

Development of a universal influenza virus vaccine based on the conserved stalk domain of the hemagglutinin

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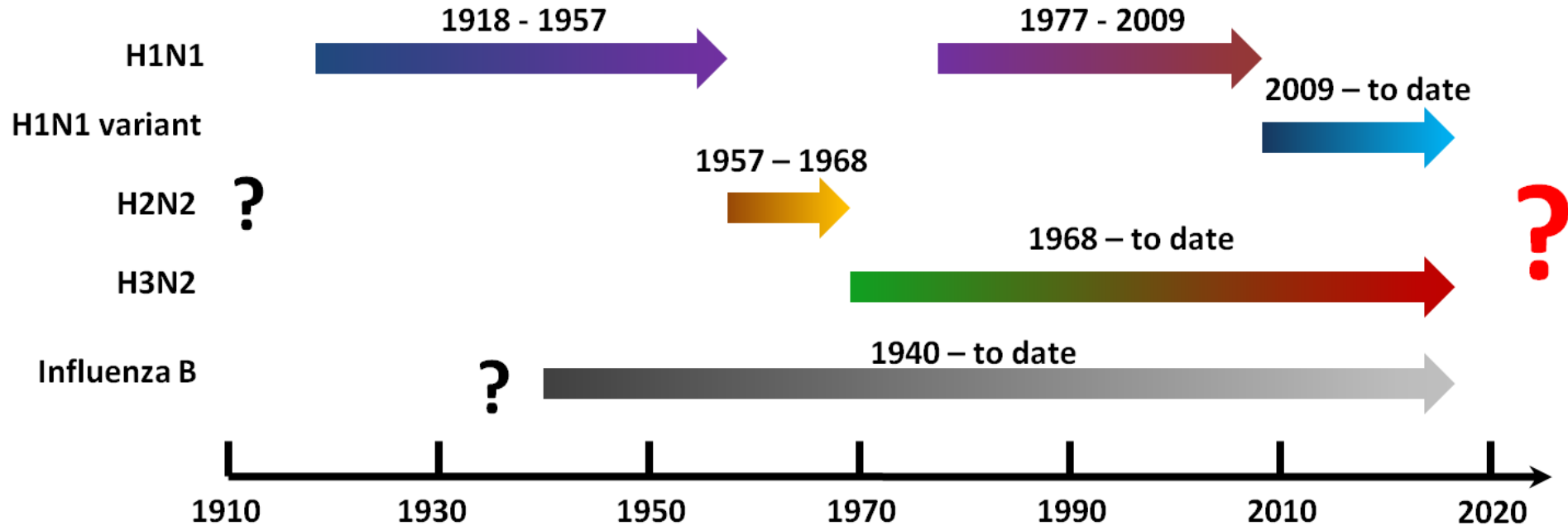
Beijing

September 9th, 2018



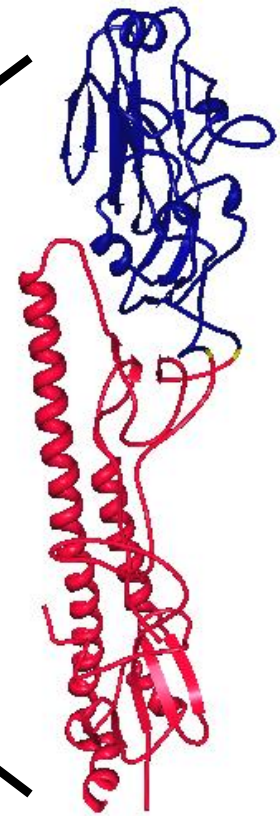
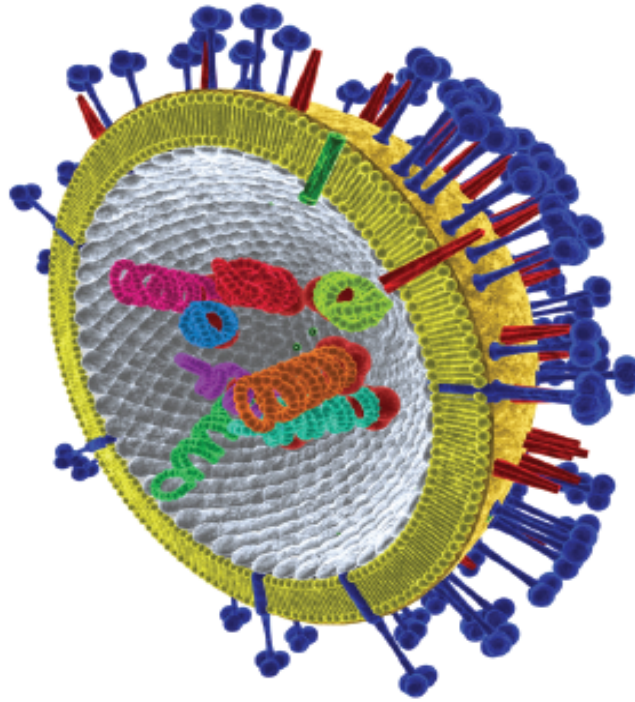
**Mount
Sinai**

