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# LETTERS

*edited by Jennifer Sills*

## Gain-of-Function Experiments on H7N9

SINCE THE END OF MARCH 2013, AVIAN A INFLUENZA VIRUSES OF THE H7N9 SUBTYPE HAVE caused more than 130 human cases of infection in China, many of which were severe, resulting in 43 fatalities. Although this A(H7N9) virus outbreak is now under control, the virus (or one with similar properties) could reemerge as winter approaches. To better assess the pandemic threat posed by A(H7N9) viruses, NIAID/NIH Centers of Excellence in Influenza Research and Surveillance (CEIRS) investigators and other expert laboratories in China and elsewhere have characterized the wild-type avian A(H7N9) viruses in terms of host range, virulence, and transmission, and are evaluating the effectiveness of antiviral drugs and vaccine candidates. However, to fully assess the potential risk associated with these novel viruses, there is a need for additional research including experiments that may be classified as "gain-of-function" (GOF). Here, we outline the aspects of the current situation that most urgently require additional research, our proposed studies, and risk-mitigation strategies.

The A(H7N9) virus hemagglutinin protein has several motifs that are characteristic of mammalian-adapted and human influenza viruses, including mutations that confer human-type receptor-binding and enhanced virus replication in mammals. The pandemic risk rises exponentially should these viruses acquire the ability to transmit readily among humans.

Reports indicate that several A(H7N9) viruses from patients who were undergoing antiviral treatment acquired resistance to the primary medical countermeasure—neuraminidase inhibitors (such as oseltamivir, peramivir, and zanamivir). Acquisition of resistance to these inhibitors by A(H7N9) viruses could increase the risk of serious outcomes of A(H7N9) virus infections.

The hemagglutinin proteins of A(H7N9) viruses have a cleavage site consistent with a low-pathogenic phenotype in birds; in the past, highly pathogenic H7 variants (with basic amino acid insertions at the cleavage site that enable the spread of the virus to internal organs) have emerged from populations of low pathogenic strains circulating in domestic gallinaceous poultry.

Normally, epidemiological studies and characterization of viruses from field isolates are used to inform policy decisions regarding public health responses to a potential pandemic. However, classical epidemiological tracking does not give public health authorities the time they need to mount an effective response to mitigate the effects of a pandemic virus. To provide information that can assist surveillance activities—thus enabling appropriate public health preparations to be initiated before a pandemic—experiments that may result in GOF are critical.

Therefore, after review and approval, we propose to perform the following experiments that may result in GOF:

(i) **Immunogenicity**. To develop more effective vaccines and determine whether genetic changes that confer altered virulence, host range, or transmissibility also change antigenicity.

(ii) **Adaptation**. To assist with risk assessment of the pandemic potential of field strains and evaluate the potential of A(H7N9) viruses to become better adapted to mammals, including determining the ability of these viruses to reassort with other circulating influenza strains.

(iii) **Drug resistance**. To assess the potential for drug resistance to emerge in circulating viruses, evaluate the genetic stability of the mutations conferring drug resistance, evaluate the efficacy of combination therapy with antiviral therapeutics, determine whether the A(H7N9) viruses could become resistant to available antiviral drugs, and identify potential resistance mutations that should be monitored during antiviral treatment.

(iv) **Transmission**. To assess the pandemic potential of circulating strains and perform transmission studies to identify mutations and gene combinations that confer enhanced transmissibility in mammalian model systems (such as ferrets and/or guinea pigs).

(v) **Pathogenicity**. To aid risk assessment and identify mechanisms, including reassortment and changes to the hemagglutinin cleavage site, that would enable circulating A(H7N9) viruses to become more pathogenic.

All experiments proposed by influenza investigators are subject to review by institutional biosafety committees. The committees include experts in the fields of infectious disease, immunology, biosafety, molecular biology, and public health; also, members of the lay public represent views from outside the research community. Risk-mitigation plans for working with potentially dangerous influenza viruses, including 1918 virus and highly pathogenic avian H5N1 viruses, will be applied to conduct GOF experiments with A(H7N9) viruses (see supplementary text). Additional reviews may be required by the funding agencies for proposed studies of A(H7N9) viruses (see scim.ag/13BK5Hs).

