Influenza Research, GoF, and Model Organisms

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Outline

The take-home: Gain-of-function research presents largely unexplored, classic philosophy-of-science questions surrounding inferences from model organisms, with social and political relevance.

Gain-of-Function Research

Gain-of-function research is research in which a virus or other pathogen is created, in the course of scientific research, that has increased virulence, transmissibility, or host range.

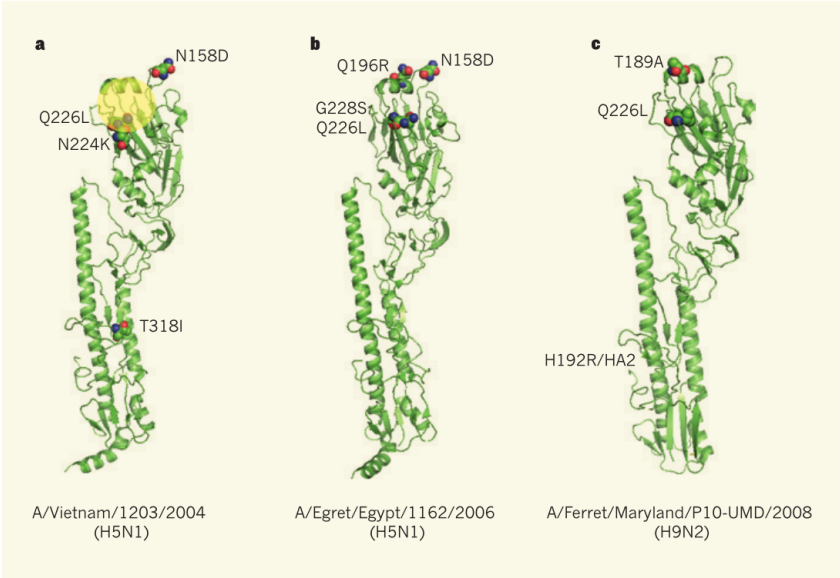


Figure 1 | Avian haemagglutinins transmissible in mammals. The haemagglutinin (HA) protein of influenza determines the type of target cell that the virus can infect. By mutating the site of the HA that binds

M. CZEK/AFP/GETTY

Pathogenic H5N1 avian influenza has led to the culling of hundreds of millions of birds. A human-transmissible form could have much worse consequences.

Adaptations of avian flu virus are a cause for concern

Members of the US **National Science Advisory Board for Biosecurity** explain its recommendations on the communication of experimental work on H5N1 influenza.

PETER PALESE

Don't censor life-saving science

Controlling who is allowed access to information about mutations in the H5N1 bird flu virus is unacceptable, says **Peter Palese**.

The recent arguments over the creation of a transmissible form of the bird flu virus (H5N1) feel very familiar. My colleagues and I were at the centre of a similar controversy in 2005, when we reconstructed the 1918 flu virus, which had killed up to 50 million

This experience has made the NSABB's latest recommendation — that the H5N1 researchers not reveal the mutations behind the virus's transmissibility — all the more frustrating. I make the same argument today that we made in 2005 — publishing these experiments without

WHO WILL WANT TO ENTER A FIELD IN WHICH YOU **CAN'T PUBLISH** YOUR MOST SCIENTIFICALLY INTERESTING **RESULTS?**

Epistemic Arguments for GoF

Although these experiments may seem dangerously foolhardy, they are actually the exact opposite. They gave us the opportunity to make the world safer, **allowing us to learn what makes the virus dangerous and how it can be disabled.** (Palese, 2012, *Nature*)

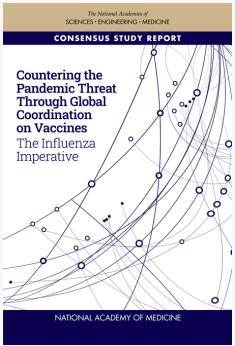
The risk of a pandemic caused by an avian influenza virus exists in nature. As members of the influenza research community, we believe that the avian A(H7N9) virus outbreak requires focused fundamental and applied research conducted by responsible investigators with appropriate facilities and risk-mitigation plans in place. To answer key questions important to public health, **research that may result in GOF is necessary and should be done.**
(Fouchier *et al.*, 2013, *Science*)

The recent lifting of the U.S. moratorium on gain-of-function research on potential pandemic viruses further illustrates the contribution of **unconventional, but responsible, research strategies to readiness.**