Dynamics of influenza virus circulation in humans



Antigenic Drift and Antigenic Shift

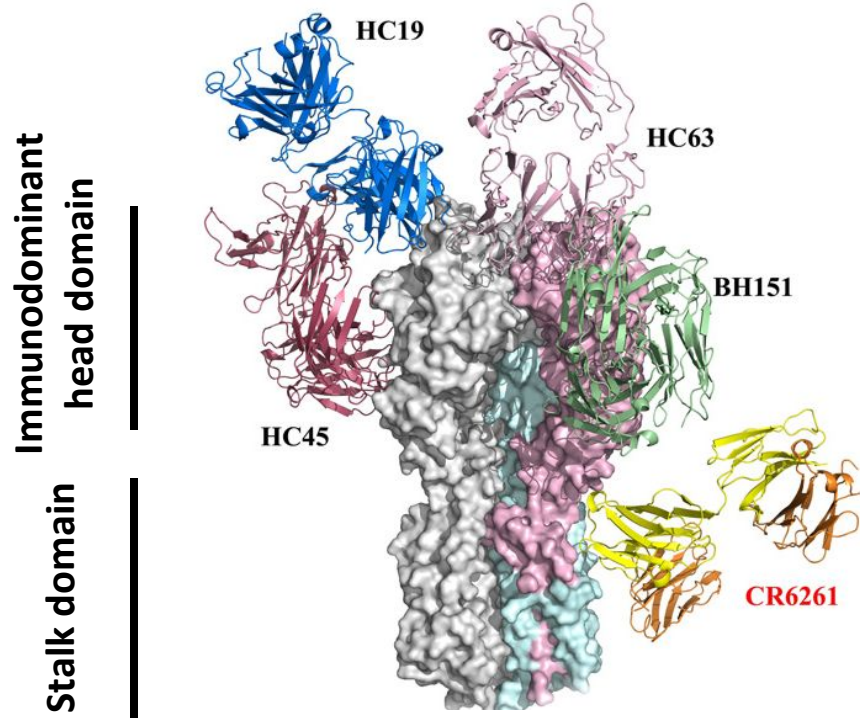
Influenza A virus hemagglutinin (HA)



