When gain-of-function research is not “gain-of-function” research

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There is ongoing discussion among the scientific and biosecurity communities over how to address concerns about “gain-of-function” (GOF) research using highly pathogenic agents [1–3]. The discussion has mainly centered on previous work by Yoshihiro Kawaoka’s group at the University of Madison-Wisconsin in the USA [4] and Ron Fouchier’s group at Rotterdam University in the Netherlands [5]. Both groups introduced mutations into highly pathogenic H5N1 avian influenza (HPAI) that could potentially increase human-to-human transmission of the virus. These mutations are classified as GOF because they increase airborne transmissibility in ferrets—a good model for human transmission. Some in the research and biosecurity communities are concerned that these experiments could result in accidental or intentional releases of the mutated pathogen, or that the now publicly available information about how to increase the human-to-human transmissibility of H5N1 influenza could be abused for developing biological weapons [6,7].

Earlier this year, Kawaoka’s group again published the results of GOF research on the PR8 influenza backbone in which they created a high-yield vaccine strain capable of hosting multiple HA/NA antigenic combinations [8]. The high-yield phenotype was observed in diverse host cells in addition to chicken embryos, which are used for influenza vaccine production. This is a potentially major breakthrough for vaccine development and production, as it would greatly reduce the time and cost of rapidly producing influenza vaccines in response to disease surveillance and prediction, as well

as to emergent pandemic strains. Nonetheless, and despite the obvious scientific and commercial value of this research, the decision whether to publish GOF-related research such as this, especially in human pathogens like influenza, is not straightforward.

The research performed by the Kawaoka group—which was finished before the current moratorium on GOF research in the USA came into place—resulted in a GOF phenotype. This work would have fallen under the current moratorium [9], but should not be classified as GOF research in our view. It is unlikely that the release of these high-yield strains from the laboratory would have any negative effect on human health because these are vaccine strains of influenza. Neither is this a case of dual-use research of concern (DURC) because the information in the paper has little potential to be applied to pathogenic strains of influenza. The mutations described are unlikely to be broadly applicable to other influenza subtypes or strains: growth-enhancing mutations from other influenza backbones did not necessarily confer a high-yield phenotype in the PR8 backbone. The decision to categorize this work as GOF—meaning that it falls under the current moratorium that has halted such research in the USA—was because of the previous experiments to increase transmissibility of avian H5N1 and HPAI’s designation as a “Pathogen with Pandemic Potential (PPP)”.

This example illustrates why we need a more appropriately structured classification system of GOF research with sufficient fidelity to consider individual pathogen strains and their features, instead of merely the

pathogen being used. As demonstrated by the lack of HPAI human pandemics—and the emergence of other known and unknown pathogens causing severe disease—singling out pathogens as having “pandemic potential” without sufficient supporting evidence is scientifically problematic. Furthermore, determining the “pandemic potential” of pathogens is sometimes only possible with GOF research. For the infectious disease community, the only way to proactively prepare for the next pandemic is to clearly define what constitutes a GOF and/or DURC in a way that is not wholly defined just by the pathogen. While the NIH and National Science Advisory Board for Biosecurity (NSABB) are reviewing the risks and benefits of GOF research, a clearer and more effective definition of what constitutes GOF research—one which circumscribes all infectious disease agents and not just a select list—should be established. The community needs to build this consensus to be able to safely continue GOF research and responsibly keep these experiments in the traditional antibiotic, antiviral, and vaccine development methodology.

The scientific community has always had a great interest in openly and accurately disseminating knowledge, which is now becoming possible with the advent of open access publications and other web-based tools; the research to increase the yield of the PR8 influenza backbone was in fact published in an open access journal. The proliferation of open access journals, preprint servers, and posting of scientific research on the internet is inherently good for science as a whole. However, it provides multiple challenges for DURC and GOF

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research to prevent their dissemination without proper review and management. It is clearly not sufficient to simply perform DURC reviews at the editorial level prior to publication in peer-reviewed journals because, in today's publication landscape, it is possible to publish work without review on pre-print servers or open-review journals. To better evaluate DURC and GOF research as a whole, a more comprehensive "systems" construct is needed. The review process should be initiated earlier, at the proposal step at the funding agency. In addition, it may require regular monitoring after the initial review to avoid "surprises", as occurred with Kawaoka's and Fouchier's original papers.

As the NIH and NSABB determine a course forward how "gain-of-function" research should be evaluated in the USA in the future, it needs to flesh out guidelines that list which pathogens and experiments require review and that standardize the review process itself. We suggest that the review and reporting should encompass the most critical phases of research from the proposal to the publications stage. Draft guidelines should be made available for public comment with meaningful responses considered for incorporation, published, and then formally reviewed on a regular basis and modified if required. These reviewing and reporting structures should be exercised prior to the formal requirement, with participation from outside actors and full transparency.

US government-funded research proposals should require a consistent, comprehensive

DURC review prior to funding and to the initiation of the research, and not only at the level of the institution (which has been recently enacted [10]) and the publication stage. This review process should be consistent across agencies. A common set of standards and guidelines should guide the review procedures of US public funding entities to determine whether research proposals present GOF and DURC concerns. Such a process will ensure that the research being funded has been cleared of these issues, and any potential dissemination of this work has been vetted. Similar to the definition of GOF research, the NIH and NSABB should establish how this work is to be reviewed, not simply whether the work has tangible merits.

The international scientific community, governments, private funders, overseers, regulators, publishers, and stakeholders should consider designing, testing, implementing, and embracing a consistent end-to-end protocol which promotes safe and valuable research while minimizing uncertainties and risks, including the misuse of science. We recognize that this is not an easy achievement to attain, but we believe that it will be worth the investment and effort and will help to prevent future funding moratoriums being placed on the GOF and DURC research communities.

Conflict of interest

R.S.M. was a former member of the NSABB from December 2009 to April 2012. The conclusions and opinions presented here are those of the authors

and are not the official policy of the National Research Council, DTRA, the US Army, ECBC, or the US Government. Information in this report is cleared for public release, and distribution is unlimited.

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