The recent H5N1 virus transmission con-

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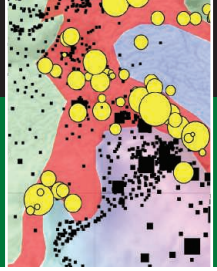
Published by AAAS



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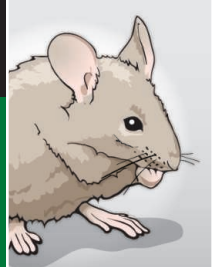

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troversy focused on the balance of risks and benefits of conducting research that proved the ability of the H5N1 virus to become transmissible in mammals (see www.sciencemag.org/special/h5n1). These findings demonstrated the pandemic potential of H5N1 viruses and reinforced the need for continued optimization of pandemic preparedness measures. Key mutations associated with adaptation to mammals, included in an annotated inventory for mutations in H5N1 viruses developed by the U.S. Centers for Disease Prevention and Control, were identified in human isolates of A(H7N9) viruses. Scientific evidence of the pandemic threat posed by A(H7N9) viruses, based on H5N1 GOF studies, factored into risk assessments by the public health officials in China, the United States, and other countries.

Since the H5N1 transmission papers were published, follow-up scientific studies have contributed to our understanding of host adaptation by influenza viruses, the development of vaccines and therapeutics, and improved surveillance.

Finally, a benefit of the H5N1 virus research controversy has been the increased dialogue regarding laboratory biosafety and dual-use research. The World Health Organization issued laboratory biosafety guidelines for conducting research on H5N1 transmission and, in the United States, additional oversight policies and risk-mitigation practices have been put in place or proposed. Some journals now encourage authors to include biosafety and biosecurity descriptions in their manuscripts, thereby raising the awareness of researchers intending to replicate experiments.

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.

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**Supplementary Materials**
www.sciencemag.org/cgi/content/full/science.1243325/DC1
Supplementary Text

Published online 7 August 2013; 10.1126/science.1243325

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## TECHNICAL COMMENT ABSTRACTS

### Comment on "The Placental Mammal Ancestor and the Post–K-Pg Radiation of Placentals"

**Mark S. Springer, Robert W. Meredith, Emma C. Teeling, William J. Murphy**

O'Leary *et al*. (Research Article, 8 February 2013, p. 662) examined mammalian relationships and divergence times and concluded that a single placental ancestor crossed the Cretaceous-Paleogene (K-Pg) boundary. This conclusion relies on phylogenetic analyses that fail to discriminate between homology and homoplasy and further implies virus-like rates of nucleotide substitution in early Paleocene placentals.

Full text at http://dx.doi.org/10.1126/science.1238025

### Response to Comment on "The Placental Mammal Ancestor and the Post–K-Pg Radiation of Placentals"

**Maureen A. O'Leary, Jonathan I. Bloch, John J. Flynn, Timothy J. Gaudin, Andres Giallombardo, Norberto P. Giannini, Suzann L. Goldberg, Brian P. Kraatz, Zhe-Xi Luo, Jin Meng, Xijun Ni, Michael J. Novacek, Fernando A. Perini, Zachary S. Randall, Guillermo W. Rougier, Eric J. Sargis, Mary T. Silcox, Nancy B. Simmons, Michelle Spaulding, Paúl M. Velazco, Marcelo Weksler, John R. Wible, Andrea L. Cirranello**

Tree-building with diverse data maximizes explanatory power. Application of molecular clock models to ancient speciation events risks a bias against detection of fast radiations subsequent to the Cretaceous-Paleogene (K-Pg) event. Contrary to Springer *et al*., post–K-Pg placental diversification does not require "virus-like" substitution rates. Even constraining clade ages to their model, the explosive model best explains placental evolution.

Full text at http://dx.doi.org/10.1126/science.1238162

## Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the past 3 months or matters of general interest. Letters are not acknowledged upon receipt. Whether published in full or in part, Letters are subject to editing for clarity and space. Letters submitted, published, or posted elsewhere, in print or online, will be disqualified. To submit a Letter, go to www.submit2science.org.

## Gain-of-Function Experiments on H7N9

Ron A. M. Fouchier, Yoshihiro Kawaoka, Carol Cardona, Richard W. Compans, Adolfo García-Sastre, Elena A. Govorkova, Yi Guan, Sander Herfst, Walter A. Orenstein, J. S. Malik Peiris, Daniel R. Perez, Juergen A. Richt, Charles Russell, Stacey L. Schultz-Cherry, Derek J. Smith, John Steel, S. Mark Tompkins, David J. Topham, John J. Treanor, Ralph A. Tripp, Richard J. Webby and Robert G. Webster

*Science* **341** (6146), 612-613.
DOI: 10.1126/science.1243325originally published online August 7, 2013