Globular head domain:
mediates
binding to
host receptors

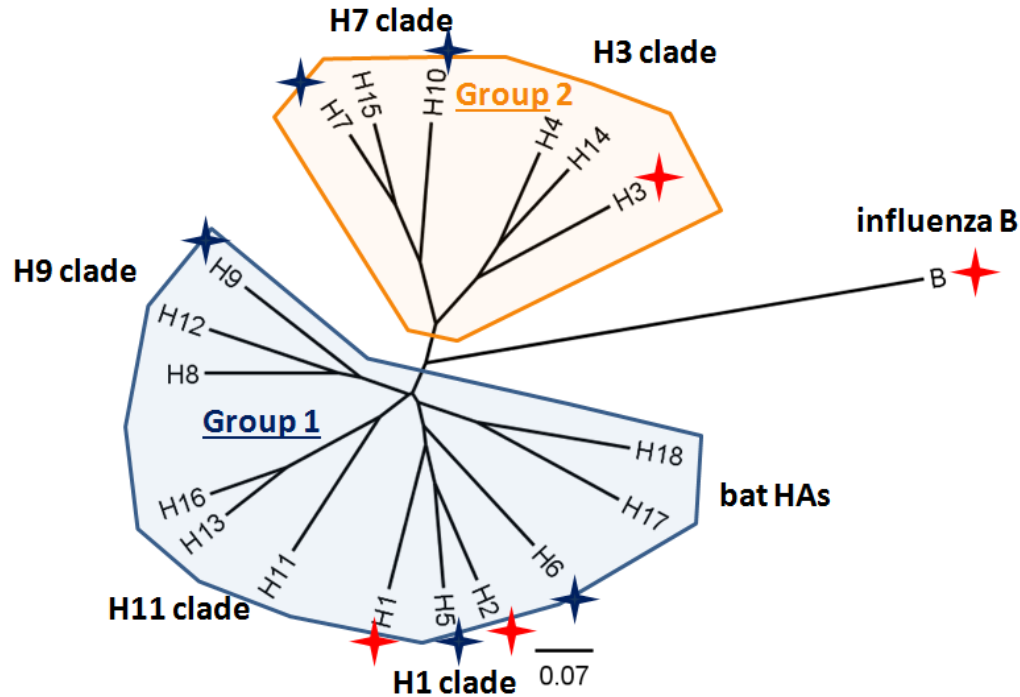
Stalk domain:
mediates
fusion of viral
and
endosomal
membranes

Antibodies against the influenza virus HA stalk domain



- Rare and not induced/boosted upon regular seasonal vaccination
- Have been isolated from humans and mice
- Cross-reactive between HAs of different subtypes
- Broad neutralizing activity
- Conformational epitopes
- HI negative

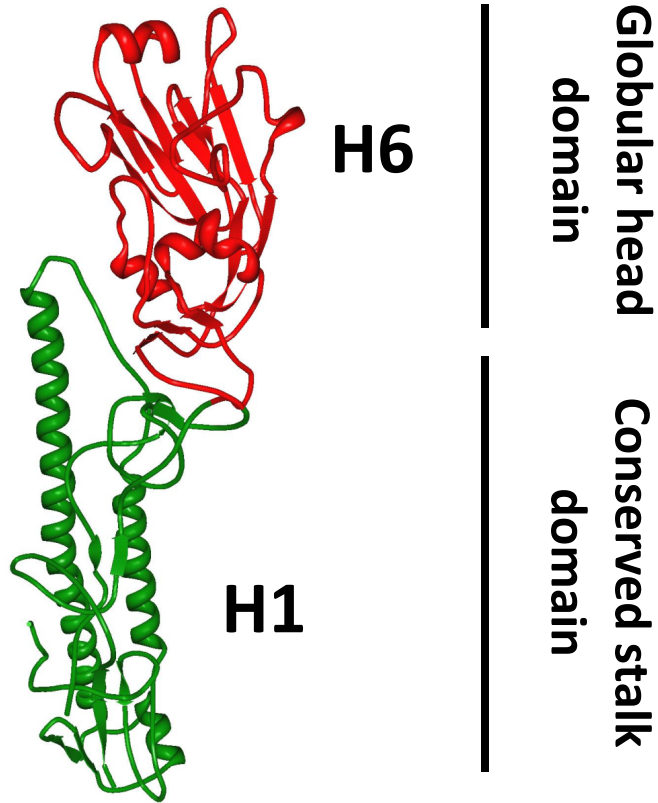
The HA stalk is conserved among group 1, among group 2 HAs and among influenza B HAs



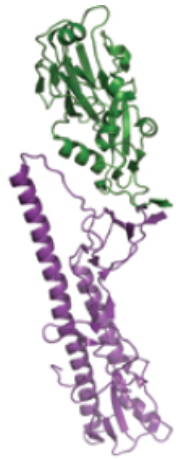
Can protective levels of broadly neutralizing antibodies be induced by vaccination?

