Risks and Benefits of Gain-of-Function Experiments with Pathogens of Pandemic Potential, Such as Influenza Virus: a Call for a Science-Based Discussion

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Influenza virus is one of a handful of infectious disease agents that can cause devastating pandemics with high mortality and morbidity in human populations. The human species is vulnerable to zoonotic infection with new influenza viruses, with the last occurring as recently as 2009. Influenza kills thousands of people each year, and the world is continuously confronting new epidemics. Today the complexity and interconnectivity of our society create vulnerabilities, such that pandemics with even low mortality have the potential to cause widespread suffering and economic disruption. Epidemics can have catastrophic effects on the social order and result in the disruption of benefits that we associate with current society, such as law and order and reliable food distribution (for a vivid and dramatic representation of the effect of epidemics on society, readers are invited to see the movie *Contagion*, where an outbreak with a new fictional virus leads to the breakdown of the social order). Hence, epidemics pose existential threats to civil society even when morbidity and mortality occur in a fraction of those infected. Given the biological characteristics of the influenza virus that ensure the continuous generation of antigenic variability, this virus poses a continuous extant threat, with the likelihood of new pandemics being determined by variables that remain poorly understood. In this environment, the influenza virus research community is humanity's best defense against influenza virus. Consequently, anything that impacts influenza virus research is of utmost importance to societal well-being.

In recent years, some members of the scientific community have been involved in a vigorous debate over so-called "gain-of-function" (GOF) experiments involving pathogens with pandemic potential (PPP), such as influenza virus. Proponents and opponents of GOF work engaged in extensive discussion about the value, safety, ethics, and validity of this type of research. The debate was initially catalyzed by research experiments published in 2012, which reported that serial passage in ferrets rendered variants of the highly pathogenic avian influenza virus (HPAIV) H5N1 transmissible in a mammalian species (1, 2). These experiments were performed, in part, because there was debate in the field as to whether H5N1 could become transmissible in humans. The result was accompanied by publication of the specific mutations associated with this new function, which was essentially a "species jump" to mammalian transmission. Although influenza virus has historically demonstrated the capacity to move across species, in this particular experiment, the GOF was the acquisition of mammalian transmissibility for a virus that previously lacked it. The debate over this type of experimentation (i.e., that which changes the transmissibility of an influenza virus to include a mammalian species) resulted in a temporary moratorium on GOF experiments involving HPAIV, followed by continuation of the work with additional biosafety precautions and regulations (3, 4). There followed a period of relative quiescence as the new status quo established itself. However, several papers describing similar experiments with other influenza virus strains have subsequently been published (5–7), along with accompanying editorials that explain the decision for publication (8, 9). In recent months the controversy over GOF experiments has been rekindled by reports of the generation of new viruses that are similar to the 1918 strain (6) and further fueled by two laboratory accidents at the Centers for Disease Control that heightened concern about accidental escape of laboratory strains with pandemic potential. With this backdrop, GOF experiments have been severely criticized in the general media, and 18 individuals, including both authors of this editorial, signed a statement of concern involving influenza virus GOF experiments (http://www.cambridgeworkinggroup.org/). The essence of this statement from the Cambridge Working Group (CWG) was a call for curtailment of such experiments, during which time there could be a risk-benefit analysis of future work and the convening of a conference to discuss the many issues involved in this developing situation. The CWG statement has been criticized, but there appears to be some agreement on the need for an Asilomar-type conference to explore the many issues involved in GOF experiments (http://www.twiv.tv/2014/07/20/twiv-294/). Most recently, a group called Scientists for Science posted its own statement emphasizing the importance of research on potentially dangerous pathogens and also calling for a conference to discuss the issues (http://www.scientistsforscience.org/). We note that both statements share many points of agreement, which provides a promising base for constructive dialog. In the past, *mBio* has provided a forum for discussion and debate on the merits of this work. Here we take up the pen (or keyboard) to highlight some issues pertinent to the ongoing debate and promote further discussion, our major goal in signing the CWG statement. We note that the issues surrounding the GOF debate are enormously complex and involve deep questions of science, philosophy, and ethics.

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WHAT IS "GAIN OF FUNCTION"?