Philosopher George Santayana pointed out, "Those who cannot remember the past are condemned to repeat it." …preparation only stems from a global commitment to share data about viral isolates, **support innovative research, and dedicate resources to assess the pandemic risk of new and emerging influenza viruses** from zoonotic reservoirs. (Belser and Tumpey, 2018, *Science*)

These new functions or phenotypes can both **inform the experimenter on the possibility that such outcomes can occur** and also provide insight into the **mechanism as to how the new function was acquired** by the microbe. (Casadevall *et al.*, 2012)

GoF: largely **absent** from the discussion of responses to or "lessons from" COVID-19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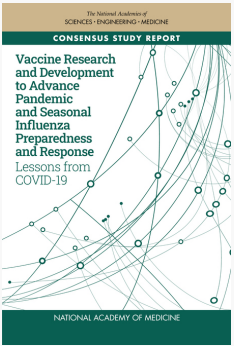
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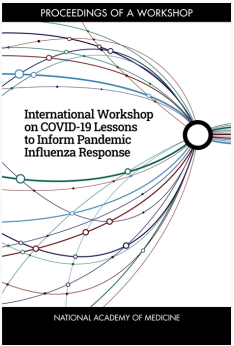
PROCEEDINGS OF A WORKSHOP
International Workshop on COVID-19 Lessons to Inform Pandemic Influenza Response
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Ferret Models

Three kinds of "model organism:"

1. the **viral strains** used as templates
2. the **genes targeted** for modification
3. the **ferret model** of transmission and illness

The Goals

Ferrets are the only model that “can present both the **pathogenic** and **transmissible** features of influenza virus infection” (Belser, Katz, and Tumpey 2011, 575)

HUMAN VS FERRET

CLINICAL SIGNS AND SYMPTOMS OF INFECTION

HUMANS

FERRETS

Fever

Anorexia

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How to choose your research organism

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ABSTRACT

Despite August Krogh's famous admonition that a 'convenient' organism exists for every biological problem, we

- **phenomenal access** to the relevant features of influenza
- **translational potential:** “physiological or genetic resemblance to humans”
- **responsiveness:** “offering better opportunities for the experimental manipulation of features of interest”

Three Open Questions

Skepticism about Ferrets

- **ease of supply** and **financial costs:** standard equipment lacking, inbred strains not developed, etc.
- **ethical considerations:** lack of best practices, more highly developed mentally
- **standardization:** unknown genetic diversity
- **viability** and **durability:** small sample sizes, usually not maintained as stocks
- **availability of methods and techniques** and **epistemic resources**: methodologies in flux, reagents unavailable, genome only recently sequenced

However, a powerful argument can be made for the value of GOF experiments, because they yield information that is **consistent with the normative standards of the fields of microbiology and infectious diseases,** and as such, they provide information that is immediately accessible and interpretable in the context of standards in the field. (Casadevall *et al.,* 2012)

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Really?

Understanding the role that these choices in experimental design can play in research studies and how these mammalian models can be further improved for use in risk assessment is critical. (Belser et al. 2016)

…**the use of ferrets for influenza studies has been limited** by factors such as animal availability, genetic heterogeneity (out-bred), the requirement of a complex husbandry facility and caging system, and a lack of immunological reagents and genetically modified mutants for immunological investigation. […] **Ideally, a larger number of ferrets should be used** but limitations such as high experimental cost, low animal availability, limited caging capacity and ethical constraint, typically restricts most studies to group sizes of five or less ferrets. (Oh and Hurt 2016)

…these confounders result in **heterogeneity with regard to procedures and practices established at all levels of research,** from individual investigators or institutions to broad country-specific regulations. (Belser et al. 2016)

Improving the Model

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RESEARCH ARTICLE

Robustness of the Ferret Model for Influenza Risk Assessment Studies: a Cross-Laboratory Exercise

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Working group on the standardization of the ferret model for influenza risk assessment

However, small sample sizes and a lack of standardized protocols can introduce interlaboratory variability, complicating interpretation of transmission experimental data. To assess the range of variation in ferret transmission experiments, **a global exercise was conducted by 11 laboratories** using two common stock H1N1 influenza viruses with different transmission characteristics in ferrets. (Belser et al. 2022)

Social and Institutional Factors

Defenders of GoF and skeptics about ferrets are largely **the same people**, in different social and institutional contexts.

Questions?

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