Influenza Universal Vaccines

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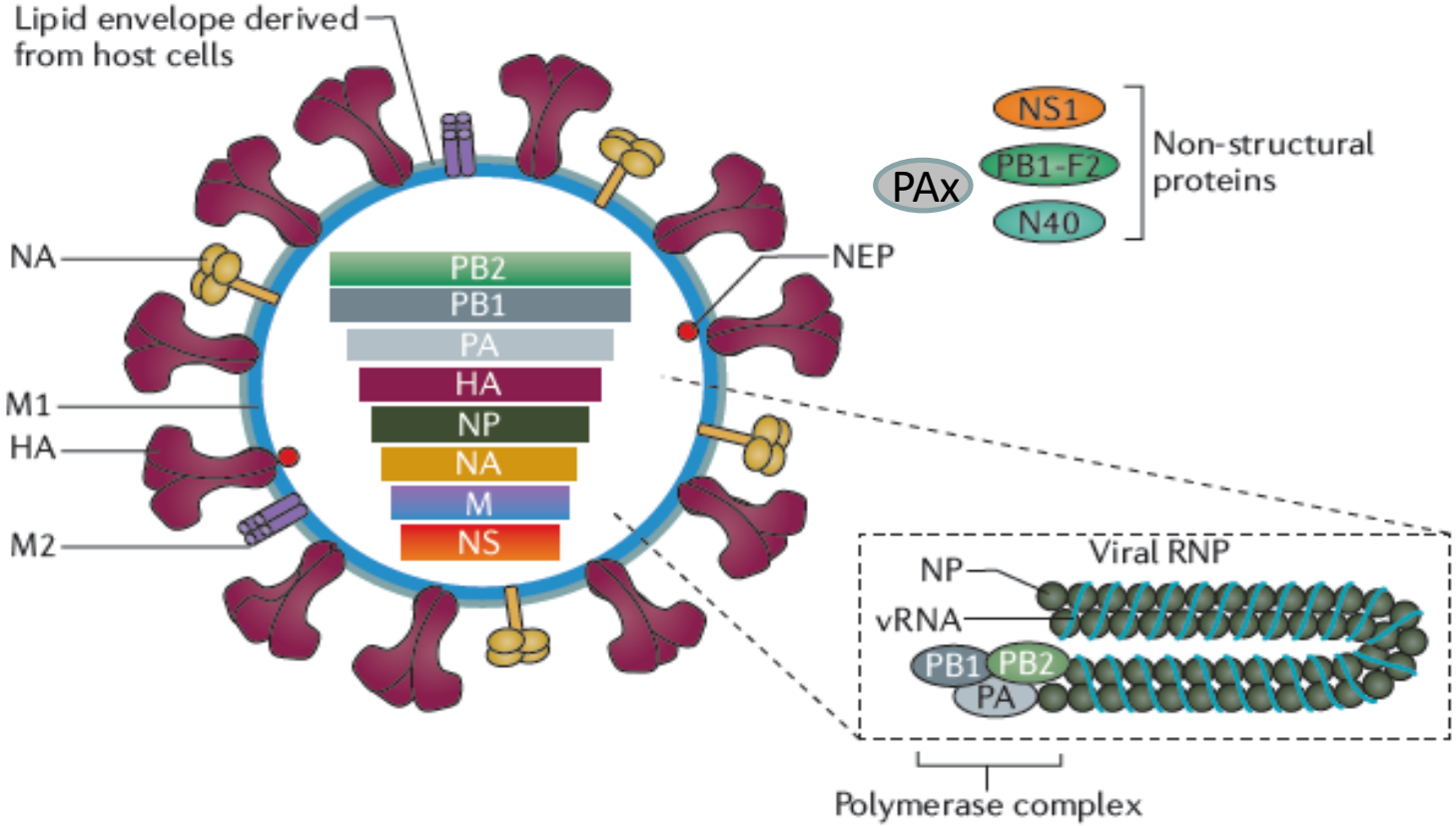
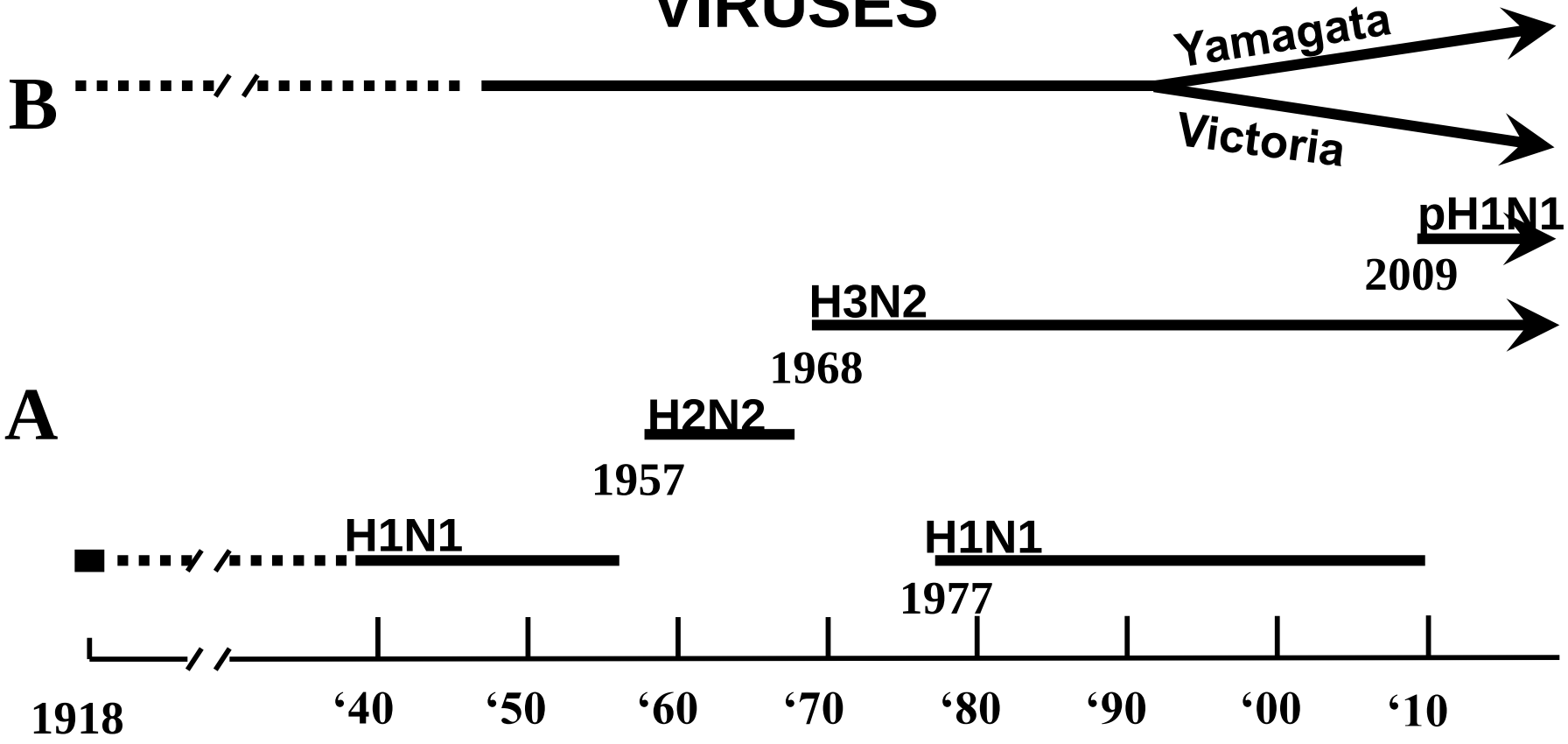
Disclosure: *Some of these studies are funded by a GSK research agreement. AG-S is inventor in patents on universal flu vaccines.*