Given that symbolic language is the basis for much of human communication, we begin with terminology and dissect the phrase "gain of function," or GOF. When applied to influenza virus research, the term GOF has taken on the meaning of something dangerous, risky, and possibly nefarious. However, GOF means exactly what it says, that the entity in question has gained a new property. In the case of influenza virus, the concern regarding GOF has been associated with the acquisition of a new function, such as mammalian transmissibility, increased virulence for humans, or evasion of existing host immunity. For example, passage of H5N1 virus in ferrets allowed selection for variants with ferret-to-ferret transmissibility, and the GOF was the acquisition of mammalian transmission. However, the same type of experiment can be beneficial to humanity, since the principle of passage in a nonnative host can be used to generate attenuated vaccines. For example, some human-pathogenic viruses, such as poliovirus, were attenuated by passage in cells of another species, such as monkey cells. In those experiments, the GOF was replication in another species, and this property reduced the efficiency of replication in human cells, thus resulting in a new attenuated strain that could be used as a vaccine. Indeed, those attenuated viruses manifested a GOF, namely, attenuation. One of us recently published a GOF experiment with BK polyomavirus, in which mutation of a regulatory microRNA (miRNA) greatly enhanced replication (10). Hence, GOF is a powerful experimental tool that is routinely used in biomedical research, and the concern with influenza virus research is not gain of function *per se* but rather the selection of variants with increased mammalian transmissibility and virulence that could affect human populations if there were deliberate or accidental release. It is clear that GOF is a problematic phrase, and this term has acquired a particular meaning in the ongoing debate and particularly in the lay media. Unfortunately, the term GOF has come to only represent something that can be used to confer dangerous properties to a microbe. Despite these problems in terminology, we use the expression GOF in this essay with the understanding that we are referring to the narrow category of experiments that involve primarily changes to the virulence and transmissibility of PPP, such as influenza virus. Although influenza virus is the subject of the ongoing debate, it is important to note that these issues extend to other PPP, such as severe acute respiratory syndrome (SARS) coronavirus.

THE VALUE OF INFLUENZA VIRUS GOF EXPERIMENTS

Recent history has shown that GOF experiments in influenza virus research can provide unique insights into the potential threat posed by influenza virus strains and mechanisms of viral pathogenesis. Much of the debate involving the H5N1 experiments which demonstrated the "gain" of ferret transmissibility focused on the publication of the specific mutations that conferred this property. However, the major scientific finding was the observation that this virus had the biological capacity to be transmitted between mammals after alterations in a few amino acids. In fact, this finding is of great value to humanity, because it suggested that a human H5N1 pandemic might be able to occur if and when similar mutations occurred spontaneously, as is characteristic of influenza viruses, along with conditions favorable for bird-to-mammal transmission. In another set of GOF experiments, the HPAIV H7N1 was shown to be capable of mammalian transmission due to mutations that did not change receptor specificity (5). As a result of these experiments humanity has much more knowledge and stands warned of the potential perils these viruses pose. This information emerged from GOF experiments. In fact, it is difficult to imagine another mechanism for obtaining the information that has been gained from GOF-type experiments, particularly because it is only through experiments that can control the expression of given determinants that proof can be obtained. Since proof of the germ theory, modern scientific proof generally requires the use of approaches that attribute a given property to a given determinant. Hence, GOF-type experiments are of particular epistemological value because they directly imply causality. Apart from informing on the potential for virulence and transmissibility, GOF experiments are powerful tools for dissecting questions concerning viral pathogenesis. For example, H5N1 mutational analysis showed that the efficiency of viral replication in avian and mammalian cells is dependent on hemagglutinin polymorphisms that facilitate activation at lower pH (7, 8). This finding could be exploited to increase the yield of virus during preparation of vaccine stocks. Furthermore, the identification of sequence changes associated with GOF could in theory lead to the identification of new antiviral targets, thus providing a potential societal benefit. The power of GOF experiments is that they are a highly efficient, reliable, and effective tool that can identify certain phenotypes that often cannot be identified by using other scientific approaches. Hence, we feel that there is ample evidence that GOF experiments can provide important information and are useful tools for investigation of influenza virus-related questions. In fact, we believe that the crux of the debate surrounding GOF experiments is not their value but their potential risk.

