

# One small step for science, a giant risk for mankind

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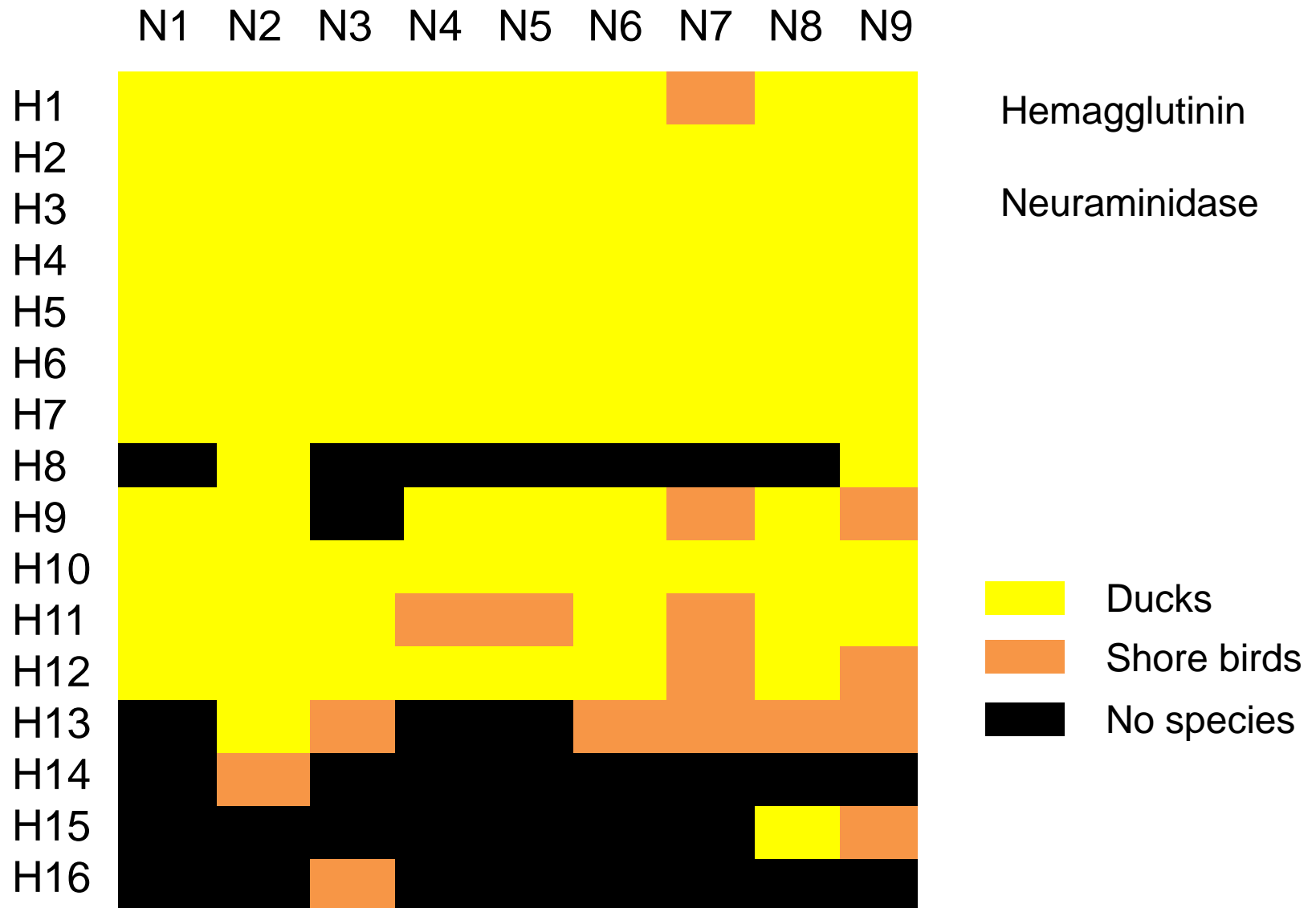
Simon Wain-Hobson  
Institut Pasteur  
Paris

Chair  
Foundation for Vaccine Research  
Washington DC

ABSA Kansas City



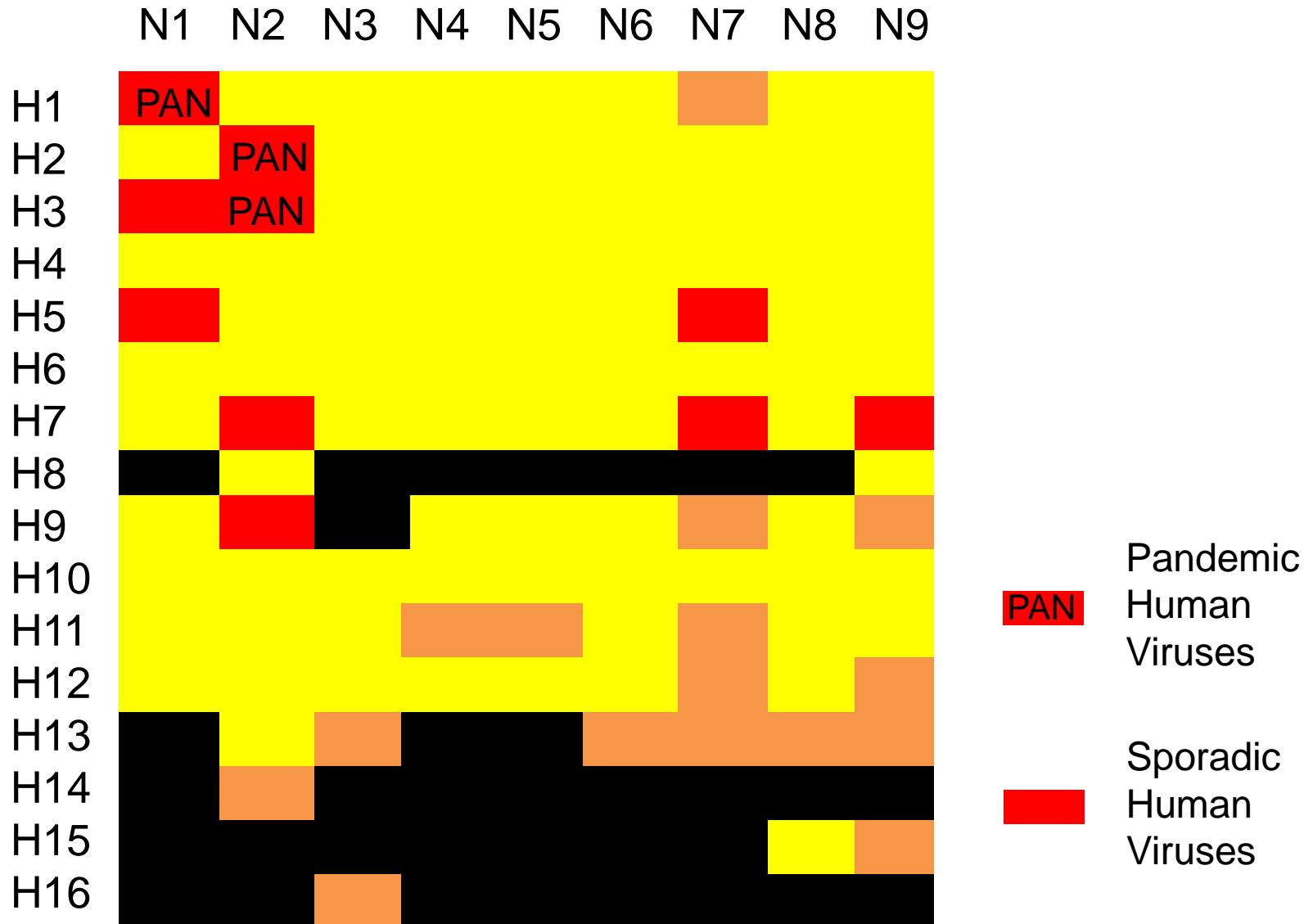
# Every influenza virus is in a duck or shore bird



