

COMMENTARY

Engineering of Viruses and Pathogens for Gain-of-Function Research

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Ethical concerns related to engineering of viruses and pathogens for gain-of-function (GoF) research has been widely debated in the literature (1). Scientists are conflicted as to the value of GoF research which has been used in the past to enhance viral pathogenicity, transmissibility, antigenicity, and tropism (2-4). The primary objective of these experiments was to gain a better understanding of the pathogen, allowing investigators to develop a more reliable predictive models for emerging infectious diseases and to combat them with effective vaccines and other therapeutic agents. This issue was recently highlighted during a U.S. congressional hearing aimed at elucidating the origin of the SARS-CoV-2 pandemic that has infected over 173 million worldwide and has resulted in the death of over 3.7 million people (5, 6). In US alone, SARS-CoV-2 has infected over 33 million and caused the death of over 594,000 people (7).

Perhaps the most controversial research related to GoF was the modification of H5N1 avian flu virus (8). In these experiments, the investigators used reverse genetics that enhanced the lethality of the virus, confirming that H5N1 can jump from birds to mammals and could be efficiently transmitted between humans. These studies that were funded by the National Institute of Allergy and Infectious Disease (NIAID) raised numerous ethical and public health concerns (9). It was argued that the risk posed by the inadvertent escape of laboratory engineered H5N1 into the community far outweighs the benefit that would be gained from these highly perilous experiments. The controversy escalated when the

National Science Advisory Board for Biosecurity (NSABB) issued its recommendation that the controversial H5N1 reports be published with significant redactions (10). NSABB recommended that methodology and other details that could enable replication of the experiments by those who seek to do harm are to be redacted. This controversial research and the NSABB recommendation divided the scientific community, which recognized that the easily transmitted laboratory engineered GoF H5N1 could be extraordinarily lethal.

In 2014, a series of mishaps in which highly pathogenic microbes were mishandled by various laboratories in the U.S. Centers for Disease Control and Prevention (CDC) resulted in closure of two labs and halted some biological shipments (11). The cases included an accidental shipment of live anthrax; the discovery of forgotten, live smallpox samples; and a newly revealed incident in which a dangerous influenza strain was accidentally shipped from CDC to another laboratory. These and other similar mishaps involving GoF experiments resulted, in the issuance of a moratorium by the U.S. Government pausing deliberative process and research funding for selected GoF research involving Influenza, MERS, and SARS viruses in 2014 (12).

Subsequent to implementation of this “pause,” both the National Research Council and the Institute of Medicine organized a number of symposiums to discuss the potential risks and benefits of GoF research. These deliberations ultimately resulted in the publication by NSABB

"Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research" (13). This was followed by the publication by the US Department of Health & Human Services "Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight" (P3CO) (14). With these P3CO recommendations in place, in 2017, the NIH lifted the moratorium into GoF research because it was deemed to be important in helping identify, understand, and develop strategies and effective countermeasures against rapidly evolving pathogens that pose a threat to public health (15).

With the lifting of this moratorium, NIAID through an intermediate organization, funded GoF research to be conducted on bat coronavirus in collaboration with the Institute of Virology, Wuhan, China (16). The primary objective of this funding was to conduct GoF research for the purpose of understanding how bat coronaviruses could mutate to attack humans. It is unclear what and/or how this GoF research on bat coronavirus may have contributed to the current COVID-19 pandemic that has devastated the social and economic fabric globally.

Despite the importance of GoF research and the fact that this recent funding has now been suspended by the NIAID, one must recognize that accidental escape of engineered pathogens and viruses do pose a catastrophic existential risk for the global human community and every effort must be exercised to prevent (not minimize) this risk.

Diclosures

SR declares no conflicts of interest.

MS declares no conflicts of interest.

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