THE RISK-BENEFIT CONUNDRUM

At the heart of the scientific debate over influenza virus GOF experiments are different perceptions of the risk-benefit ratio of such experiments. Proponents of continued GOF experiments emphasize the benefit and downplay or even deny the risk, while opponents do the converse. Since both risk and benefit involve quantitative assessments, in this case with limited information, the debate is fueled by the reality that weighing risks and benefits involves judgment calls. The risks fall into two general categories that are separate but related: namely, biosecurity and biosafety. Biosecurity risk is the likelihood that someone would use products or information gained from GOF experiments that led to a more pathogenic virus to carry out intentional damage in the form of bioterrorism. Biosafety risk is the likelihood of accidental escape that could trigger an outbreak and epidemic. When the National Science Advisory Board for Biosecurity (NSABB) considered the H5N1 GOF papers, the original discussions were focused on biosecurity, which was the charge of the NSABB, but as time passed, the concern evolved from biosecurity to biosafety. Biosecurity estimates are difficult, because they involve a calculation of the risk of deliberate nefarious action, and such information is simply not always available. In fact, these assessments are so difficult that we have called for the formation of a national board to handle questions related to dual-use research of concern (11). On the other hand, biosafety estimates can rely on historical data. Prior experience with lab accidents was used by Lipsitch and Bloom to suggest that there is a significant likelihood that a major lab accident could occur with GOF influenza virus strains (12). In fact, there is strong circumstantial evidence that the reintroduction of H1N1 into human circulation in 1977 after its disappearance in 1950 began with

the accidental release of a laboratory strain (13). Calculations of risk must also consider that researchers have learned from mistakes in the past, that the biosafety precautions being taken today have improved over historical standards, and that new regulations were recently put in place for the laboratory of HPAIV (4), with the important caveat that the recent problems at the CDC show that even the most advanced laboratories are vulnerable to serious mishaps. While no one appears to have been harmed by the lapses at the CDC laboratories, there have been recent cases in which laboratory workers were infected with *Yersinia pestis* (14) and *Brucella* sp. (15), among others, highlighting the fact that laboratory accidents with virulent pathogens continue to occur despite knowledge of their potential danger and modern biosafety practices. Calculating the benefits of GOF research is also a somewhat challenging task, since the history of science shows that unexpected results can be more important than those that were originally anticipated when the experiment was designed. The importance of scientific findings is often not apparent at the time of discovery (16). Hence, the argument from GOF opponents that such experiments have little value due to their risk must be considered with caution, given historical precedents showing that the value of scientific information cannot always be judged with current understanding or knowledge.

Given the problems in calculating the numerator and denominator of a risk-benefit assessment, we urge both sides to approach this complex problem with consideration of the opposite view and with humility. To argue that the risk is overwhelming relative to the perceived benefit is not a tenable position, given the precedent that GOF experiments have arguably already provided useful information and the fact that the actual benefit may not be appreciated at present. Similarly, to argue that the risk is minimal relative to the benefit defies hard evidence of human fallibility and a history of serious laboratory accidents. Perhaps an initial meeting point for GOF proponents and opponents would be to agree that risk-benefit calculations are difficult to perform with the data at hand. That said, we note that in other contexts, risk-benefit calculations are routinely done in everyday science and medicine, even with incomplete data. For example, institutional biosafety and human subjects review committees debate risk routinely and do make decisions despite having to make judgment calls. We assert that actually doing a risk-benefit analysis with available data can lead to discussions and experimental modifications that could minimize risk and enhance benefit. Even though proponents and opponents of influenza virus GOF research place very different values on the parameters of the calculations, both sides are actually already doing risk-benefit analyses and using them to support their respective positions. Despite the disagreements on the value of the numerator and the denominator, risk-benefit analyses are always a good idea. They stimulate discussion, and such discussion can lead to improved experimental design and safety, and generate and prioritize the acquisition of additional knowledge. Therefore, we argue that risk-benefit discussions should not be avoided because the parameters are difficult to quantify.

UNANSWERED QUESTIONS

Swirling around the GOF debate are a series of unanswered questions which are amenable to scientific study and which if answered could dramatically inform the debate.

What is the case-fatality ratio of HPAIV in humans? The mortality associated with H5N1 virus is a key driver of the GOF risk-benefit debate. Although there seems to be no debate that the case-fatality ratio of individuals who come to medical attention with H5N1 is high, the ratio of asymptomatic to symptomatic infections has been the subject of debate in the literature (17, 18). This is a key parameter for which additional information could become available with additional studies. If the case-mortality ratio is indeed as high as 50%, then the risk is greater, while a much lower ratio would portend a significantly reduced risk. It is worthwhile for experts on serological studies and influenza epidemiology to come to agreement on the type of information needed and then carry out the studies to address this important issue. Such studies should be prioritized. Irrespective of where one stands in the case-fatality debate, it is worthwhile to note that even a case-fatality ratio as low as $<0.1\%$, such as that associated with the 2009 pandemic, would cause immeasurable suffering to affected individuals and could create significant societal havoc.