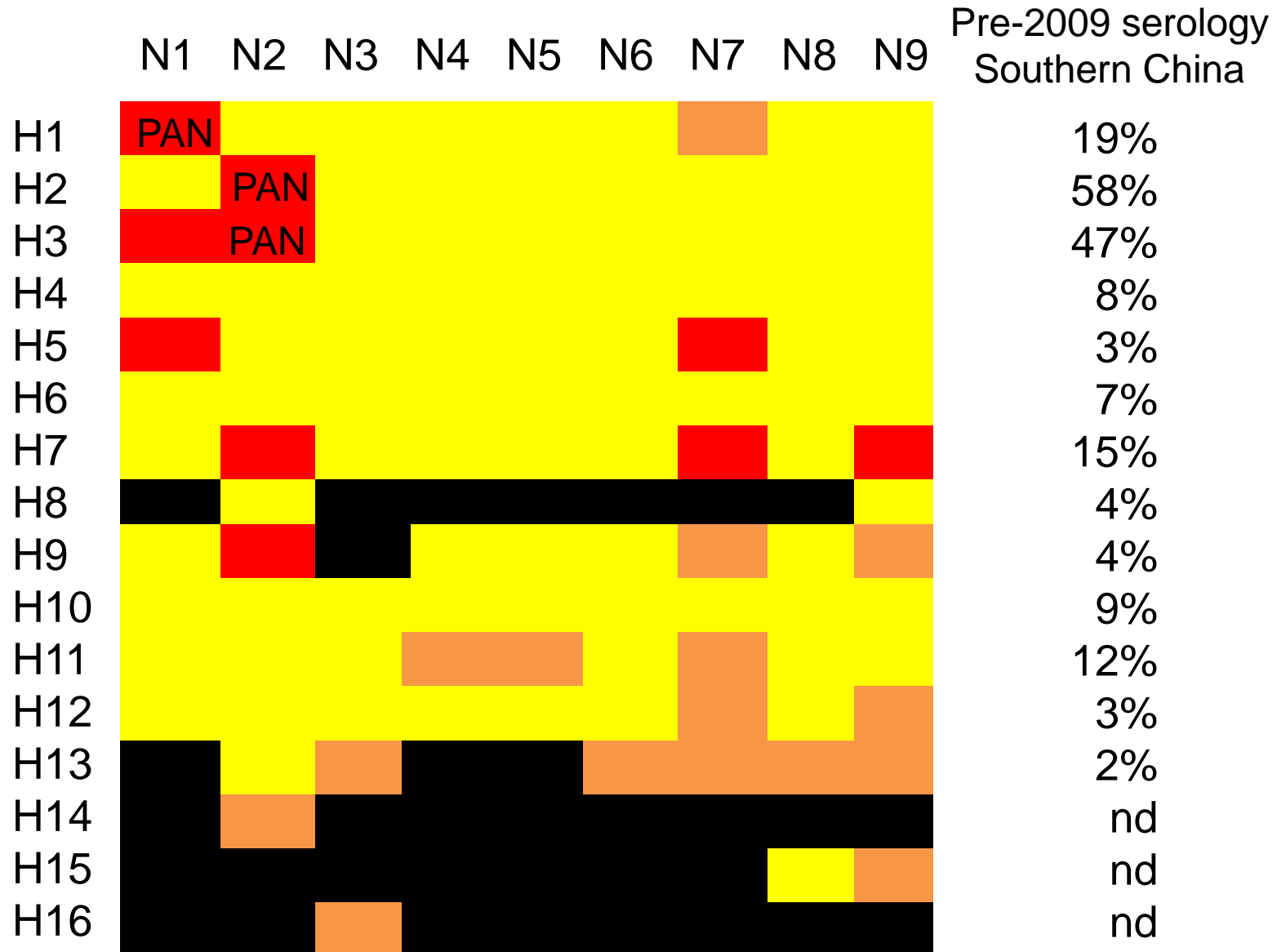
# Pandemic influenza virus are but three