P01AI097092

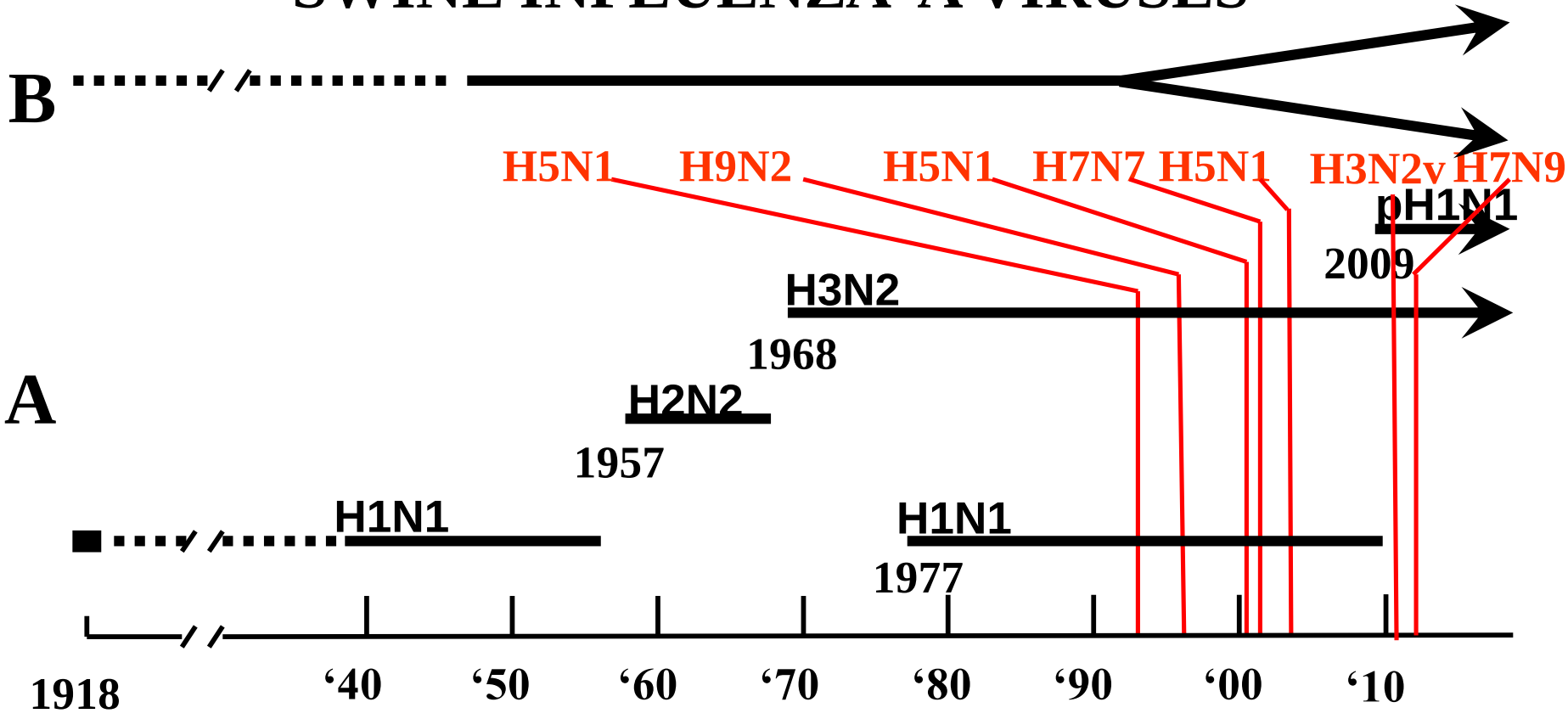
INFLUENZA VIRUSES



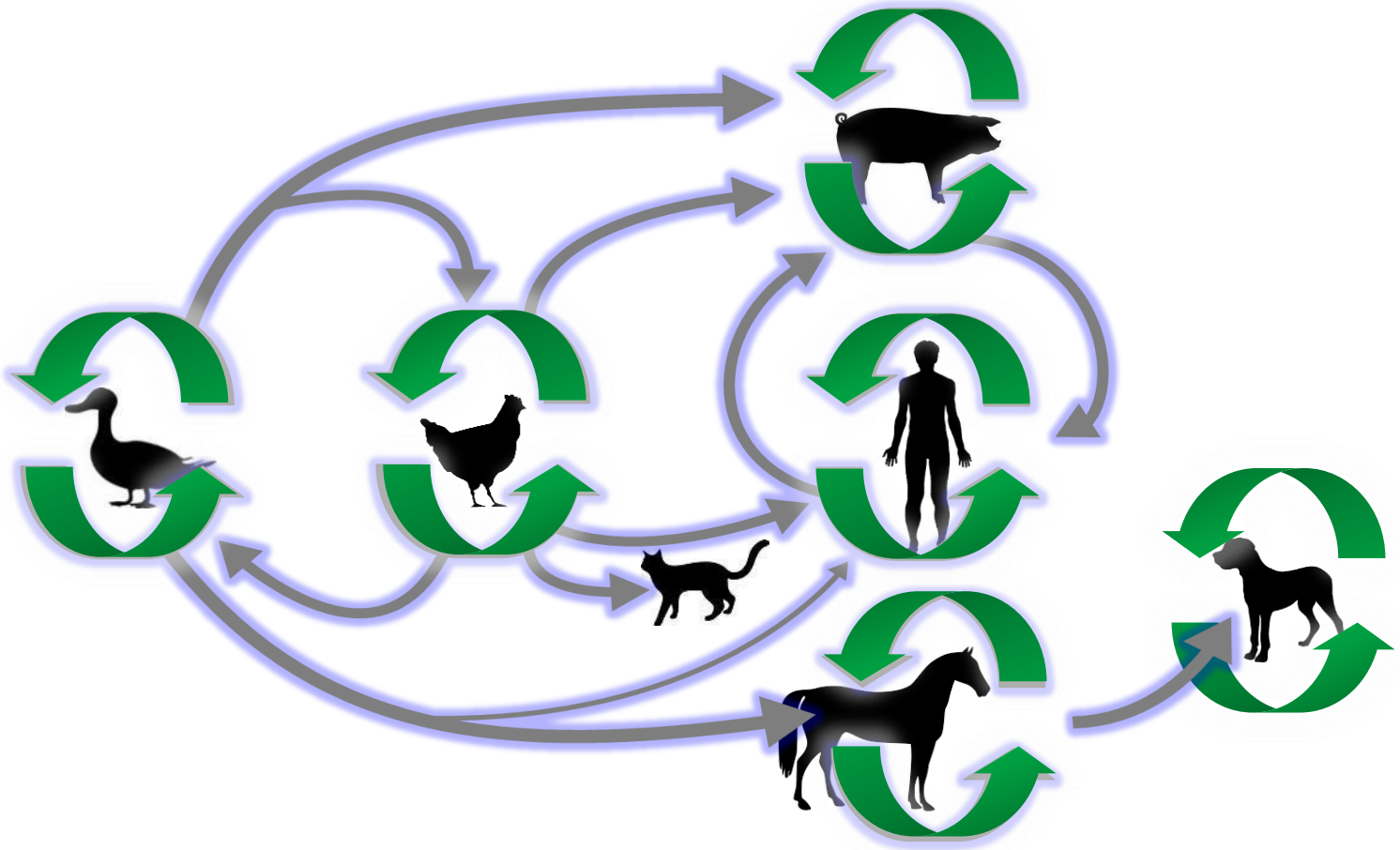
EPIDEMIOLOGY OF HUMAN INFLUENZA VIRUSES



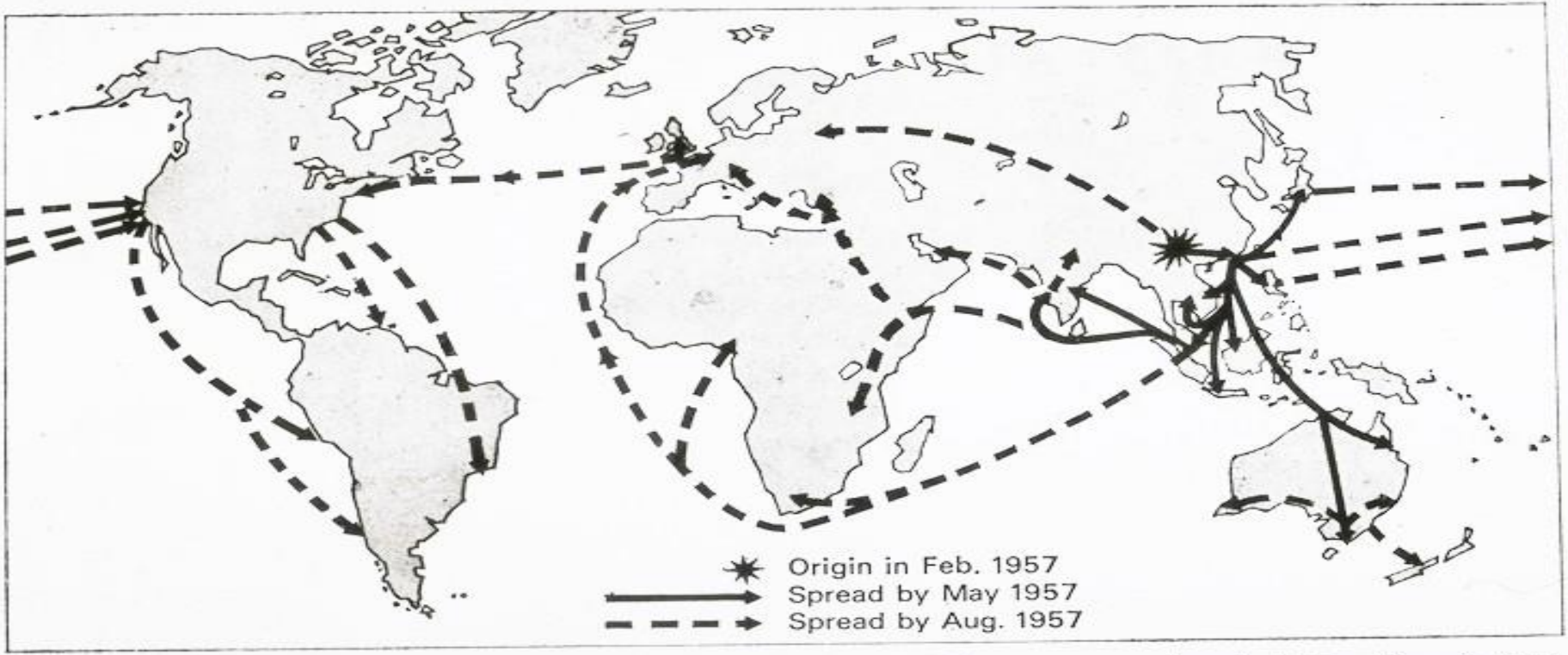
INFECTIONS IN HUMANS WITH AVIAN AND SWINE INFLUENZA A VIRUSES