Chimeric hemagglutinins (cHA)

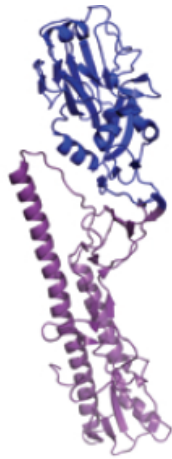
chimeric H6/1



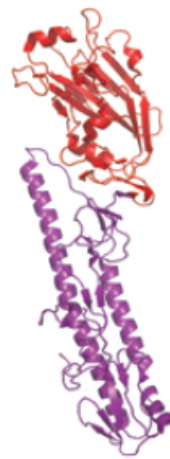
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice



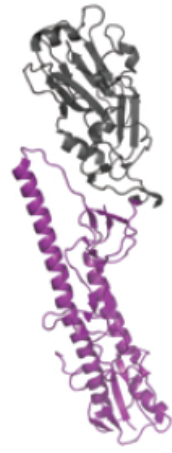
CH9/1 DNA



CH6/1 protein



CH5/1 protein

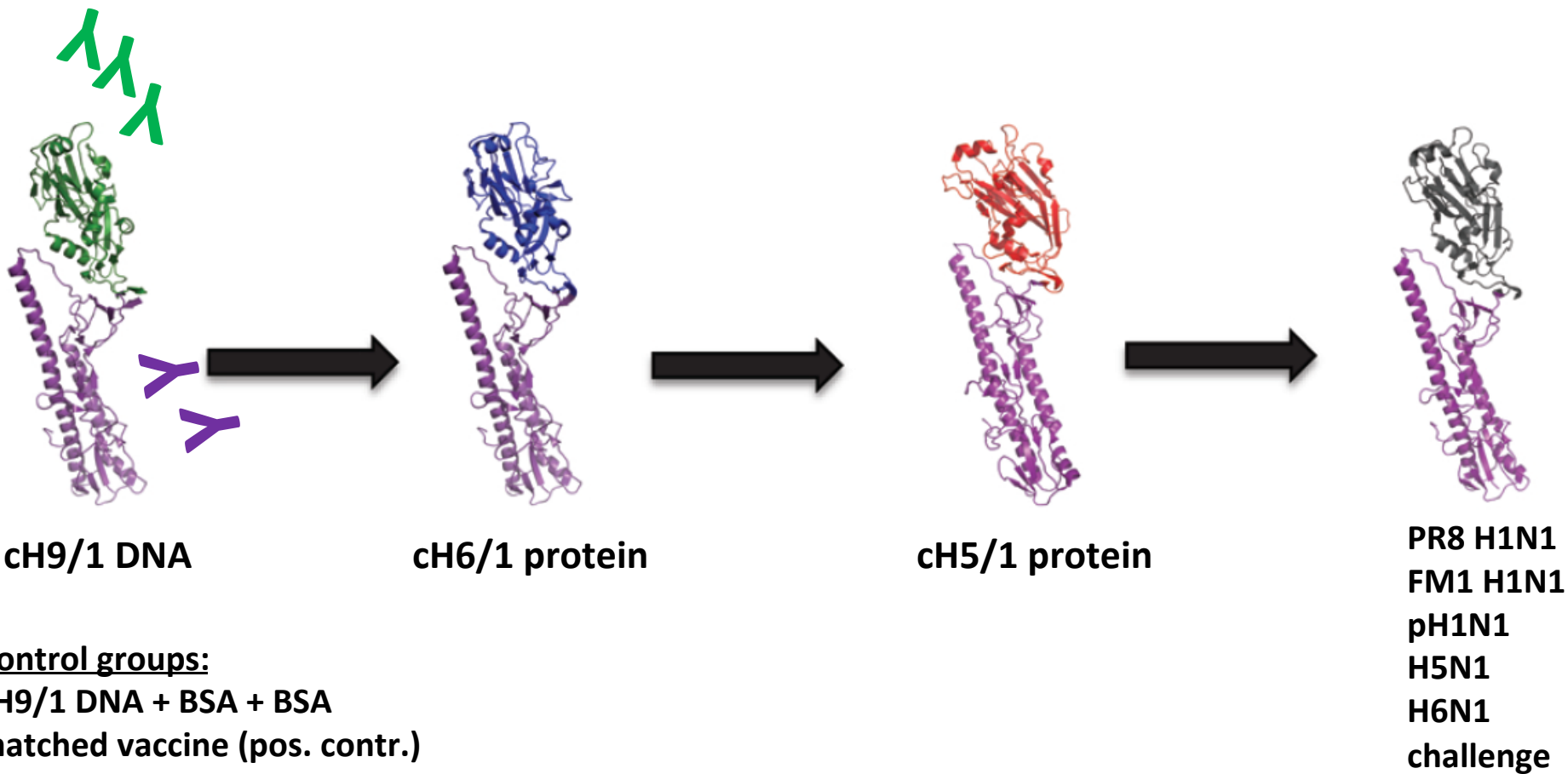


PR8 H1N1
FM1 H1N1
pH1N1
H5N1
H6N1
challenge

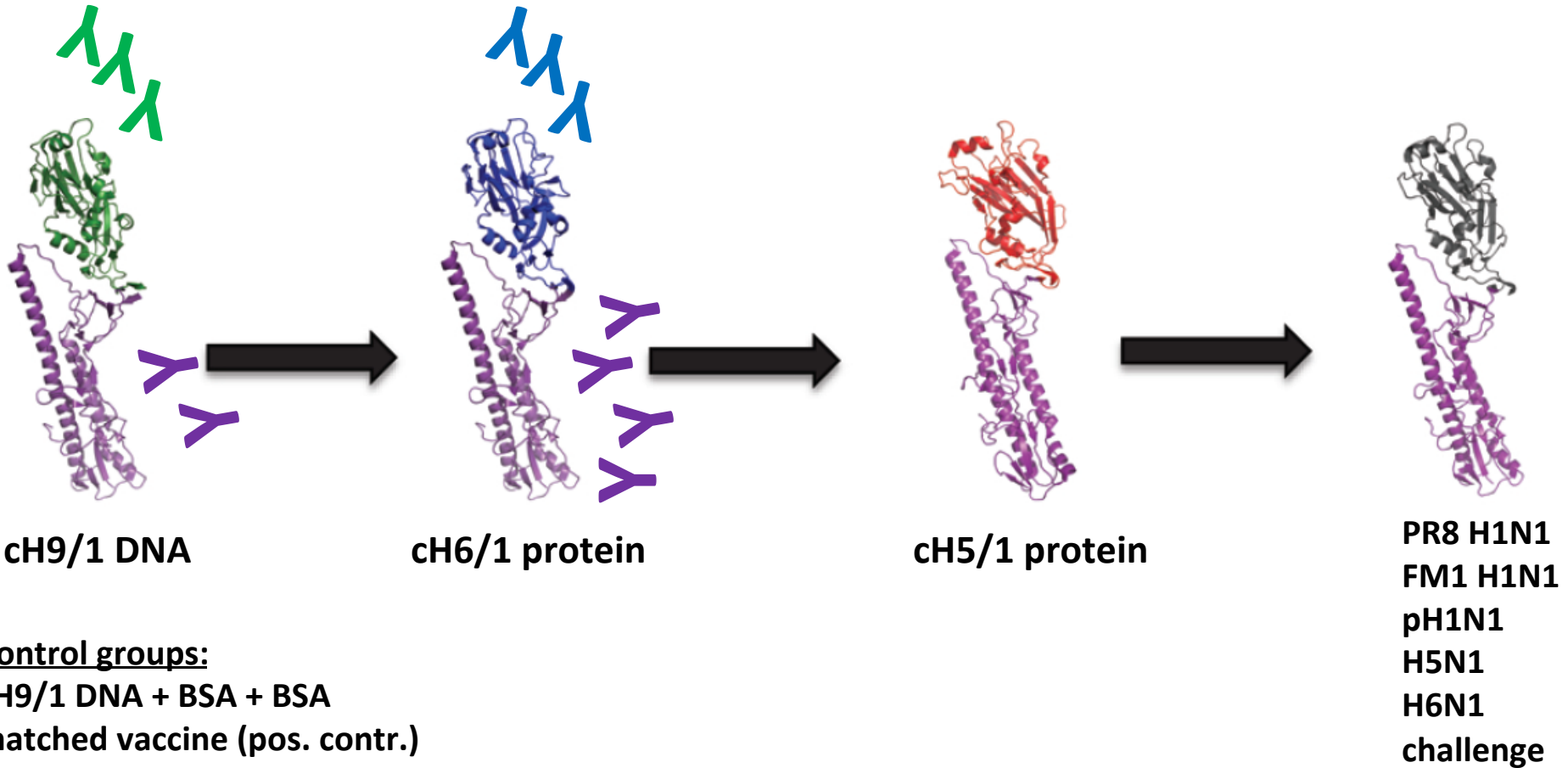
Control groups:

CH9/1 DNA + BSA + BSA
matched vaccine (pos. contr.)