What is the relationship between transmissibility in one mammal to that in another? Much of the furor with the GOF H5N1 was experimental work showing that the virus could become transmissible in ferrets (19). However, we do not know the relationship between ferret transmissibility and human transmissibility. Opponents of GOF research worry that ferret transmissibility portends a high likelihood for human transmissibility, while proponents of GOF argue that such data do not exist and minimize any extrapolation from ferrets to humans. Clearly, information about this point would be valuable to estimating the risk associated with these experiments, and this should be a focus of future research.

What is the relationship between transmissibility and virulence in HPAIV? Virulence and transmissibility are different properties of pathogenic microbes that can be related but are also distinguishable. BK virus is highly transmissible among humans but is associated with disease only in transplant recipients. In contrast, *Mycobacterium tuberculosis* spreads by aerosol during coughing associated with pulmonary disease. Hence, transmissibility from host to host appears to be associated with virulence for some microbes and not others. Are virulence and transmissibility separable for influenza viruses? Knowing the relationship between transmissibility and virulence is important for understanding the basic biology of this virus and could inform the risk-benefit debate.

What is the relationship between laboratory-engineered and naturally selected influenza viruses with regard to pathogenicity? GOF opponents worry about laboratory-engineered viruses, while GOF proponents argue that nature is far more effective in selecting new dangerous variants than any laboratory experiment. However, this point and counterpoint misses important biological questions. Viruses recovered in the laboratory can be evolved in the absence of natural hosts and thus are not constrained by the environment of those hosts. Without host selection, such viruses may be more or less pathogenic, and there is no way of predicting their capacity for pathogenicity unless we understand the parameters that determine virulence. Consequently, efforts to understand the mechanism of virulence pertaining to naturally derived and laboratory-derived viruses could provide valuable insights, with the important caveat that virulence is an emergent property and as such may not be predictable (20).

What are the possible public health benefits of the knowledge gained? This question can probably not be answered prospectively, but at least there should be a discussion of potential

benefits in the context of existing public health capabilities. GOF experiments have been justified on the grounds that the information is helpful for surveillance and vaccine design. Opponents have argued, however, that vaccine design can be accomplished without changing transmission properties. In addition, it has been posited that current surveillance strategies are inadequate and cannot readily incorporate knowledge of the exact mutations that may lead to enhanced human virulence or transmission (21, 22). However, even if the information is not useful today, the availability of such information could drive new capabilities, such as the development of more robust surveillance methods.

OTHER DANGERS

Outside the debate on the usual GOF risk-benefit calculations, there are other dangers that need to be considered. First is the possibility that increased scrutiny of experimental science and regulation of influenza virus research will hobble the field. This is already occurring, as influenza virus investigators are forced to respond and adapt to increasing regulation of their field. One must also balance the possible effects on the careers of postdocs and graduate students in the field with increasing oversight due to the desire to protect against possible accidental releases. As the difficulty of carrying out experiments and meeting regulations increases, it may be hard to recruit the best and the brightest to this important field. Second is the danger posed by the absence of work that is simply not done to avoid controversy. Although the importance of work not done is impossible to document, experiments that are not being done could provide major insights simply because they provide more information to inform discussion and debate. Third is the possibility that additional laboratory mishaps will lead to even more draconian regulations that will curtail research more broadly. These dangers are interrelated but have in common a high likelihood that, singly or together, they could pose major disruptions to research on influenza virus and microbiology research in general. Given the importance of the influenza virus research community to preparedness against pandemics, anything interfering with this work is of societal concern, and these dangers need to be incorporated into any discussion of GOF risk-benefit analysis.

AN ASILOMAR-LIKE MOMENT?