Evolution and spread of flu viruses

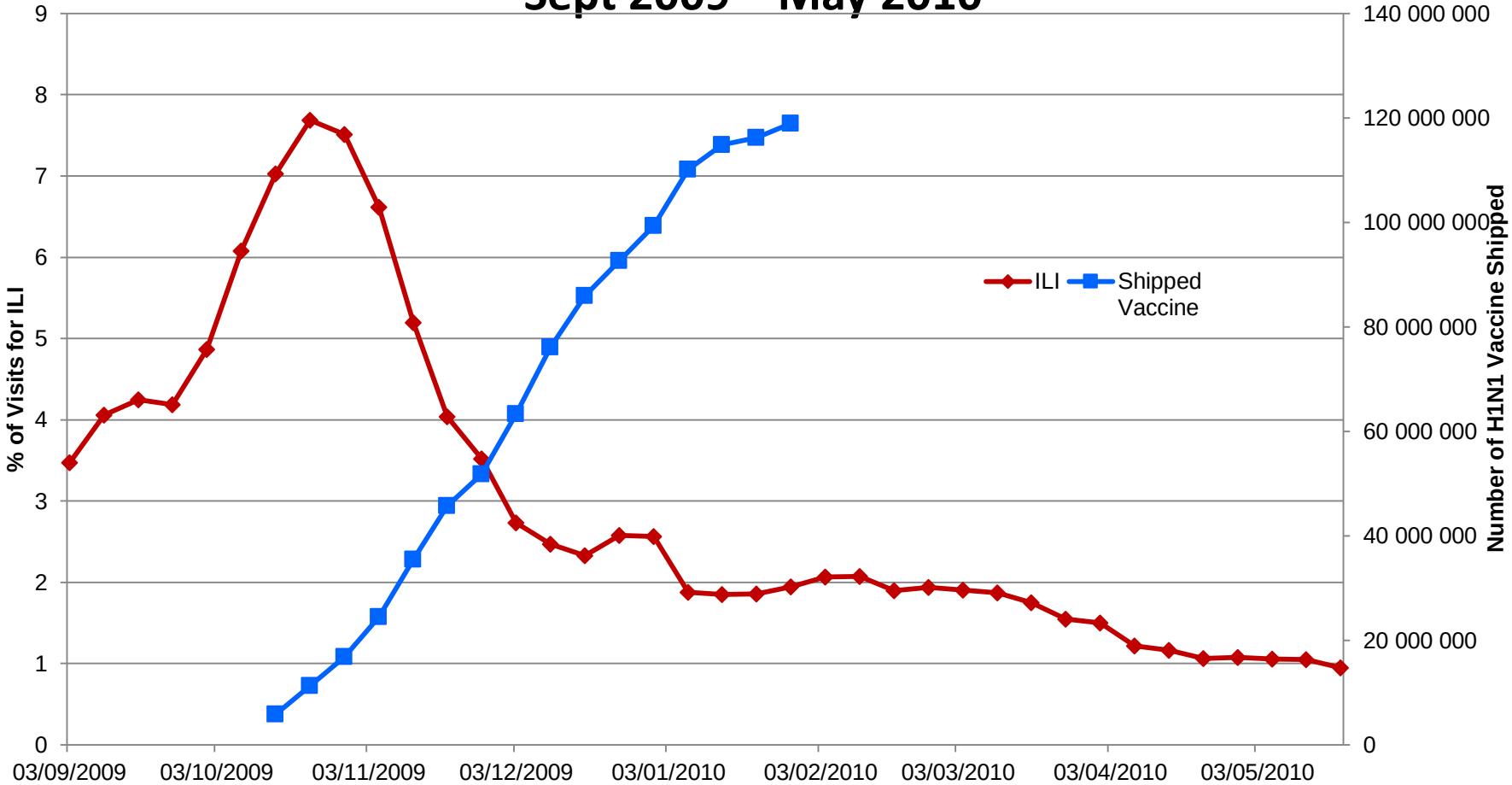


Spread of the pandemic H2N2 virus, 1957



The spread of Asian influenza around the world. It started in China in February 1957 and reached Hong Kong in April. The solid black lines indicate the spread up until May, the broken lines the spread up until August. (Data from Chronicle of World Health Organization, Sept. 1957.)

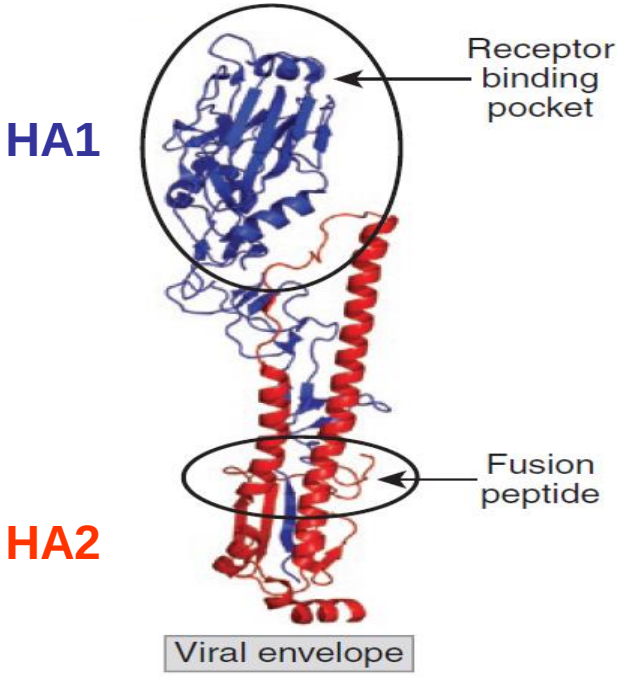
Pandemic H1N1 cases and vaccinations in US
Sept 2009 – May 2010

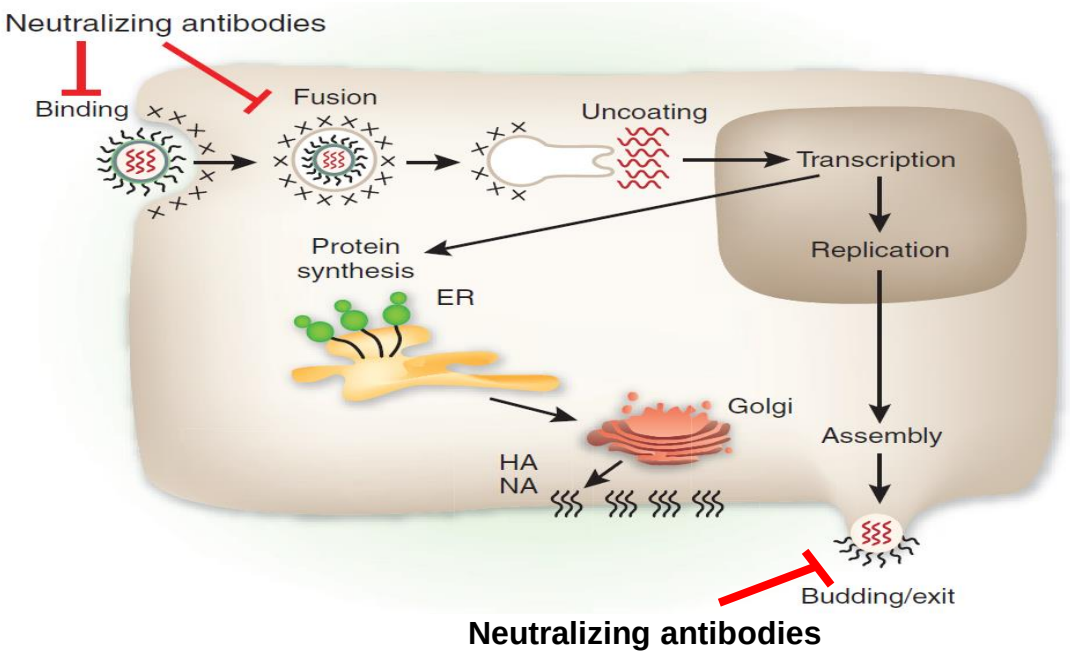


Source: CDC ILI and Vaccine Distribution Data

Universal flu vaccines?

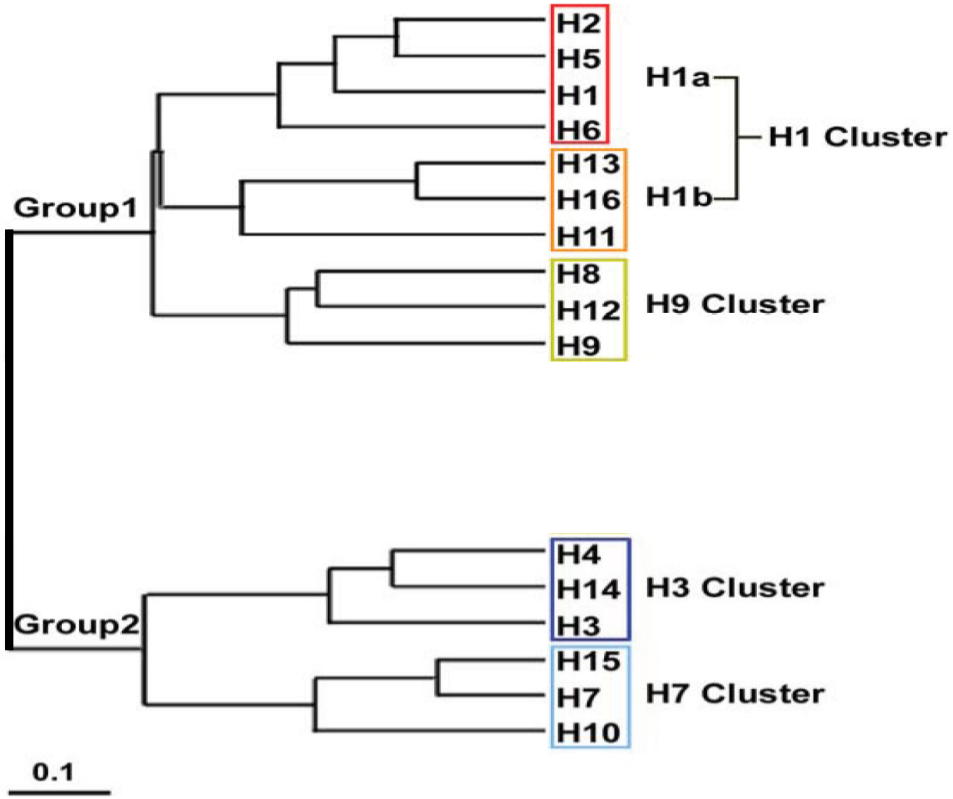
Neutralization of influenza viruses





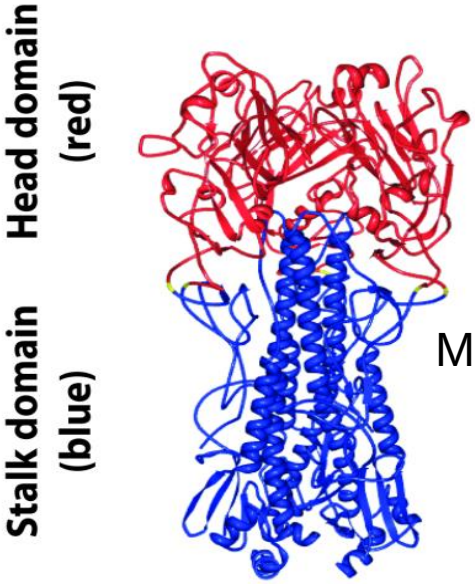
Nat Struct Mol Biol. 2009 Mar;16(3):233-4.