# Sporadic influenza virus are few but...



... most go nowhere - dead end infections



# Dead end infections are all around us

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Rabies

55 000 deaths per year

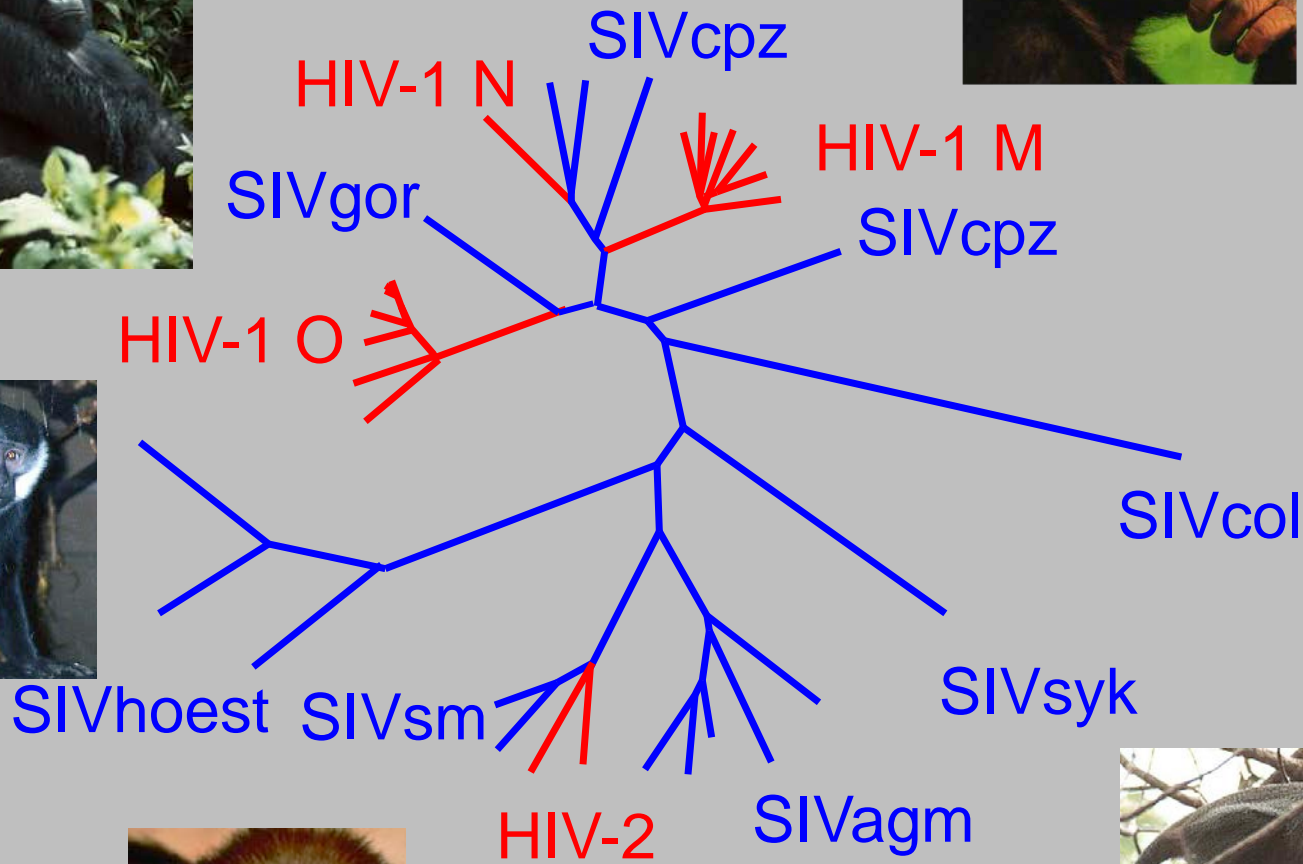
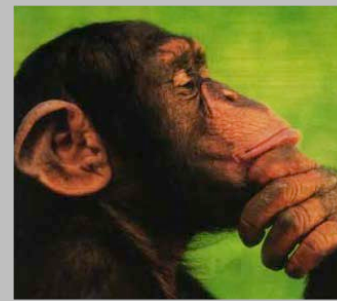
Nipah and Hendraviruses

MERS coronavirus

LCMV

Pulmonary hantaviruses

Simian retroviruses (Foamy, STLV, SIV)



# How?





# How?



~15% SIV positive

# How?



~15% SIV positive

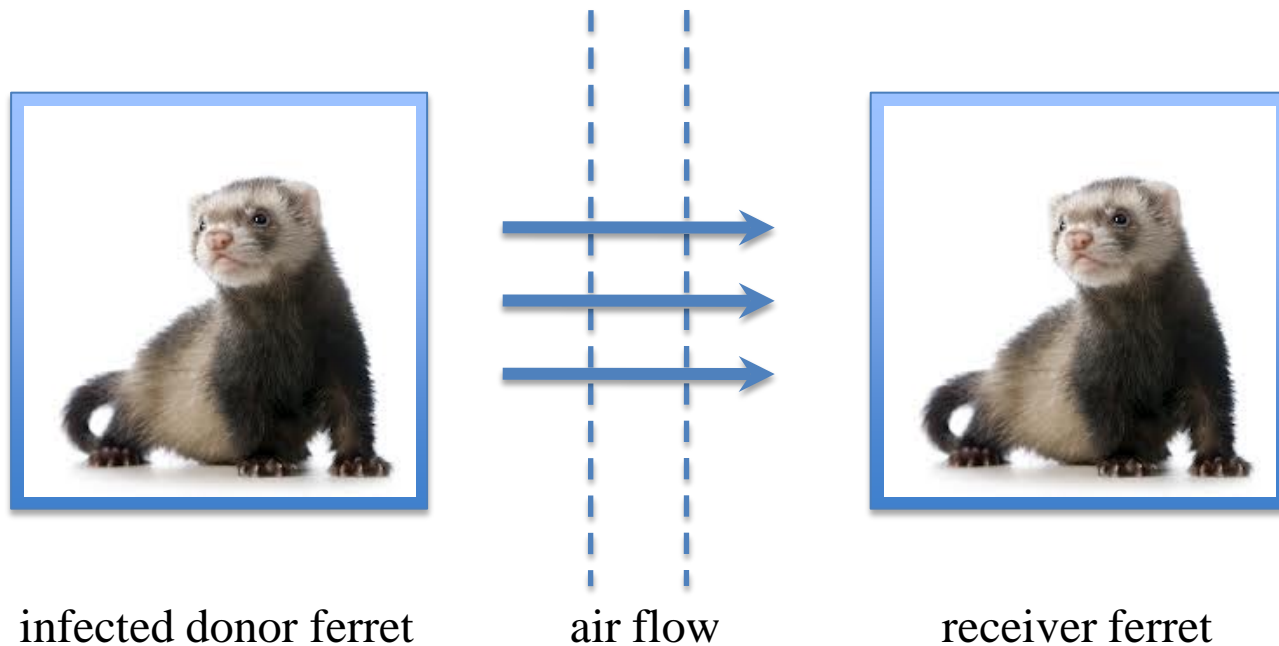
Evidence for continuing cross-species transmission of SIVsmm to humans:  
characterization of a new HIV-2 lineage in rural Côte d'Ivoire  
Ahidjo *et al.*, AIDS 27, 2488 (2013)

# We mustn't confuse reality & novelty

Dead end infections	Next to no transmission. Can be highly pathogenic Rabies 55K (case fatality rate CFR>95%) H5N1 < 700 cases in 16 years MERS coronavirus HIV-1 N, P
Outbreaks	Transmissible yet limited chains SARS coronaviruses Some HIVs, Ebola (CFR~70%) coxsackie-poliovirus recombinants HIV-1 O, HIV-2
Epidemics	Common cold viruses, enteroviruses
Pandemics	Very rare Flu, HIV-1 M

# What is influenza virus gain-of-function research?

Gain-of-function (GOF) research means **deliberately** transforming avian influenza viruses that are not transmissible between mammals into viruses that are capable of efficient transmission



# The controversy – summer 2011 to present

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The pro-GOF group says that it will help prepare for a pandemic while the risks can be mitigated and contained

