The H5N1 Moratorium Controversy and Debate

The pause in gain-of-function experiments involving highly pathogenic avian influenza virus to dissect mechanisms of mammalian transmission and virulence is a historic moment for science. The scientific community and the greater society that it serves are currently engaged in a vigorous debate on whether and how to carry out experiments that could provide essential information for preparedness against a pandemic of avian influenza. To foster discussion and to provide a venue to record the arguments for or against this moratorium, *mBio* has commissioned a series of views from experts in the field. In addition to these views, we note a need for a clear scientific rationale for gain-of-function studies and suggest that many of the current concerns involving such experiments can be circumvented by efforts to generate safer systems that could provide comparable information with much-reduced risk.

In the winter of 2012, a group of influenza virus investigators announced in a joint letter a "voluntary pause of 60 days on any research involving highly pathogenic avian influenza H5N1 viruses leading to the generation of viruses that are more transmissible in mammals" (1). The pause came at a time of great controversy in science, which was caused by the recommendation of the National Science Advisory Board for Biosecurity (NSABB) to redact details from two manuscripts that provided molecular information on mutations which allowed H5N1 to become transmissible in mammals (2). Although the self-imposed moratorium was originally meant for 60 days, experimental work has presumably not resumed. In the summer of 2012, the U.S. Government proposed an indefinite continuation of the moratorium on gain-of-function studies with H5N1 viruses that could affect mammalian virulence and transmissibility until a consensus emerges on what type of experiments should be done and the level of containment that should be imposed. In this fluid environment, *mBio* has commissioned five articles (3–7) from leading authorities in the field of biomedical research that have provided a variety of views on the road ahead, ranging from pro- to antimoratorium to concerns about containment and reflections on a similar pause in molecular research that occurred after the Asilomar conference (8). We are living in a historic time for science. It is the goal of *mBio* to provide a venue for recording these extraordinary events in essays written by scientists and to foster discussion which we hope will enable decisions that are in the best interests of humanity.

The best defense against a new influenza pandemic is scientific and medical information, and we have much to learn about the biology of influenza virus. It goes without saying that we must develop a much deeper understanding of the selective pressures acting on influenza virus as it passes through avian and mammalian populations, and of course, it is essential that we delineate the impact of specific sequence alterations on the ability of the virus to be transmitted between and cause disease in humans. Gain-of-function experiments are a direct and powerful tool for the study of influenza virus transmission. However, the outcome of gain-of-function studies involving mammalian virulence and/or transmissibility for H5N1 is also of concern because the product of these experiments could itself theoretically unleash a pandemic if there were a breach of containment or a laboratory accident. Hence, it is imperative that any such experiment be carried out under the safest conditions possible and that the information generated be worth the risk of carrying out such work.

Any cessation of experimental research, even if it is placed only on a single path among many that may provide new insights into the biology of influenza virus, must be viewed as a cause for concern. However, now that a moratorium is in place, a lifting of the ban must be accompanied by a clear scientific rationale for carrying out gain-of-function experiments. In other words, it is important to answer the following question: is there information from gain-of-function experiments that is critical for pandemic preparedness that cannot be obtained by other means? To us, this is a critical question that has not been adequately answered to date. For example, is it possible to obtain comparable information from sequence analysis of naturally occurring influenza virus strains that differ in mammalian transmissibility? Are there alternatives to gain-of-function studies that would provide comparable information? Another question is how such information will be used to forestall or ameliorate the possibility of an avian influenza pandemic. Here we can imagine scenarios whereby surveillance efforts identify strains circulating in avian populations that are near the point where naturally occurring mutations have a high likelihood of generating mammalian-transmissible virus strains and public health authorities could respond by culling the bird flocks and/or by emergency vaccine production. However, timely surveillance efforts are remarkably patchy in their coverage (9) and it is uncertain how this information will be immediately useful for pandemic preparedness. Lastly, there is the concern that information on the precise mutations needed for mammalian transmissibility can be used by bad actors to create a biological weapon. Although opinions differ widely on the likelihood of this possibility, such concerns were important elements in the original recommendation of the NSABB to redact the molecular information from the two manuscripts previously mentioned (10).

If gain-of-function experiments relating to H5N1 virulence and transmissibility in mammals are to be performed, it will be prudent and highly informative to continuously monitor the ability of heterotypic, as well as H5N1, vaccines to protect against challenges with new variants. In the longer term, one option with potential to circumvent the difficult problems posed by gain-of-function experiments is to devote effort to generating safer strains of influenza virus that could allow much of this work to be done under biosafety level 2 (BSL-2) or BSL-3 conditions. In this regard, we note that much of the recent progress in understanding the pathogenesis of Ebola virus, such as the mechanism of viral entry, has been made under BSL-2 conditions by expressing proteins in safer vectors (11). Influenza virus reverse genetic ap-

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proaches are well advanced, providing a platform to generate modified replicons with desirable safety features. Finding new approaches to obtain the data needed for influenza preparedness without posing risks to the society that supports such work, while at the same time maintaining the research enterprise, is a critical challenge if humanity is to successfully confront future pandemics. We note with anxiety and alarm that the moratorium, redactions, and publishing controversies could make it very hard to recruit talented investigators into this field, as many young scientists might search for more fertile pastures in safer areas of science. Given the known deadliness of influenza viruses, it is imperative that society maintain a healthy research enterprise which includes the identification of mechanisms to conduct research unencumbered and share the information gathered between scientists and public health authorities.

The H5N1 gain-of-function moratorium defines a historical moment in which society has asked for a pause in research that could potentially arm that same society with critical information needed to cope with a future catastrophic pandemic. There was a similar pause after the Asilomar conference on recombinant DNA research. However, that pause was followed by careful experimentation, which eventually led to a revolution in biology, medicine, criminology, paleontology, archeology, and perhaps yet to come, computational sciences. It is worthwhile to note that today we have entire industries dependent on molecular biology and that the fruits of that work include forensic DNA fingerprinting, numerous drugs from recombinant DNA technology, gene therapy, and the prospect of individualized medicine. Society has reaped these benefits because science was able to go forward.

It seems fairly obvious that Asilomar is pointing the way forward again today. Asilomar ushered in a period of cautious experimentation that was prevetted and then executed under conditions that combined biological and physical containment. This careful experimentation documented the safety of the technology, allowing most constraints to be relaxed and recombinant DNA technology to be widely practiced. Gain-of-function experiments with the potential to generate dangerous viral variants can follow a similar path. However, uncertainty was greater in 1975. Today we have a much better understanding of the risks involved, so the path to a safe and effective global effort should be easier to chart.

Like Asilomar, the moratorium represents a pause in some aspects of influenza virus research, and the challenge now is to find ways of framing questions in the context of the available scientific knowledge to decide what experiments need to be done and when and how to do them.

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