Hemagglutinin subtypes



HA-STEM BASED UNIVERSAL FLU VACCINES?

Strategies to overcome HA-head immunodominance



1. Use of headless constructs

Sagawa *et al.* (1996). J Gen Virol *77 (Pt 7)*, 1483-1487.
Steel *et al* (2010). MBio *1*.
Bommakanti et al (2012). J Virol *86*, 13434-13444.
Mallajosyula *et al.* (2014). Proc Natl Acad Sci USA *111*, E2514-2523.
Lu *et al.* (2014). Proc Natl Acad Sci U S A *111*, 125-130.
Wohlbold *et al.* (2015). Vaccine *33*, 3314-3321.
Impagliazzo *et al.* (2015). Science
Yassine *et al.* (2015). Nat Med *21*, 1065-1070

UNIVERSAL FLU VACCINES?

2. Repeated vaccination with influenza virus chimeric HA vaccines induce protective antibodies against multiple subtypes of influenza virus.

Irina Margine
Florian Krammer
Rong Hai
Gene Tan

Peter Palese

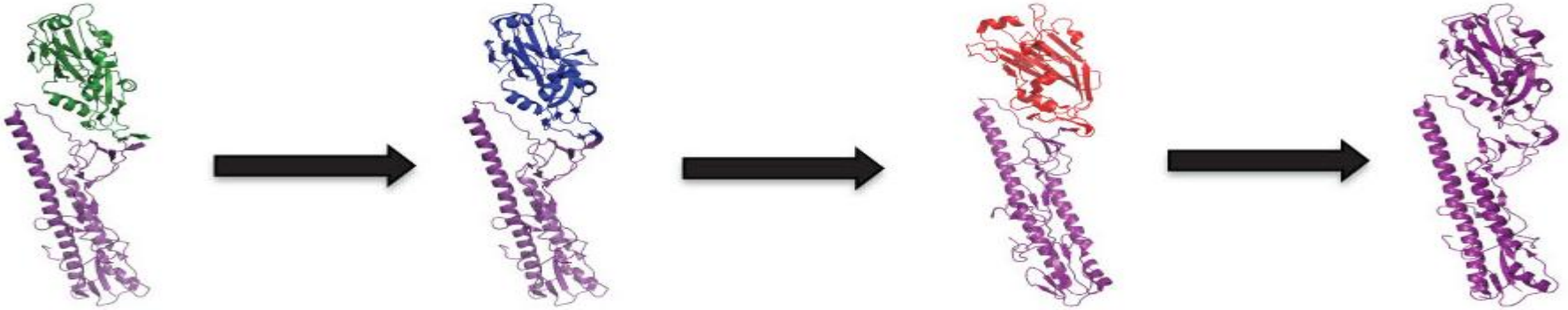
Randy Albrecht

Patrick Wilson
S.A. Andrews

Jon Runstadler

Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

Proof of principle



3 weeks
cH4/3 DNA

3 weeks
cH5/3 protein boost

4 weeks
H3 protein boost

Shanghai (H7N9) challenge

<u>Control groups:</u>
cH4/3 DNA + BSA + BSA
naïve (neg. contr.)
matched vaccine (pos. contr.)

Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

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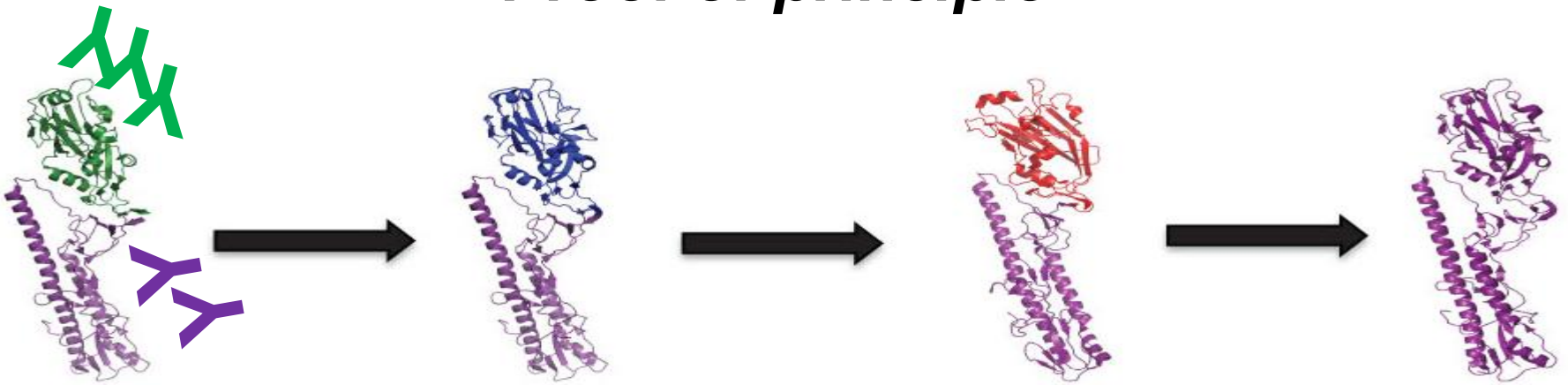

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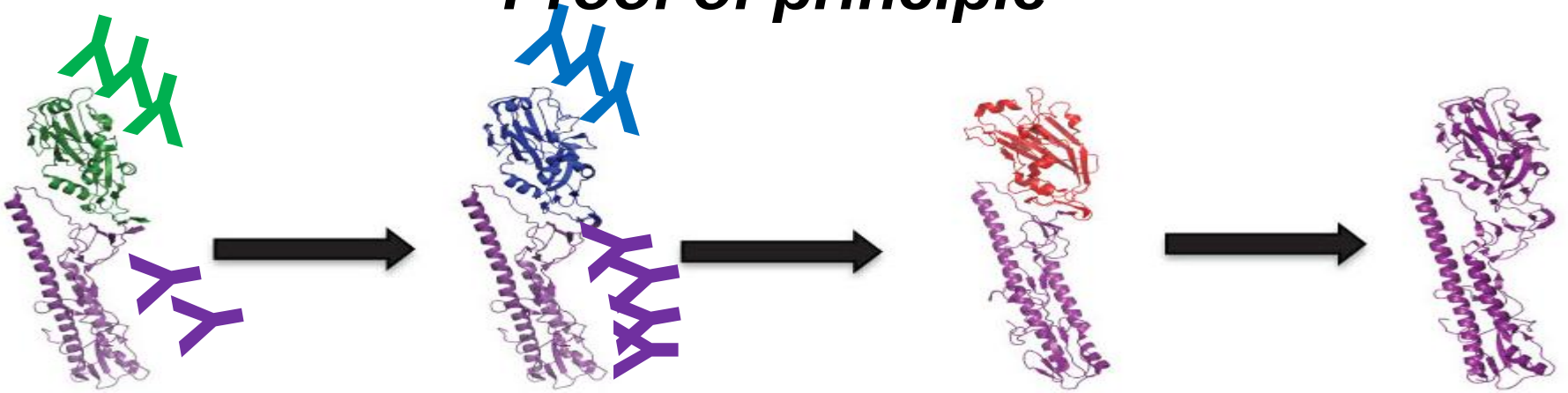

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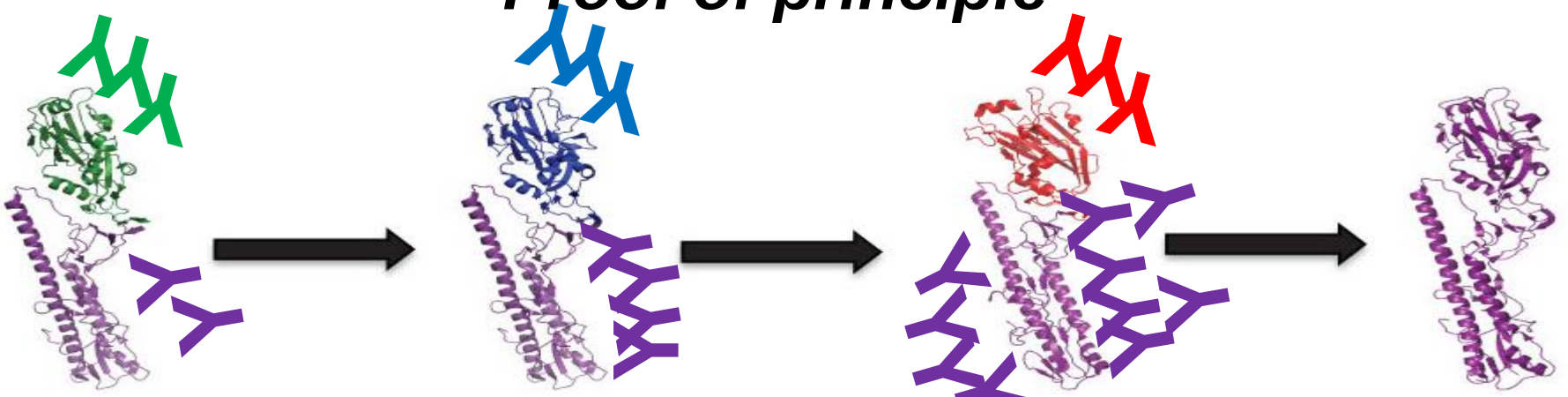