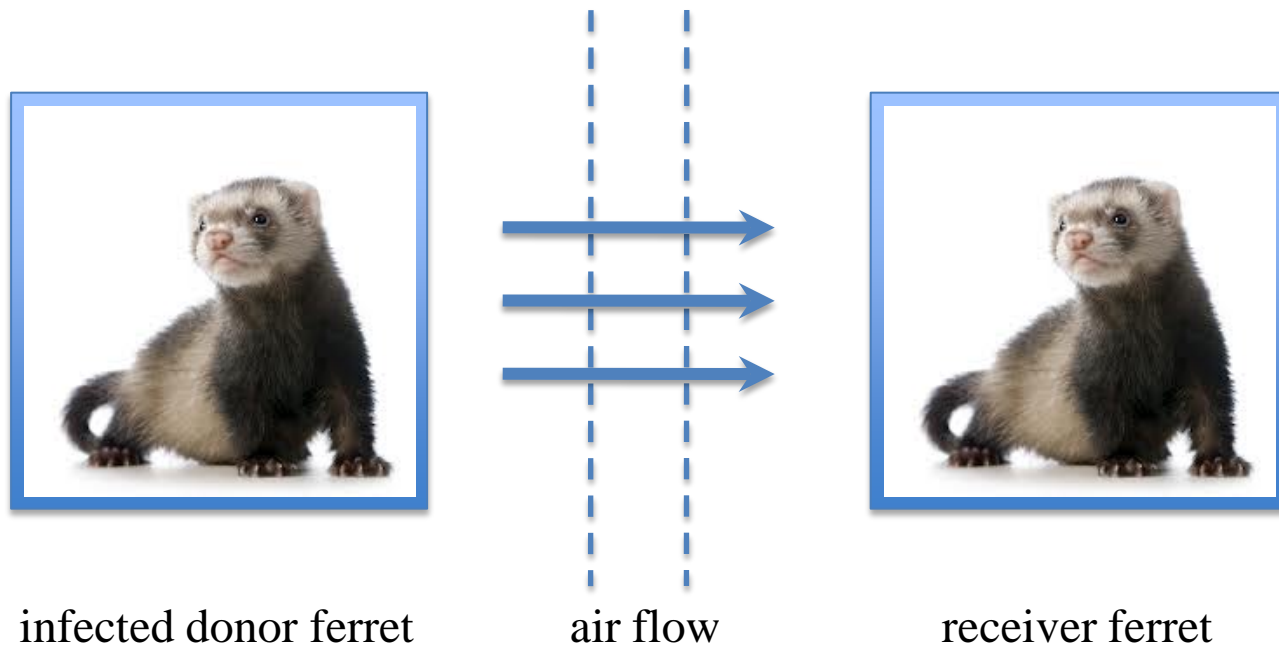
Useful for:

- Vaccine development
- Drug design
- Pandemic preparedness
- Interpreting naturally arising mutations in the field

# The controversy – summer 2011 to present

The anti-GOF group says there is nothing in the research to help a Health Minister make robust decisions

- A selection screen will come up with what you select for





Selective screens - you get what you select for



# Less than 50 years was enough



Dmitri Belyaev  
selected  
Siberian silver  
foxes for  
reduced fear of  
humans

Lower  
adrenaline  
in serum



# The controversy – summer 2011 to present

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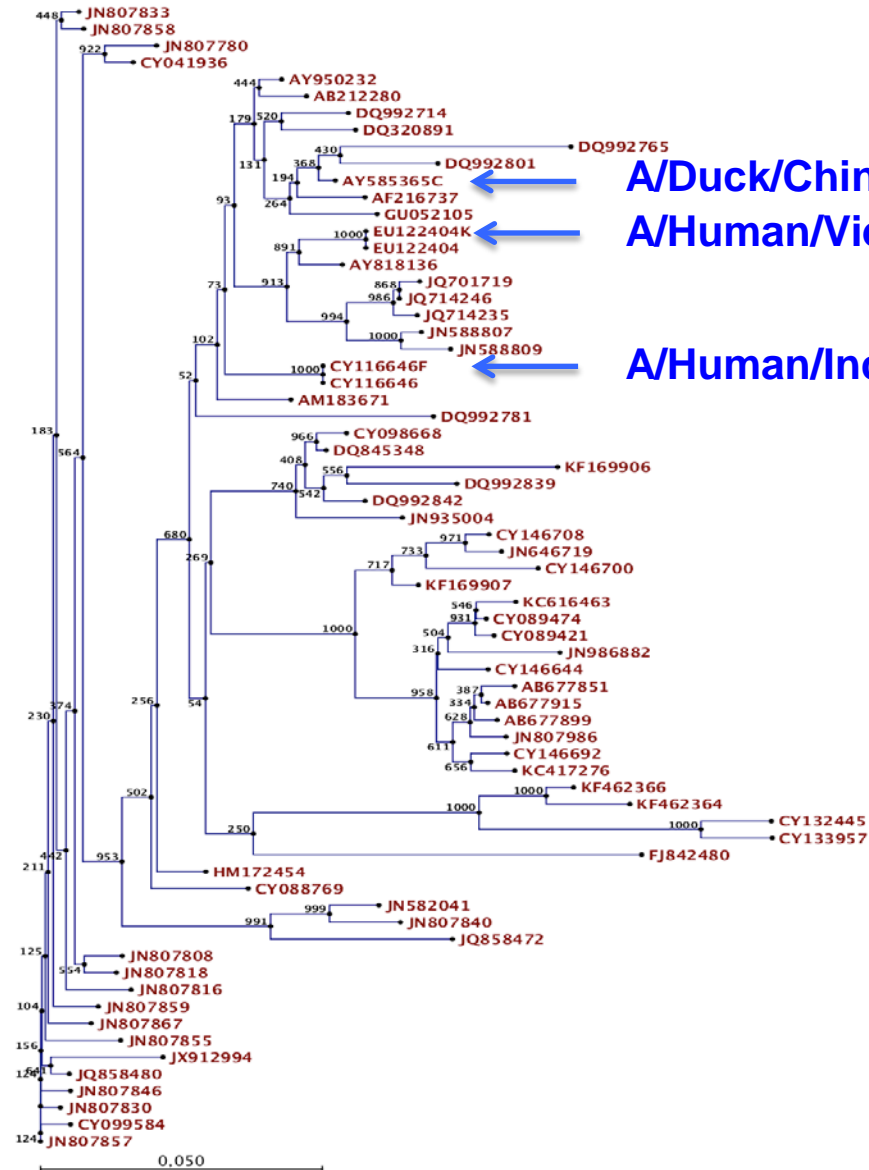
- Vaccines      No way!

Adel Mahmoud former President of Merck Vaccines  
This week's issue of Science

Presently many clades of H5N1 circulating  
Which will make it big time?

