Gain-of-Function Research and Model Organisms

Les enjeux éthiques et épistémologiques de la pandémie de Covid-19, 16/2/2021

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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.

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.

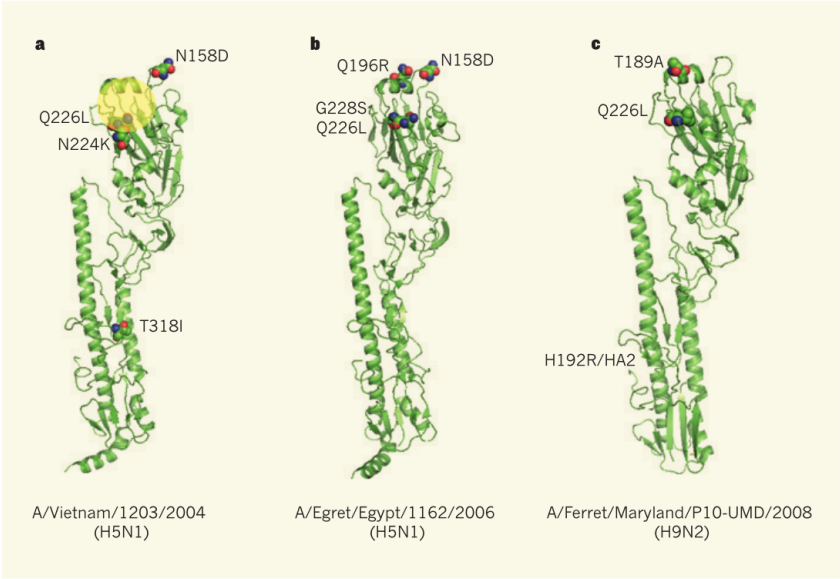


Figure 1 | Avian haemagglutinins transmissible in mammals. The haemagglutinin (HA) protein of influenza determines the type of target cell that the virus can infect. By mutating the site of the HA that binds

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 those 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*)

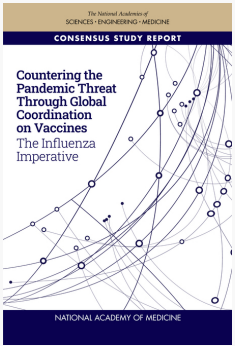
The recent lifting of the U.S. moratorium on gain-of-function research on potential pandemic viruses further illustrates the contribution of **unconventional, but responsible, research strategies to readiness.**

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 and COVID-19

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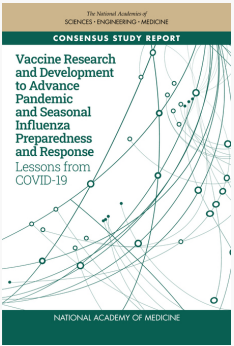
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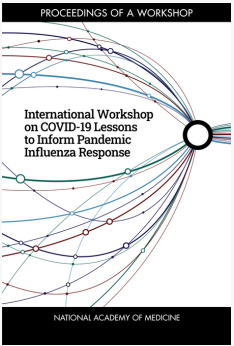
PROCEEDINGS OF A WORKSHOP
International Workshop on COVID-19 Lessons to Inform Pandemic Influenza Response
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Ferret Models

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”

Skepticism about Ferrets

Difficulties for at least **eight** other features:

- **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

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)

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?

Two Open Conclusions

1. Are ferret studies sufficiently guaranteeing the kind of knowledge promised by their defenders? (Related point: The defenders and skeptics are often the same people, in different contexts!)
2. Along the lines of the Dietrich *et al.* paper, what could we do to improve the quality of ferret models?

Questions?

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