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H3 protein boost

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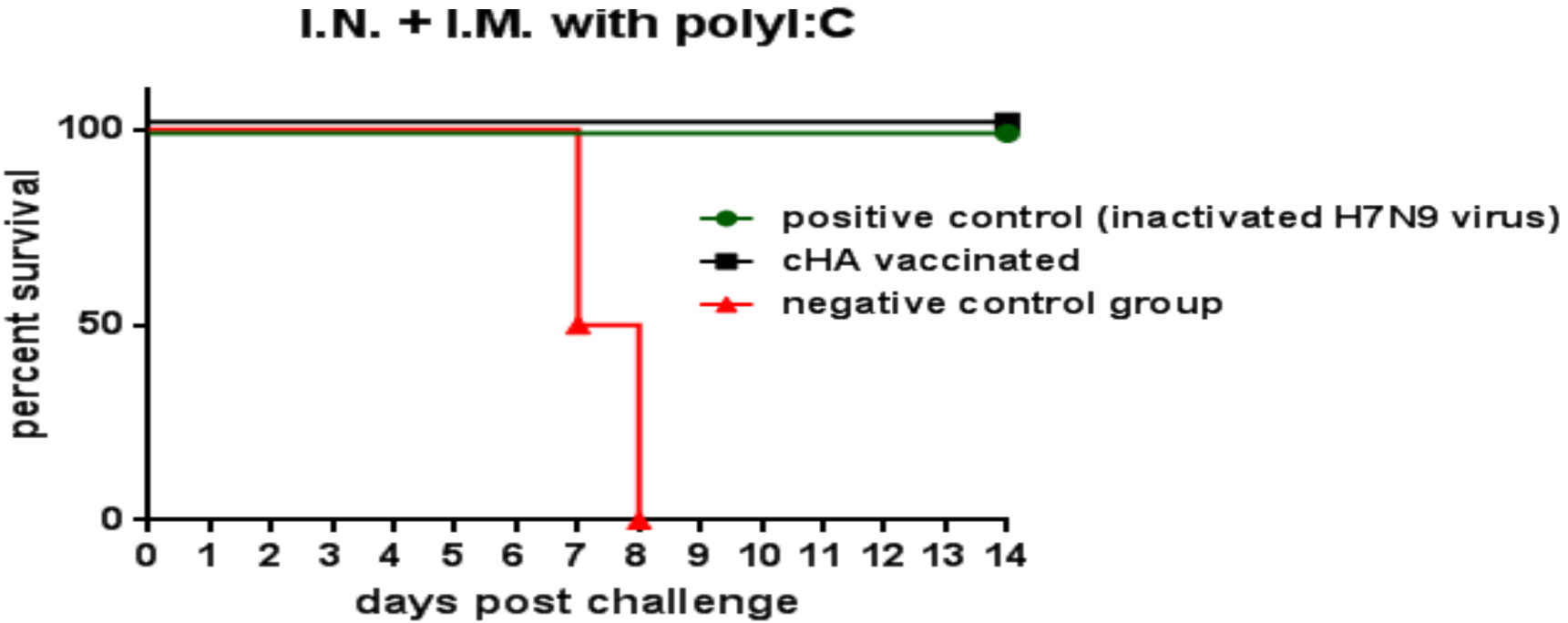
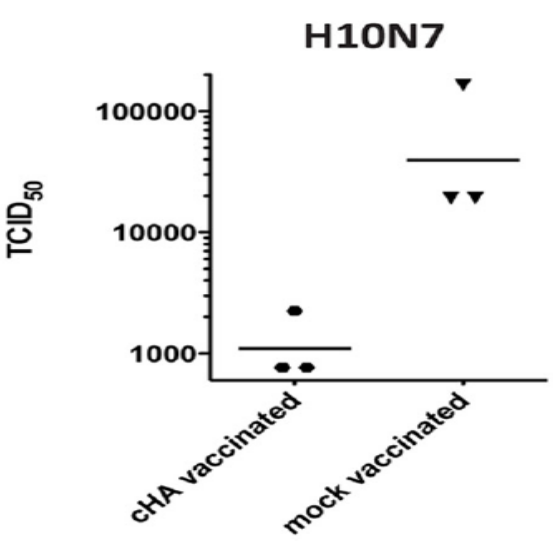
naïve (neg. contr.)
matched vaccine (pos. contr.)

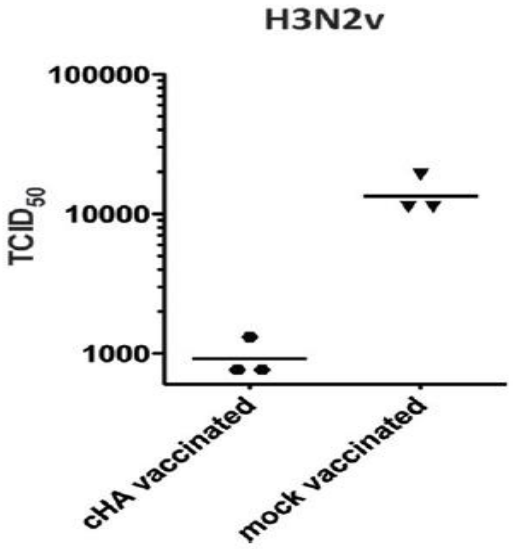
cHA vaccine protects against challenge with novel H7N9 virus