H5N1 GOF viruses of Asian origin are “old”  
Chen 2001, Fouchier 2005, Kawaoka 2004

# Don't know which antigenically different strain will jump



# The controversy – summer 2011 to present

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- Drug design

Can only hope that the next pandemic virus is drug sensitive

- Pandemic prediction and preparedness

We missed H1N1 from Central America  
H7N9 came out of the blue,  
as did the SARS and MERS coronaviruses

Stockpiling of drugs - obvious

Stockpiling of vaccines – less obvious

# The controversy – summer 2011 to present

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- Interpreting mutations in the field

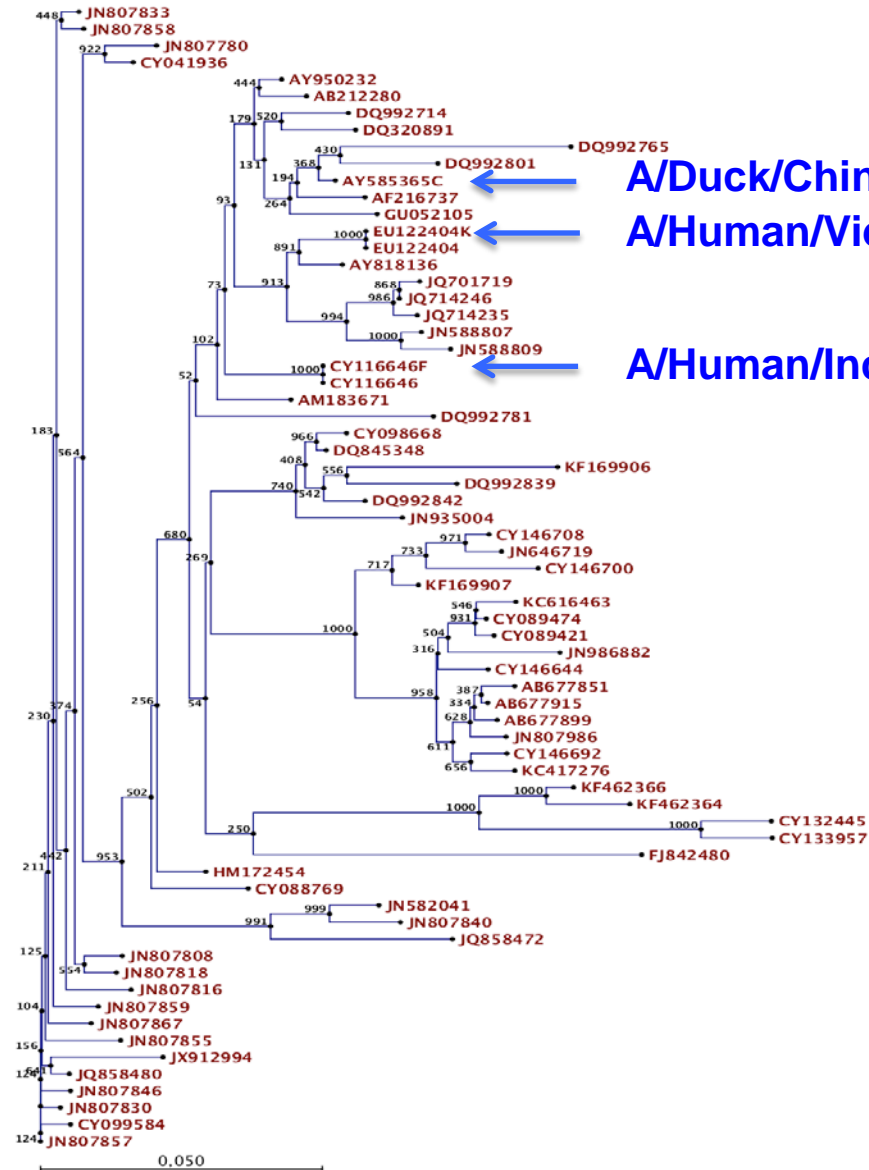
The data can be obtained by testing individual mutations in a gene or reference virus but not in transmission studies

Saturation mutagenesis of the receptor pocket in the HA gene

Exhaustive analysis of rare human to human transmission cases which do exist

Fouchier or Kawaoka mutations in Asian strains do NOT confer growth on human cells for 2009 Egyptian H5N1 strains