When recombinant DNA technology first came into use, scientists and others convened at Asilomar to discuss the risks and benefits and to chart a path forward that would allow this important technology to be used safely (23, 24). The controversy over the HPAIV GOF experiments has led to calls for another Asilomar-like conference. The goal of such a conference would be to bring the parties interested in the issues related to GOF experiments together with the hope of finding common ground and finding a way to allow GOF research to go forward with minimal risk and maximal benefit. We think this is a good idea, and this was our primary intent in signing the CWG document. However, we caution that the times are very different now than in 1975, when the Asilomar meeting took place. Today, communication by e-mail and Twitter is instantaneous, and the information conveyed by these new media is different than the phone conversations and mail correspondence of that time. In fact, to date, much of the discussion between the interested camps on GOF research has been "Twitter-like," with statements made via general media or e-mail messages to supporters. This type of communication reduces complex issues to terse, often definitive-sounding statements that can be polarizing. Thus, we think that there must be a broad-based, rational, face-to-face discussion. Hence, if such a conference is to be convened, we call on the organizers to assemble groups with wide representation of individuals with a direct stake in this research as well as thoughtful scientists with no skin in the game, to tackle such issues as risk-benefit, ethics, biosafety, biosecurity, etc. Ideally, just like treaty negotiations between countries, much of the work should be done by smaller groups that explore the various issues and identify areas where consensus is possible and those where both sides must agree to disagree. The conference would then function to inform on areas that hopefully have been agreed to, or explored and found to have no common ground, as well as involving all participants in more focused discussions. Interestingly, a similar call for discussion of the risks and benefits was recently raised with respect to the rapidly advancing use of gene drives, a research area ripe with risk-benefit uncertainties similar to those of the influenza virus GOF experiments (25, 26).

THE WAY FORWARD

Irrespective of where one stands on the GOF, it is important to reflect on the issues at stake. Perhaps most important is that there is a need to lower the level of rhetoric and focus on the scientific questions at hand. Proponents of GOF research are not reckless scientists but rather individuals who are driven to answer important scientific questions and hope to make a difference in the human struggle against this deadly virus. Opponents of GOF are not unsophisticated luddites determined to hinder influenza virus research but rather individuals who are primarily concerned about biosafety issues related to the work. A disheartening aspect of the GOF debate is that many participants seem to be focused on only one aspect of the controversy without considering the enormous complexity of the issues involved and the potential dangers associated with taking extreme views. Such dangers include catalyzing further polarization, proliferation of GOF research in laboratories that lack proper safety precautions, creating misinformation, and eliciting overreactions by elected officials and/or government agencies. Each of these dangers has the potential to hinder future research and leave society more vulnerable to influenza and other diseases. In writing this essay, we hoped to dissect the issues involved and provide a broader canvas for discussion.

For the near horizon, a conference sponsored by neutral parties appears to be one mechanism for further communication about which both parties appear agreeable. We are optimistic that most people in the pro- and anti-GOF camps are believers that information, discussion, and reason can lead the way to the best solutions to the intricate problems posed by this research. Despite all the uncertainties about risks and benefits, there must be a risk-benefit calculation, with proponents providing their reasons for benefit and opponents their assessment of risk. Obviously, one way to help achieve a consensus is for benefits of the work to be clearly articulated and for the risks to be minimized. For example, it may be helpful to revisit the biocontainment regulations to ascertain whether existing protocols are adequate or should be modified, keeping in mind that it is impossible to decrease the risk of an accident to zero. However, we must also face the possibility that there will be no consensus in this matter. If an impasse develops, it will be important to channel the debate into different areas of discourse. For example, if pro- and anti-GOF research proponents reach an impasse, perhaps the debate could refocus on identifying

the important questions in influenza virus research that both groups feel should be answered and in finding new creative experimental alternatives that satisfy both camps. Looking at the farther horizon, the influenza virus research community should consider making safer laboratory strains that would further mitigate the possibility of harm should lab accidents occur (27). Finally, we note that although this article and much of the debate are focused on HPAIV and PPP research, the issues considered here are relevant to the larger fields of microbiology and infectious diseases and that the outcome of these discussions will echo in other fields. It is possible that the GOF debate represents a historical moment for research in the microbiology community comparable to the advent of recombinant DNA technology in 1975 that led to the Asilomar conference. We note that the decisions made during and after Asilomar resulted in society's reaping the benefits of the molecular biology revolution, including many new therapies made possible by recombinant DNA technology (11). Given the potential threats posed by PPP and the capacity of this debate to affect the course of microbiological research in the 21st century, we must get this right. We are confident that the scientific community can tackle this problem in a manner that will maximize our ability to continue to generate important knowledge that will protect the public in the future.

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