GOF studies in the Perez Lab

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MY BACKGROUND

- **I am a virologist who has been working with influenza viruses for >20 years (and on transmission for the last 15 years). ~100 peer-reviewed publications**
- **Current interests**
  - Host range and reassortment
  - Alternative vaccines and use of influenza as a vector
  - Influenza as an oncolytic agent – turning a foe into an ally
- **I serve on NIH, USDA, CDC, and other scientific review panels**
- **I am on the editorial board of J. Virol, Virus Genes, Virus Research, associate editor of PLoS Pathogens and editor of Influenza Research and Treatment**
- **I signed the Scientists for Science statement and consider GOF studies essential parts of the scientific method**
- **I have been married for 24 years, I am the father of three who cares about the well being of his family and of other people**

Interspecies Transmission of H9N2 LPAIV avian influenza viruses

Interspecies Transmission of H7N1 HPAIV avian influenza virus

Studies follow a common theme: Introduce mutations in avian influenza viruses by either site-directed mutagenesis, or reassortment with human influenza viruses and/or adaptation in a mammalian animal model (ferret)

Major goal: To determine the minimal changes necessary to produce a virus that can transmit by respiratory droplets (in ferrets).

Why? Because the mechanisms that control airborne transmission of avian influenza viruses in mammals is poorly understood and a comprehensive analysis of the factors involved in this process help us with risk assessment analysis of the pandemic potential of these strains.

PNAS

Minimal molecular constraints for respiratory droplet transmission of an avian–human H9N2 influenza A virus

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PNAS

Compatibility of H9N2 avian influenza surface genes and 2009 pandemic H1N1 internal genes for transmission in the ferret model

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Edited by Peter Palese, Mount Sinai School of Medicine, New York, NY, and approved June 10, 2011 (received for review May 19, 2011)

Journal of Virology

Airborne Transmission of Highly Pathogenic H7N1 Influenza Virus in Ferrets

Troy C. Sutton, Courtney Finch, Hongxia Shao, Matthew Angel, Hongjun Chen, Ilaria Capua, Giovanni Cattoli, Isabella Monne and Daniel R. Perez

J. Virol. 2014, 88(12):6623. DOI: 10.1128/JVI.02765-13. Published Ahead of Print 2 April 2014.

MAJOR FINDINGS

L226 in the RBS of the HA containing H9N2 viruses, which provides human-like receptor specificity, is essential for direct contact mammalian transmission (ferrets). No signs of disease.

T189A (in HA1) and G192R (in HA2) allowed airborne transmission of an avian/mammalian (2:6 reassortant) H9N2 virus in ferrets. Signs of disease similar to human influenza.

T189A, G192R, L226 H9N1 virus reassortant (1:7 with 2009 pdm backbone) shows the most efficient airborne transmission in ferrets. This finding could not have been predicted from sequence analysis and/or what it is currently known about HA and NA activities. Signs of disease similar to human influenza.

A change in receptor specificity is NOT required for a H7N1 HPAIV to become airborne in ferrets. HPAIV H7N1 < LPAIV H9N1

A better appreciation of changes in internal gene segments as contributors of airborne transmission of influenza viruses.

RISK MITIGATION

- Unlike in agricultural practices that promote emergence of zoonotic/potentially pandemic pathogens, the use of protective equipment including power air respirators are required for work under BSL3+ conditions
- Use of protective equipment including power air respirators are required for work in animal studies under BSL2+ conditions when using avian or swine influenza viruses
- Influenza Medical Surveillance Plan
  - Sera collected from lab personnel to monitor…
    - Seroconversion to influenza strains used in the lab
      - HI and MN assays
      - Development of mAbs and species independent ELISAS to monitor seroconversion to avian and swine influenza viruses
- Exposure/Illness evaluation response plan – TRAINING
- Annual Influenza Vaccination
- Tamiflu on site

GOF in the Global Context

- Any doubts regarding the airborne transmission potential of influenza virus subtypes other than those that have already cause human pandemics?
- A switch in receptor specificity is required by some but not all subtypes.
- *Not a single release of the 2009 pdm H1N1 virus from a lab when these viruses were handled under strict BSL3+ conditions*
- *>100 years of work with HPAIV, not a single outbreak of HPAIV in birds linked to an accidental lab release*
- *Experimental biology (Perez, et al. PLoS currents influenza) helped predict that the pdm H1N1 virus did not need to reassort to transmit efficiently in mammals. Modeling would not have been able to predict such phenotype.*