# The controversy – summer 2011 to present

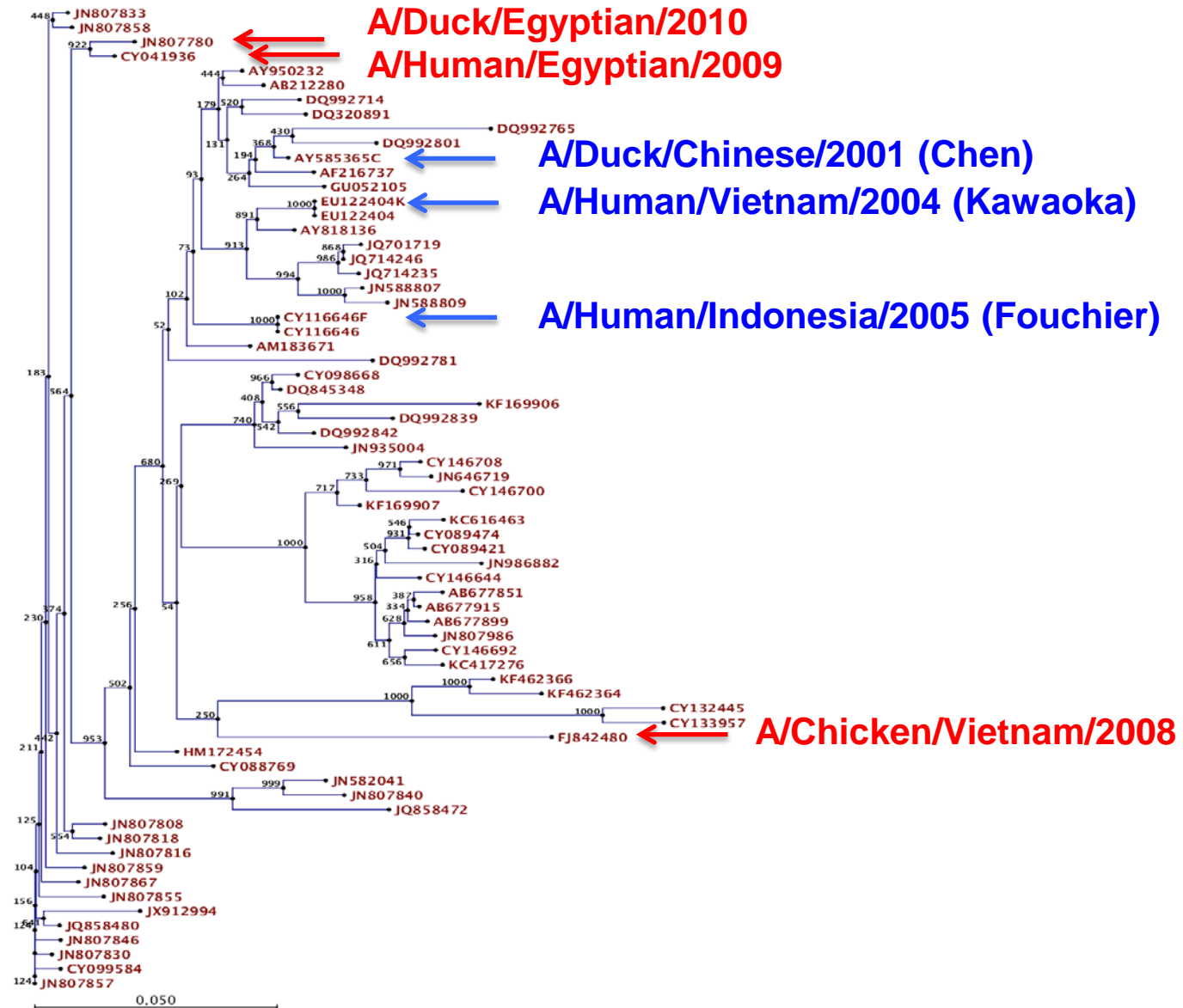


A/Duck/Chinese/2001 (Chen)

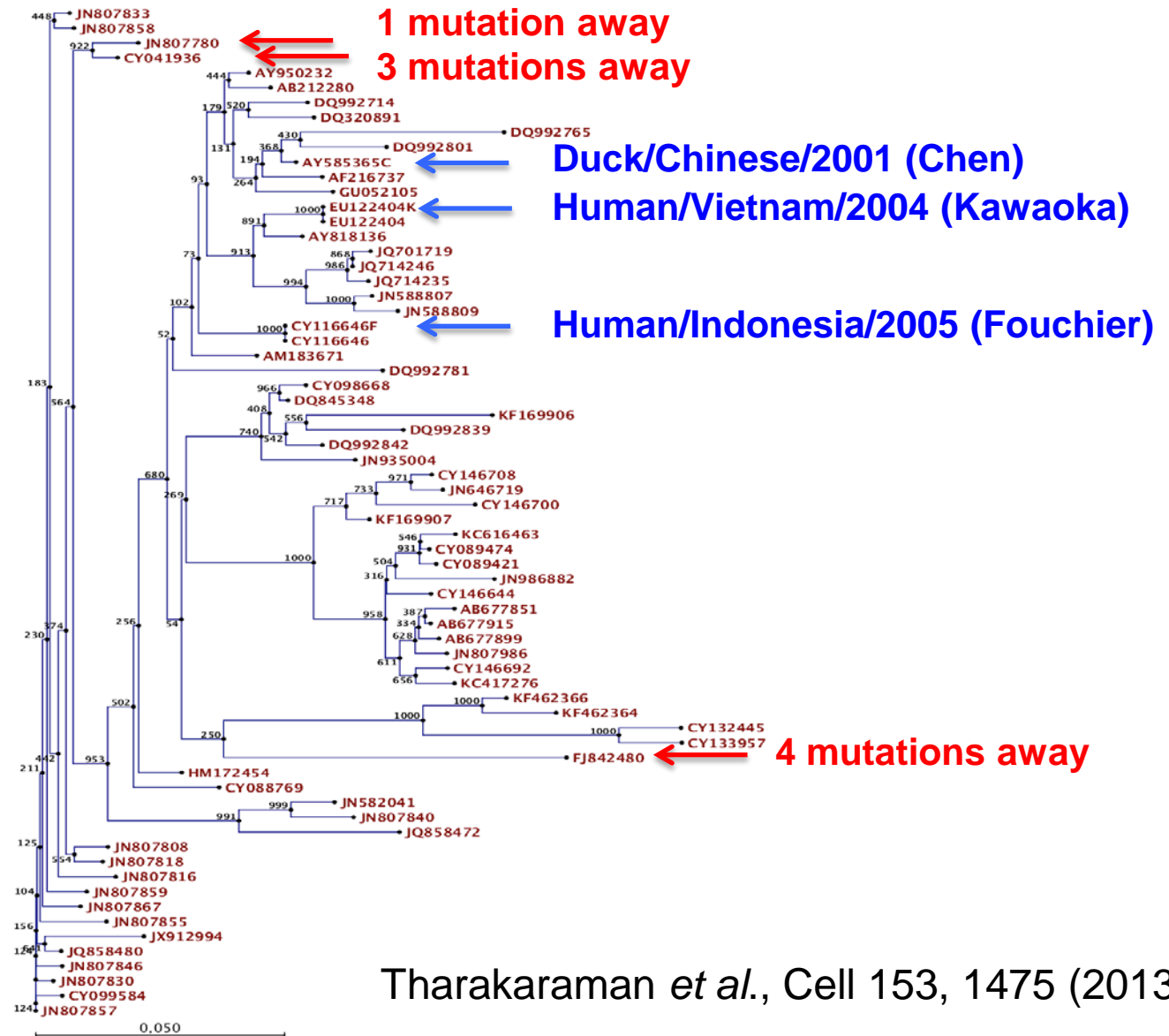
A/Human/Vietnam/2004 (Kawaoka)

A/Human/Indonesia/2005 (Fouchier)