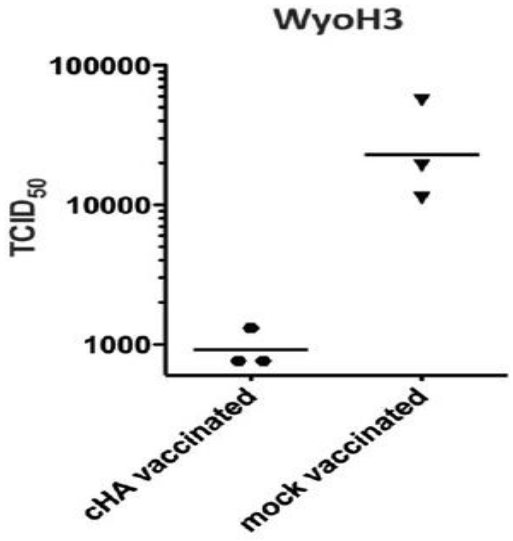


cHA vaccine protects against challenge with H10 and H3 viruses

Titers in mouse lungs, day 3 postinfection



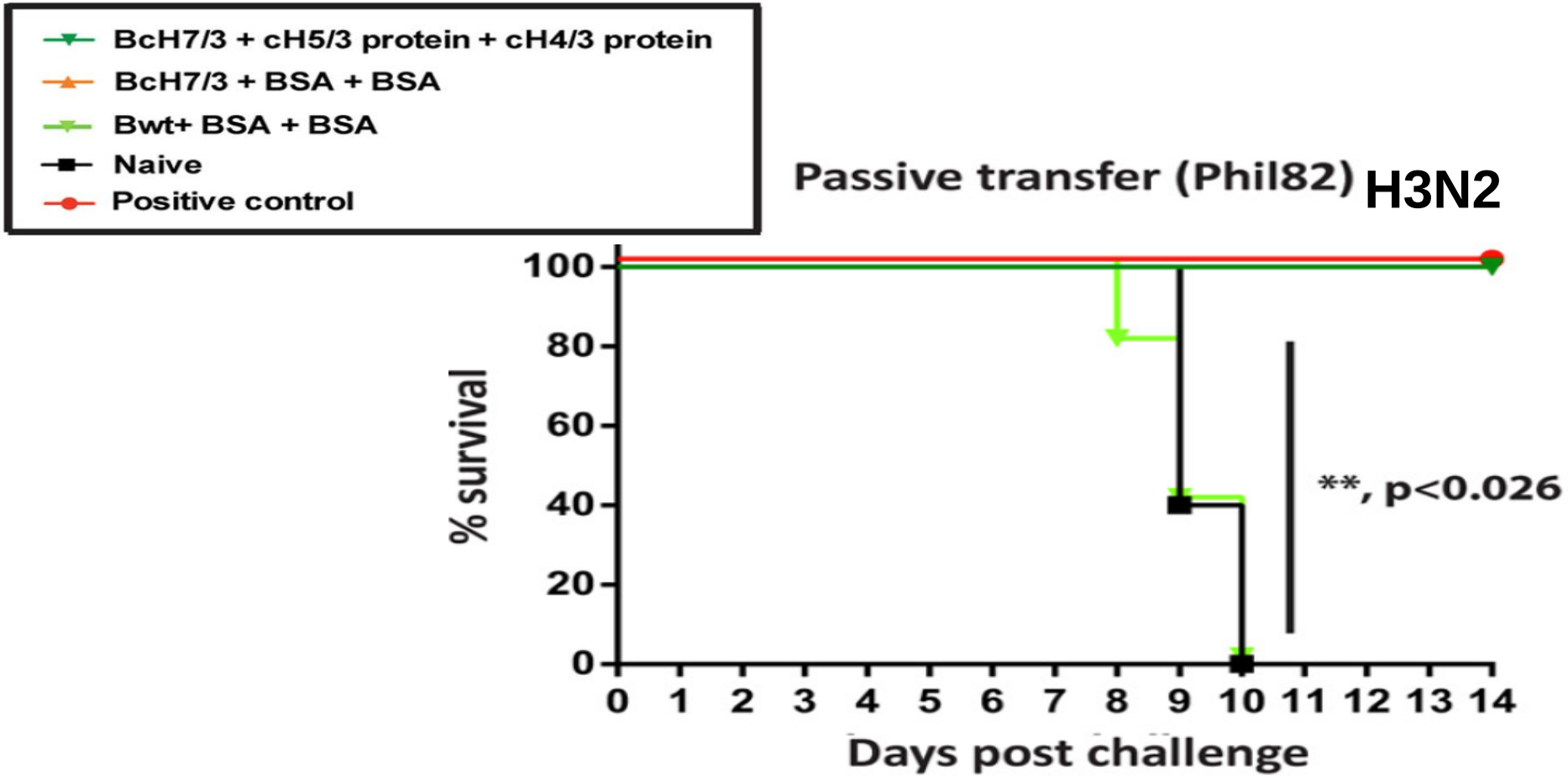




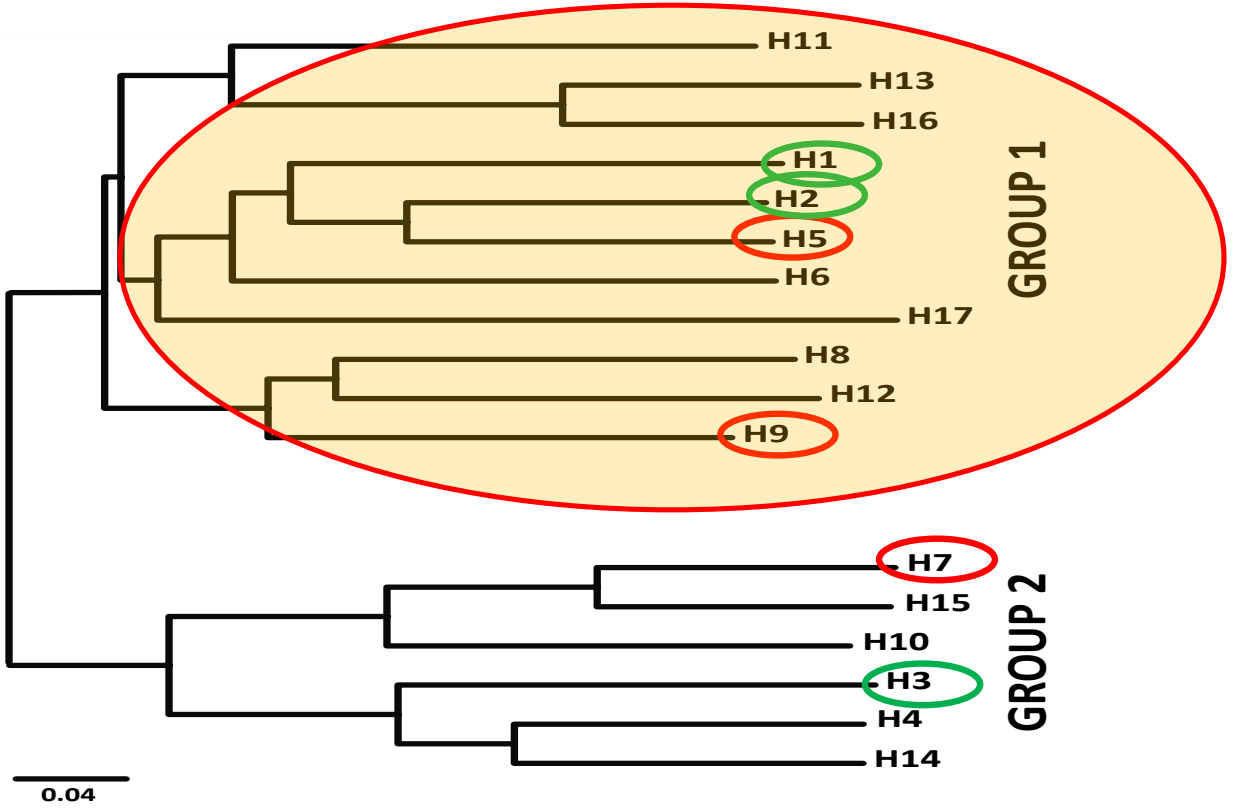
cH4/3 DNA + cH5/3 protein + H3 protein

cH4/3 DNA + cH5/3 protein + cH7/3 protein

Abs mediate protection

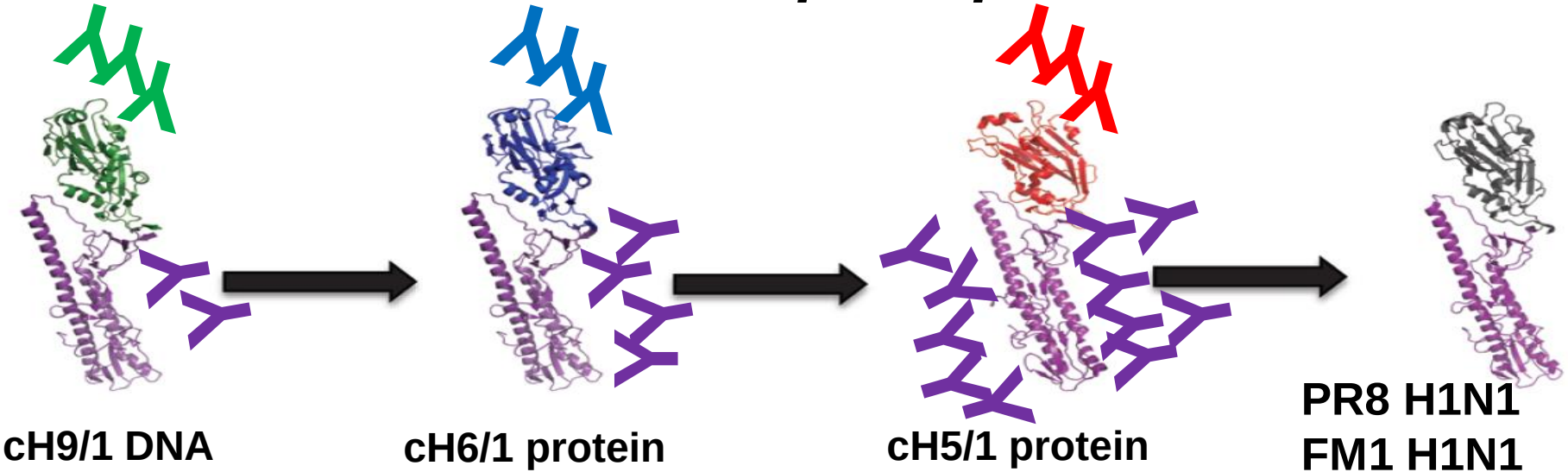


Targeting group 1 HA viruses



Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

Proof of principle



cH9/1 DNA

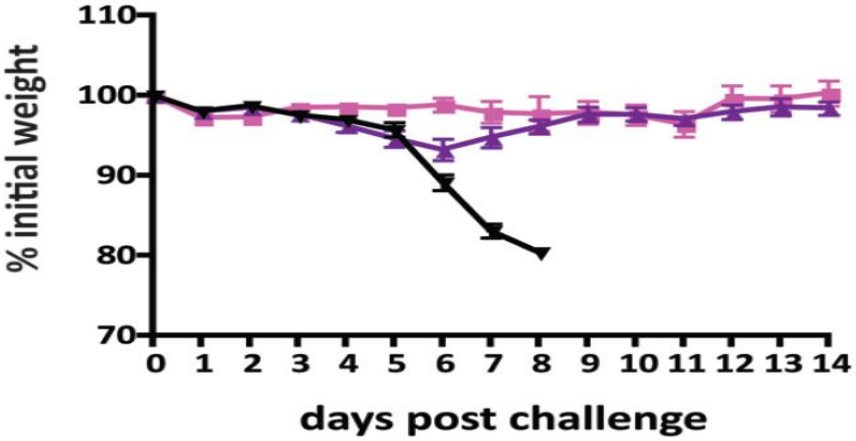
cH6/1 protein

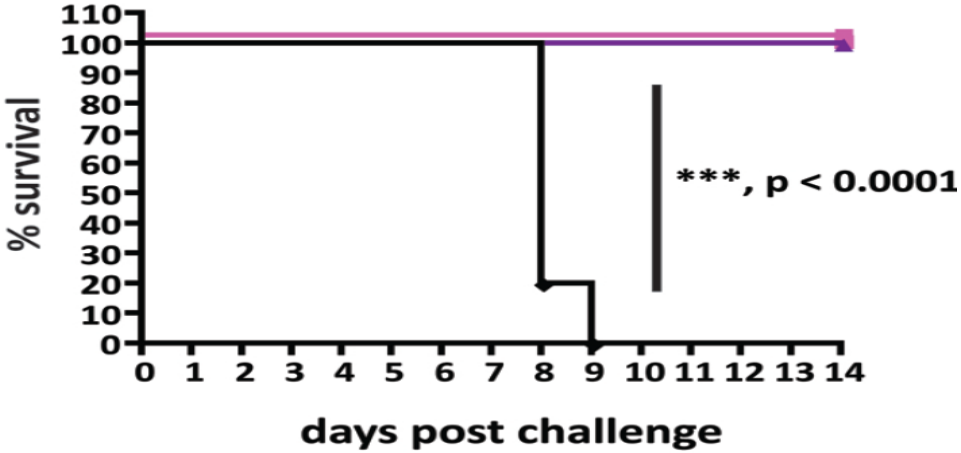
cH5/1 protein

PR8 H1N1
FM1 H1N1
pH1N1
H5N1
H6N1
challenge

Control groups:
cH9/1 DNA + BSA + BSA
matched vaccine (pos. contr.)

