aspiration is the morality of the Good Life, of excellence of the fullest realization of human powers. The violation of such a moral norm does not lead to the punishment of the state, but to the public's evaluation of his or her quality. In such a case, man or woman would be condemned for shortcoming, instead of wrong doing.

an assessment of the benefits and risks involved in the synthesis of SARS-CoV-2 virus [1]15-16. Regarding dual-use biological research, Switzerland utilizes the regulation mode where an independent biosafety committee and government agencies share the determination right: the Swiss Federal Office of Public Health (FOPH)[5]and the relevant ethics committee (the Swiss Expert Committee for Biosafety,[6]in this case), and other regulators (the Federal Office for Environment and the Federal Food Safety and Veterinary Office, in this case) communicate and negotiate, and finally the FOPH gives permission according to the review of the aforesaid institutions. However, it is unclear whether the balance between social safety/security and biotechnological innovation has been sufficiently evaluated and whether the representative public participation has been absorbed before acquiring administrative permission, due to the brief ethical statement.

In fact, there has always existed controversy pertaining to the gain-of-function research on engineering viruses in the scientific community. In 2011, Ron Fouchier of Erasmus Medical Center, the Netherlands, and Yoshihiro Kawaoka at the University of Wisconsin, Madison, USA, separately performed the genetic alteration of the H5N1 virus, which was found to be easily transmissible between ferrets through the air. Fouchier claimed that it was "probably one of the most dangerous viruses you can make" [5]. Regarding this, scientists and critics believed that this highly transmissible virus could cause a huge risk to human beings if it was accidentally leaked or was misused by bioterrorists [5]. In 2014, the U.S. Government instituted a pause on funding for any new studies that included certain gain-of-function experiments involving influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) viruses, and encouraged those currently conducting this type of work to voluntarily pause their research while the risks and benefits were being reassessed by the National Science Advisory Board for Biosecurity (NSABB) and the National Research Council (NRC) [6].

From the perspective of responsible development of biotechnology, regarding to the risk assessment of a highly dangerous virus like SARS-CoV-2, it is necessary to clarify the items of risk assessment. For instance, whether the yeast-based synthetic genome method in the paper is irreplaceable in the development of therapeutics or a vaccine? If there are alternative safe methods to develop a vaccine and select therapeutics with recombinant DNA technology, such as recombinant viral protein, production of a pseudovirus, or transfection with mRNA fragments of viral structure proteins, why should such a huge risk be undertaken? Especially, the risk of this virus reconstruction technique (transformation-associated recombination, TAR) is in the production of not only the novel coronavirus, but also other dangerous RNA viruses, such as other coronaviruses and the Zika virus (ZIKV). Faced with the situation where other laboratories or universities (such as the University of North Carolina) are also trying to create a copy of the virus from scratch [7], how can we ensure that this technology is not misused or abused in the future? For such technologies, which can be easily applied or converted to risk, the risk of publication needs to be strictly assessed, for example, whether to publish, to which group of people, and under what circumstances could the research be published? In addition, how should we compare and quantify which groups will benefit and which groups will undertake the risk, and what is the

[5] More information can be seen in: https://www.bag.admin.ch/bag/en/home.html
[6] More information can be seen in: https://www.efbs.admin.ch/en/homepage/

criterion of determination? Whether scientists have enough expertise and intelligence to fully assess the dual-use risks of a synthesized virus (including the assessment of the motivation, condition, and capability of bioterrorists to acquire SARS-CoV-2 or to design and synthesize it) [3][54]? Once the risks become a reality, who or which organization should take responsibility for them? Whether it is sufficient to deal with and resolve the risk only depending on the "responsibility after the event"? Furthermore, the ratio of benefits to risks is not only a scientific issue, but also involves differences in risk perception and value judgment of different subjects; the views about the risks involved often differ between the experts and the public. Then, which subject's risk sense should be taken into consideration in the prior ethical review and for the determination of the value balance between social safety/security and biotechnological innovation?

According to the "AREA" theoretical framework [8], which was proposed by the Engineering and Physical Sciences Research Council of the UK (EPSRC) on the basis of Responsible (research and) Innovation (RI/RRI), its contents include: Anticipation, Reflection, Engagement, and Action (AREA). We believe that research transparency and public participation are very important in the research of pathogen synthesis technology. Scientists and regulators should cooperate with the public and other stakeholders to encourage dialogue with the public to address key issues, such as public acceptability. Although scientific research requires a spirit of freedom and autonomy, for such dual-use biotechnology with a high-risk potential, no single scientist and scientific community can undertake the responsibility, once the risks materialize into real dangers. For that reason, in addition to enhancing the "self-government" and self-discipline of scientists and scientific communities, government supervision must be reinforced, laws and regulations should be improved, and global regulation framework ought to be constructed. Therefore, we appeal to scientists to be highly prudent and responsible while undertaking the research and development involving pathogen synthesis technologies. We share the same earth, interests, risks, and destiny and therefore, we are supposed to assume equal responsibility to protect our world. The whole world should join hands and overcome the challenge posed by this novel virus together. Only through joint participation and effective regulation can we guide dual-use technologies like engineering SARS-CoV-2 to benefit human society.

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