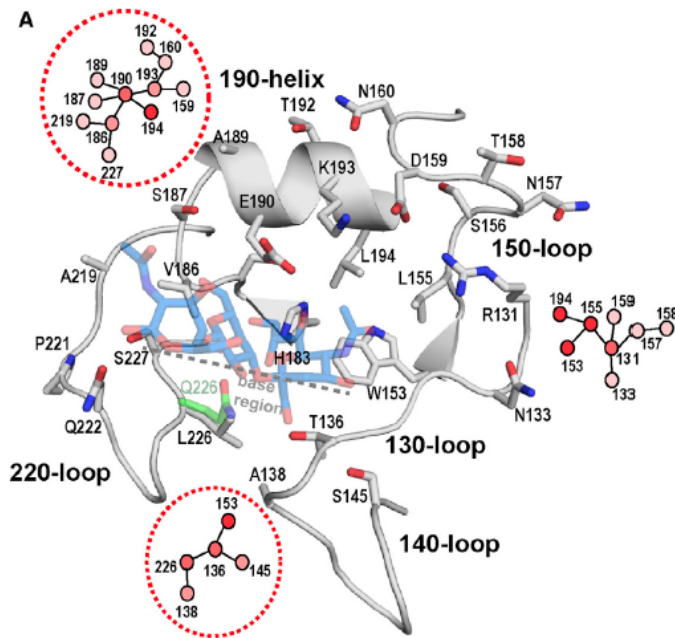
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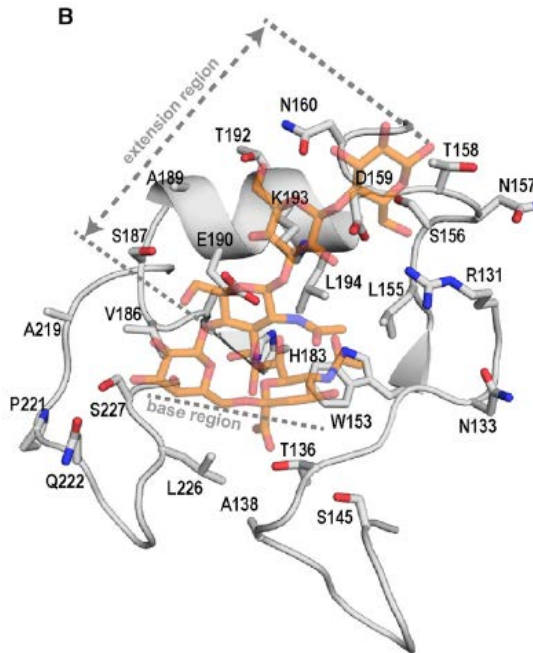
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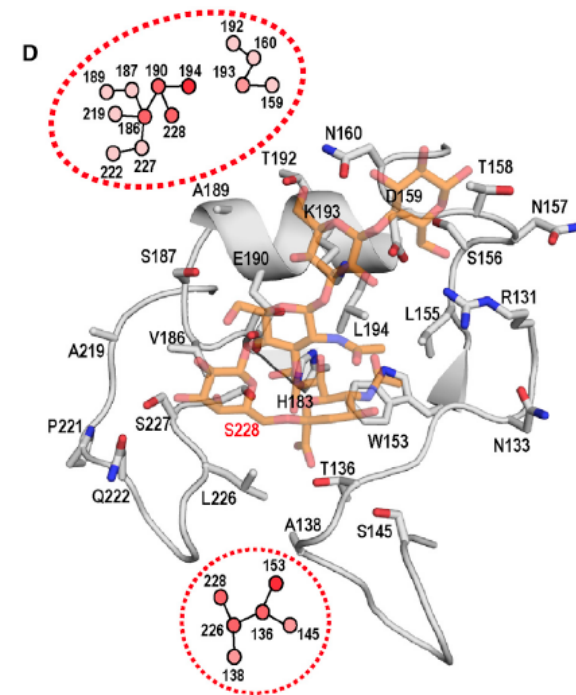
# H7N9 – just one mutation away



H7 with avian receptor



H7 with human receptor



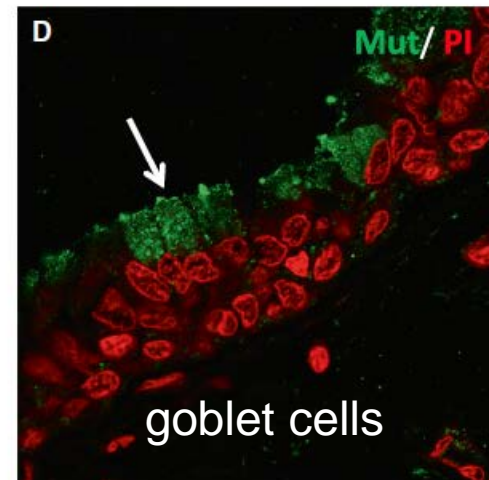
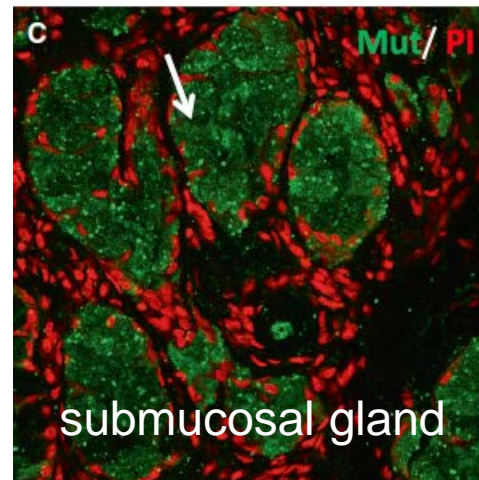
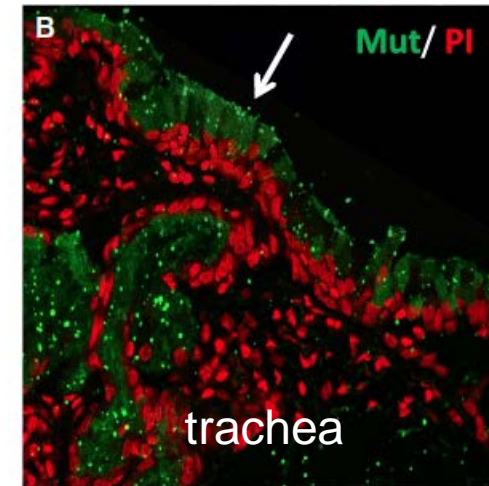
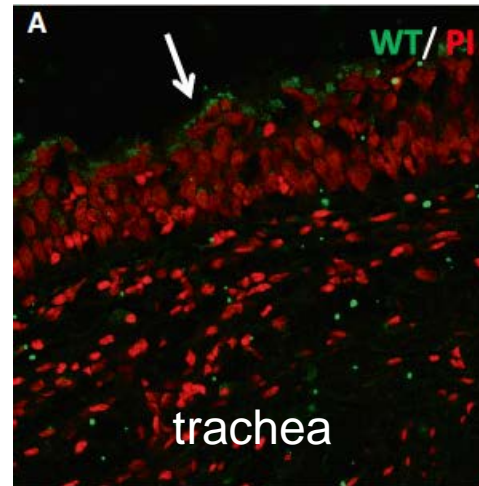
H7 G228S with human receptor



# H7N9 – just one mutation away

- H7 G228S mutant binds apical surface of trachea, submucosal gland and goblet cells
- Just like other human adapted influenza A viruses

Tharakaraman *et al.*,  
Cell 153, 1486



# Influenza GOF research

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- Many virologists feel that in nature pathogenesis (case fatality rate, CFR) would be “traded in” for increased transmission

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# Influenza GOF research

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- Many virologists feel that in nature pathogenesis (case fatality rate, CFR) would be “traded in” for increased transmission
- However, morbidity, mortality and economic impact is greater for a highly transmissible flu virus with a lower CFR (Verikos *et al.*, 2011)
- H5N1 CFR ~60%  
<700 cases infected
- Spanish flu CFR ~2%  
Most of the world

BUT

# Influenza GOF research

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- If you select for a HIGHLY pathogenic GOF virus that is highly transmissible among ferrets then you WILL succeed