Vaccination with cHA constructs protects from pH1N1 (A/Netherlands/602/09) challenge



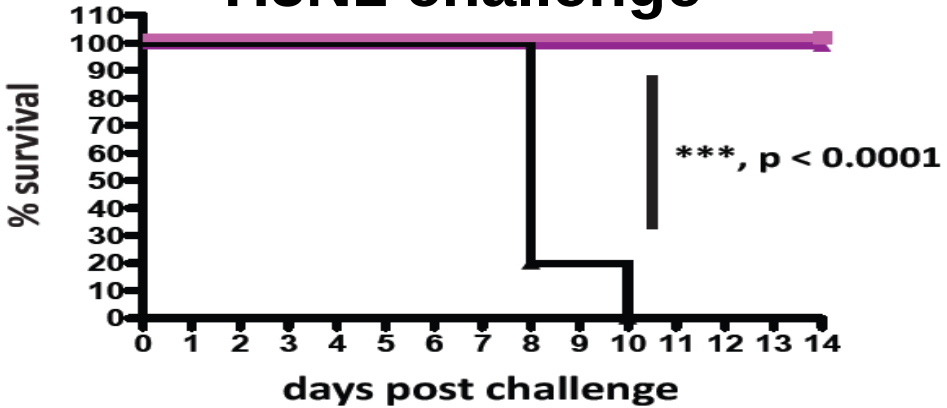


positive control (matched inactivated)
cH9/1 DNA + cH6/1 protein + cH5/1 protein
cH9/1 DNA + BSA +BSA

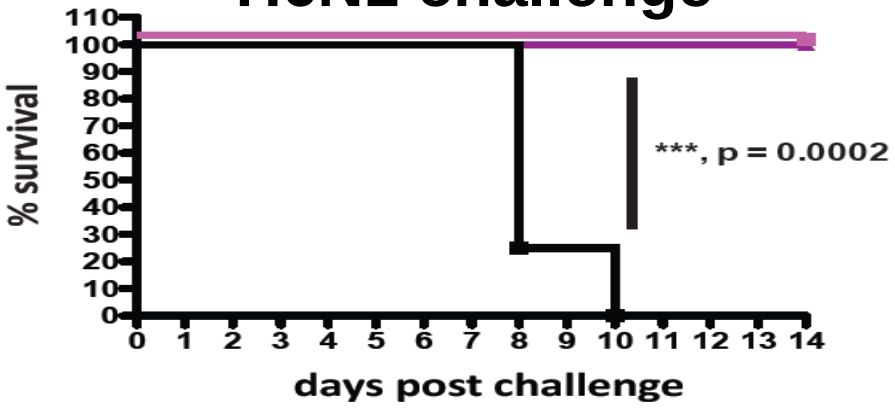
Similar results for A/PR/8/34 H1N1 and A/FM/1/47 challenges

cHA constructs protect mice from heterosubtypic challenge

H5N1 challenge



H6N1 challenge

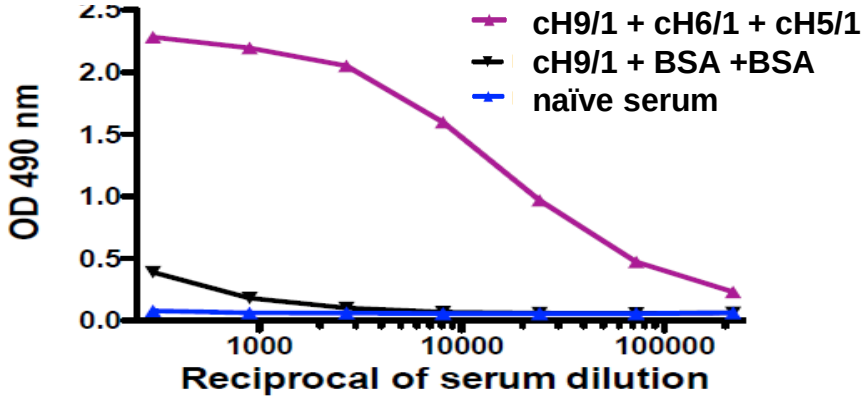


- positive control (matched inactivated)
- cH9/1 DNA + H1 protein/cH6/1 protein + cH5/1 protein/H1 protein
- cH9/1 DNA + BSA +BSA

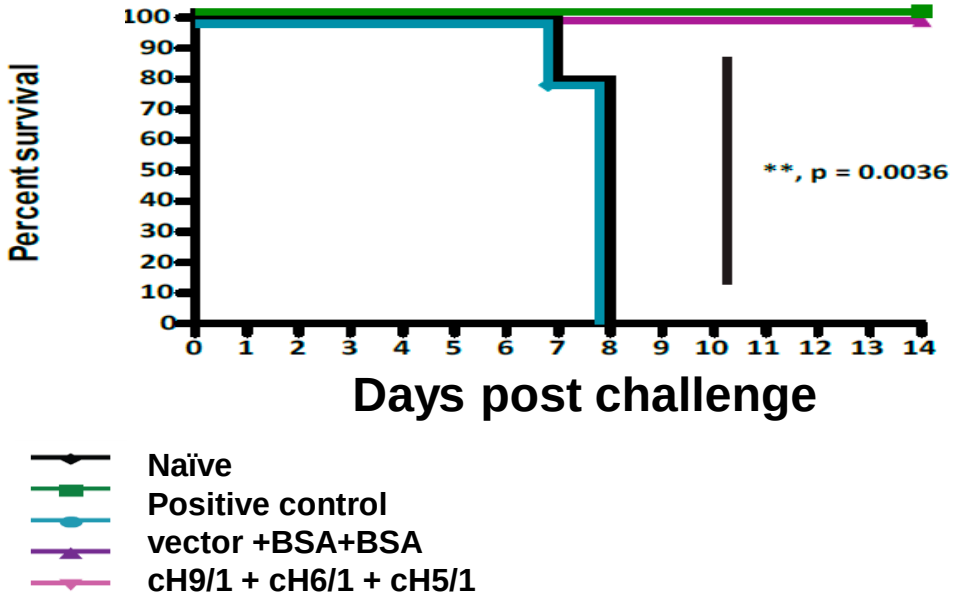
cH5/1 (H5 challenge) or cH6/1 (H6 challenge) protein was replaced by full length H1 protein to exclude head-based protection

Protection is antibody mediated

ELISA reactivity to Cal09 (pH1N1) protein



Passive transfer of serum protects from viral challenge



Prime–Boost cHA vaccines based in LAIV and IIV platforms

Florian Krammer, Raffael Nachbagauer,
Adolfo García-Sastre, Peter Palese and Randy A. Albrecht

Mount Sinai

PATH

BILL & MELINDA GATES foundation

gsk

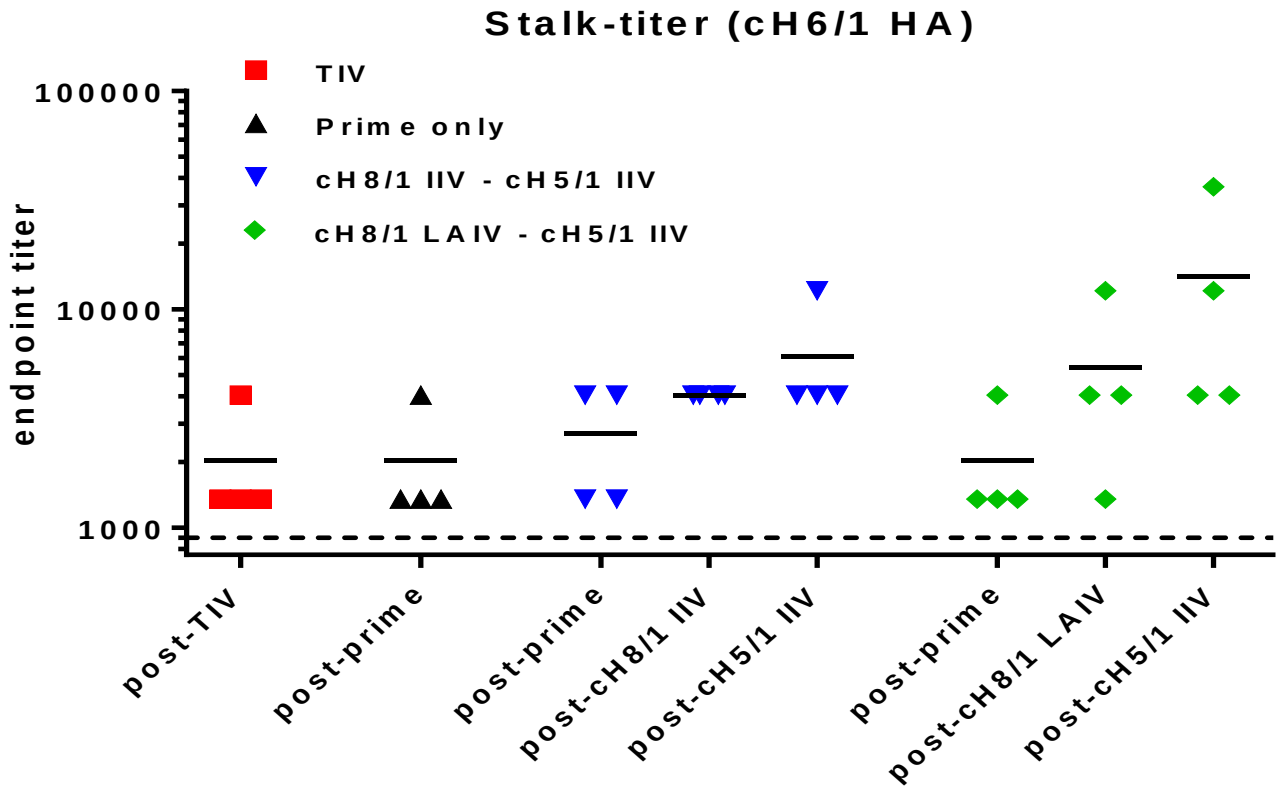
Prime–Boost cHA vaccines based in LAIV and IIV platforms