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# Influenza GOF research

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- If you select for a HIGHLY pathogenic GOF virus that is highly transmissible among ferrets then you WILL succeed
- Smallpox 300-500 M deaths in 20<sup>th</sup> century
- Variola virus didn't infect most of the world
- Virologists are playing with a biological bomb on a very short fuse

# Poor science

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- The potential of these avian influenza GOF viruses can never be assessed because the crucial experiment – infecting humans – is unethical
- How do you design a pandemic experiment?
- The pro-GOF group can never prove their case they can infer, surmise, project
- There is nothing robust for a Health Minister
- Meanwhile avian influenza GOF work is proceeding

# GOF risk – unusually high stakes

- Can mitigate the risks but no system is perfect
- Some risk factors

Mechanical failure	Human error
Earthquake	Overconfidence
Hurricane	Disgruntled scientist
Tornado	Weak oversight
- One slip, but of gigantic ramifications
  - a man made flu pandemic
- No risk analysis has been published!
- Meanwhile avian influenza GOF work is proceeding

# My own opinion – Nature March 2013



*risks posed by gain-of-function research, says **Simon Wain-Hobson**.* *s the*



# Other recent opinions worthy of note

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**We have no plans to pursue such H7N9 GOF studies**

Chen Hualan, Director of China's National Avian Influenza Reference Laboratory in Harbin  
*Science* August 8, 2013

**I think such [avian influenza GOF] experiments should never be repeated. Existing samples should be destroyed**

Zeng Guang, Chief epidemiologist  
Chinese Centre for Disease Control  
*Handelsblatt* August 8, 2013

# No *consensus* as to the benefits

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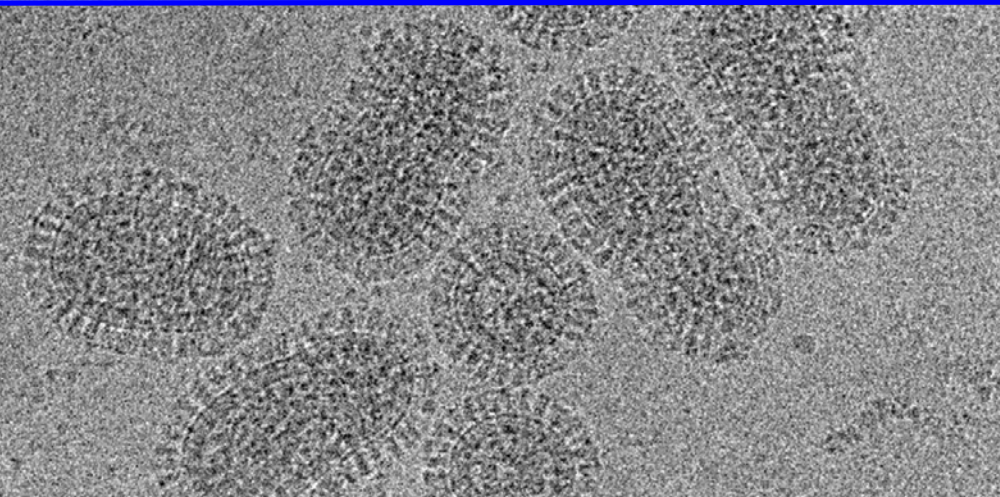
- There is no *consensus* as to the merits of the science
- Hence the benefits are not presently quantifiable
- There is tremendous tension among virologists
- There has NOT been adequate discussion and debate between stakeholders
- Learned societies, regulators and governments have FAILED to show leadership
- Meanwhile avian influenza GOF work is proceeding

# Pragmatic suggestions

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- FREEZE
- Need an international conference with all the stakeholders  
  
Virologists, infectious disease clinicians, epidemiologists, biosafety and biosecurity experts, lawyers, ethicists, government officials, university presidents, insurers, military, intelligence services, diplomats, press
- Need a risk & liability analysis
- Need a considered moral opinion
- Need leadership

# One open meeting on GOF research



H5N1 research: biosafety,



GY

THE BILL & MELINDA GATES FOUNDATION

FONDATION MERIEUX

THE GERMAN NATIONAL ACADEMY OF SCIENCES LEOPOLDINA

INSTITUT PASTEUR

THE SOCIETY FOR GENERAL MICROBIOLOGY

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# Leadership has been in short supply

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- Mainly closed or limited meetings in the US
- Biological Weapons Convention Geneva  
August 2013
- Dutch National Academy of Science  
Report pending
- German National Ethics Committee  
Spring 2014
- ASBA October 2013

# Biggest issue since the Manhattan project

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- This is the Asilomar moment. **We are there**
- It's about doing robust science
- It's about responsibility in science
- It's about trust in biomedicine

# Biggest issue since the Manhattan project

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- This is the Asilomar moment. **We are there**
- It's about doing robust science
- It's about responsibility in science
- It's about trust in biomedicine
- It is NOT about freedom of scientific enquiry
- **Meanwhile avian influenza GOF work is proceeding**

# We have come this far...

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Our tool box is so powerful that biologists  
should have an obligation to do no harm



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InterAcademy Panel statement on biosecurity

- Scientists have an obligation to do no harm

# ASBA, we have a problem



# ASBA, we have a problem



[simon.wain-hobson@pasteur.fr](mailto:simon.wain-hobson@pasteur.fr)

- Meanwhile avian influenza GOF work is proceeding



# Selective screens - you get what you select for



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Would nature have come up with any of these?

# H5N1 & H7N9 GOF research

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- Functional sequence space is so huge that there are many ways to be a successful virus
- Unlikely that these studies will come up with a single solution if performed 10 times
- Fouchier or Kawaoka mutations in 2009 Egyptian H5N1 strains don't confer growth on human cells
- Chen virus dates from 2001, Fouchier virus 2004, Kawaoka virus 2005

# Publish it, publish it not

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- Major theme of early NSABB discussions involved Nature and Science
- Papers were already in the cloud thanks to email and uploading to Nature and Science web sites!
- Discussion was unbelievably cloud naïve
- BP Hanley Security in a goldfish bowl: the NSABB's exacerbation of the bioterrorism threat

J Bioterr Biodef 2013

# Although we live in a dangerous world

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- There are more viruses than cells on the planet
- All species are under threat from tens of viruses
- RNA viruses mutate rapidly (influenza > HIV)  
can recombine (HIV) or reassort (influenza)  
massively

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- RNA viruses mutate rapidly (influenza > HIV)  
can recombine (HIV) or reassort (influenza)  
massively
- The presence of so many species means that in the  
predator-prey game we do rather well



# We are there, and naturally!

- RNA viruses are mutation machines
- A virus stock contains every single point mutation
- The mutant is at a frequency of  $\sim 10^{-4}$