	Prime	Boost	Boost
“cH8/1 LAIV- cH5/1 IIV”	B-cH9/1	cH8/1 - LAIV ★	cH5/1 - IIV
“cH5/1 IIV- cH5/1 IIV”	B-cH9/1	cH8/1 - IIV	cH5/1 - IIV
“Prime-only”	B-cH9/1	Mock	Mock
“TIV”			TIV
“Naive”			Mock

Ferret vaccination groups (n=4)

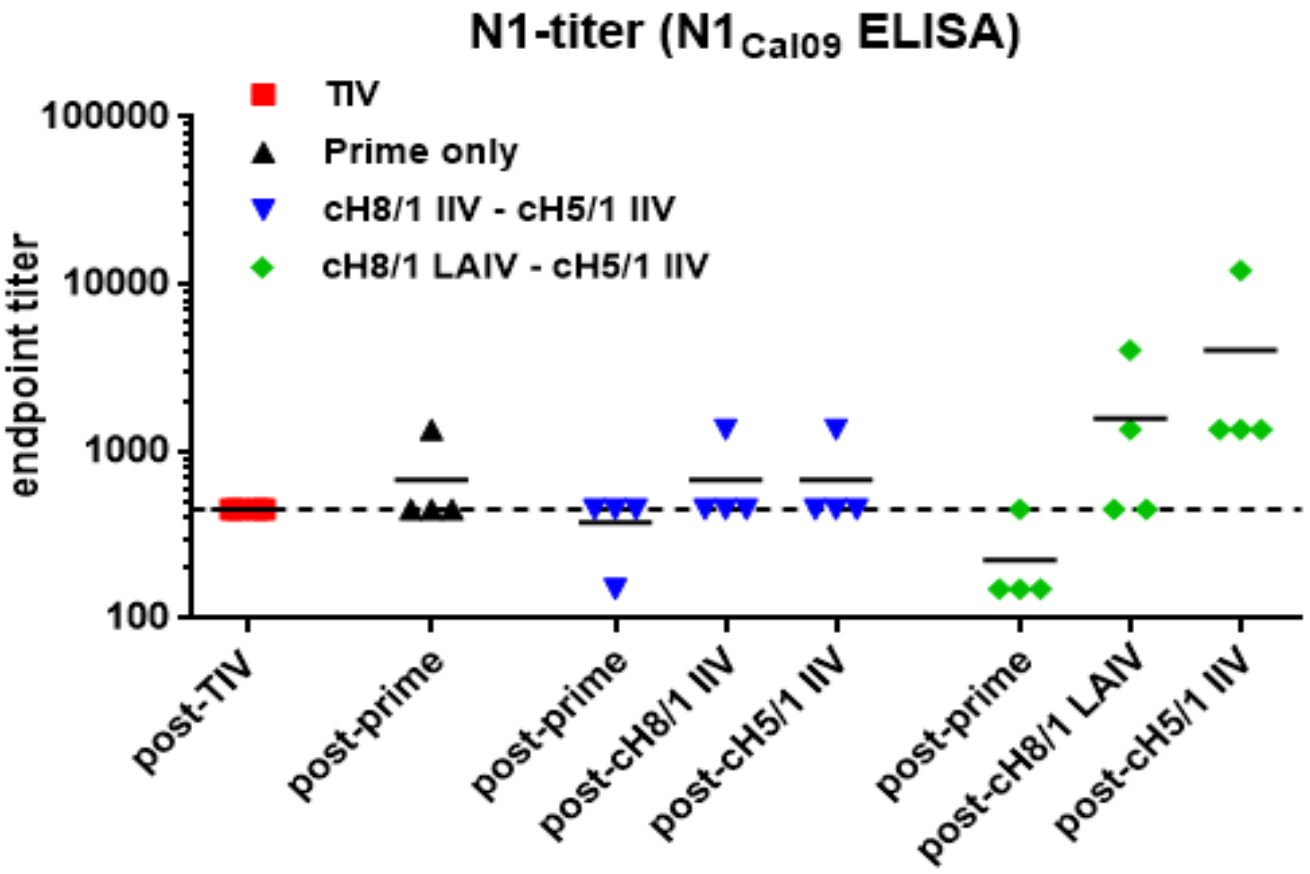
★ LAIV is based on the Ann Arbor backbone

Induction of HA stalk-specific antibodies (ELISA)

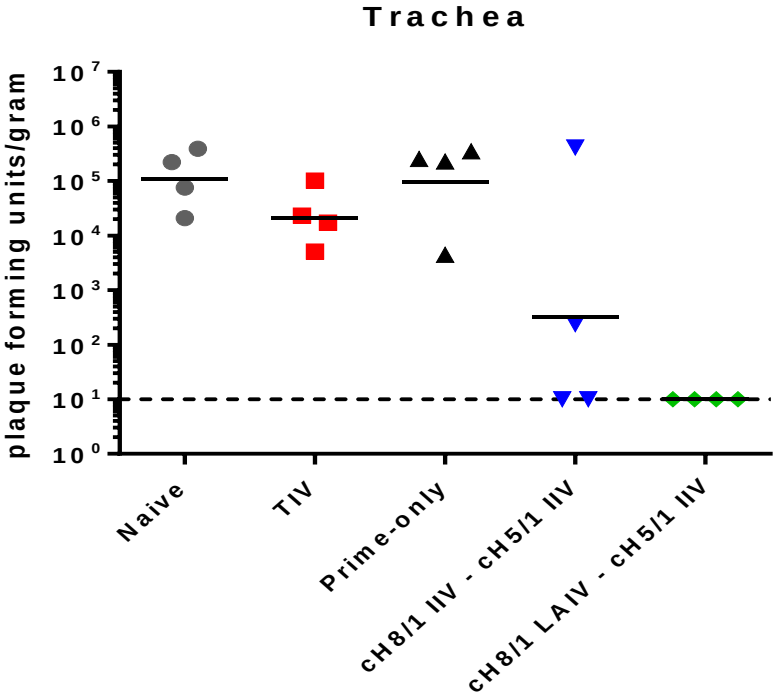


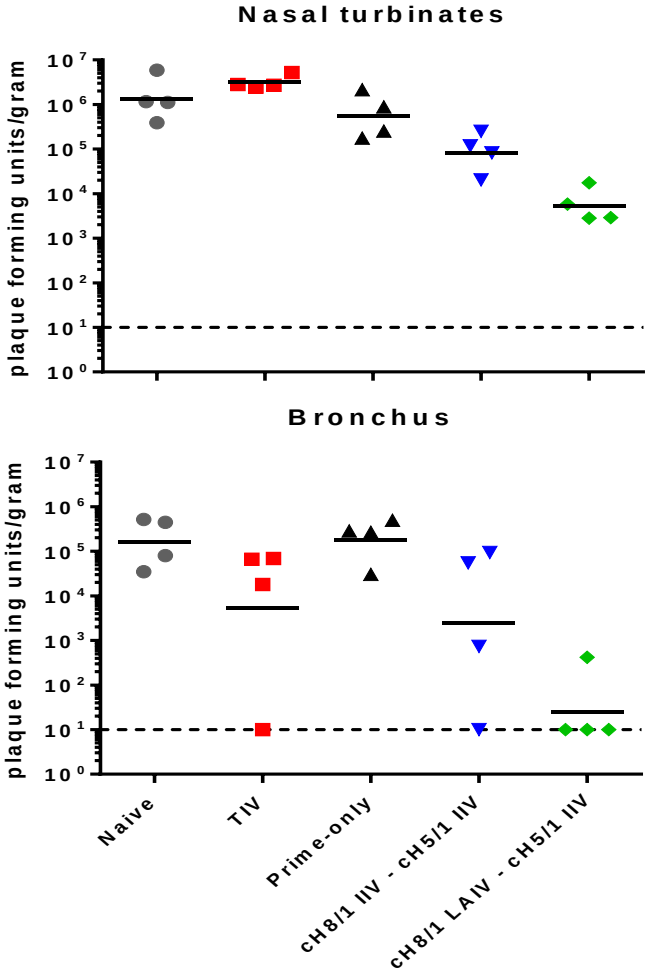
*No detectable HI titers following vaccination

Induction of NA-specific antibodies (ELISA)



Viral titers in tissues following H1N1 challenge infection, day 4





CONCLUSIONS

LIVE ATTENUATED FOLLOWED BY INACTIVATED CHIMERIC HA VACCINES INDUCE HA STEM AND NA ANTIBODIES,

AND HIGH LEVELS OF PROTECTION AGAINST HETEROSUBTYPIC CHALLENGE IN FERRETS

Acknowledgements

Randy Albrecht
Michael Schotsaert
Angela Choi
Juan Ayllon

Raffael Nachbagauer

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Rafi Ahmed
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