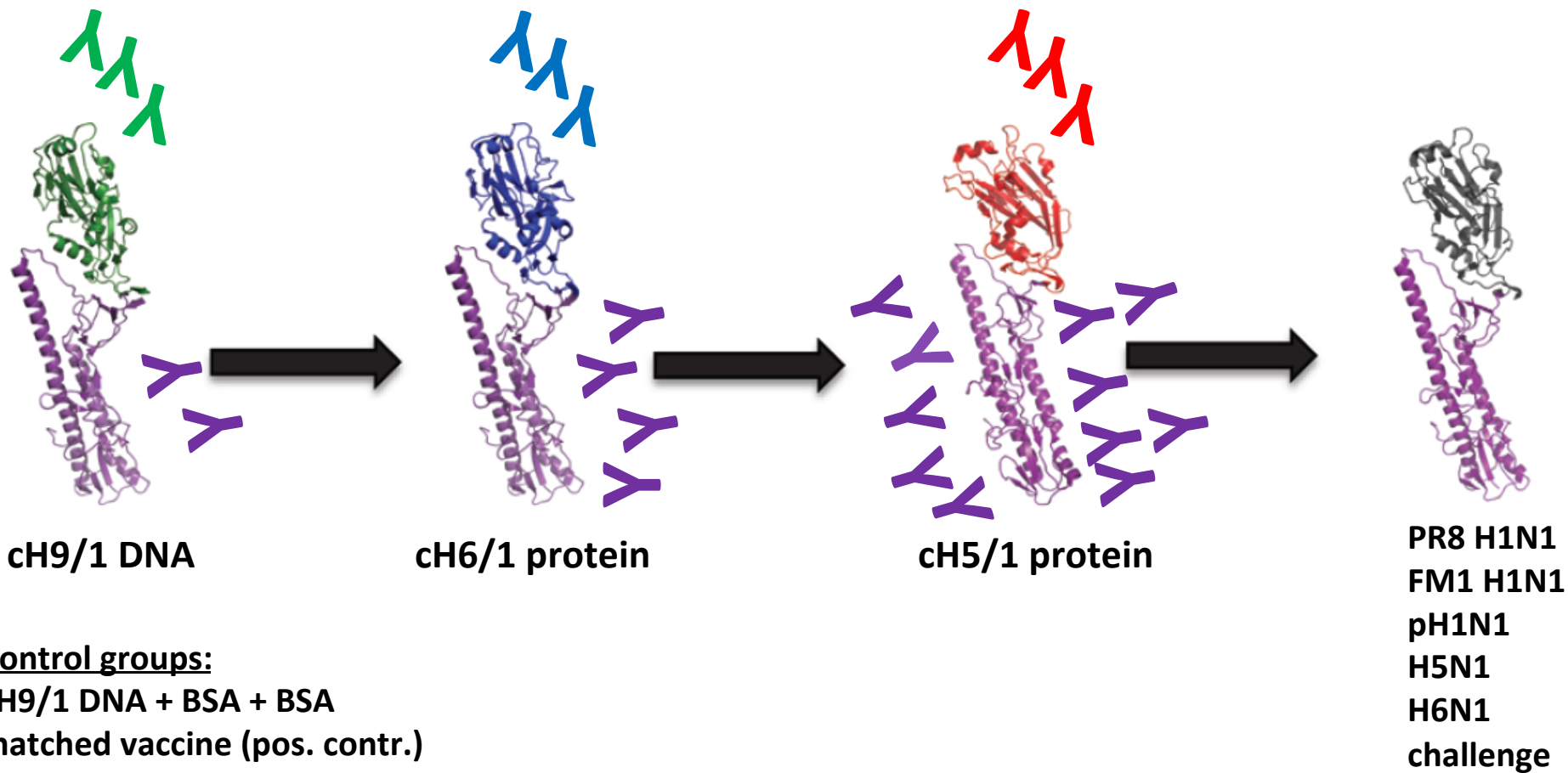
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice



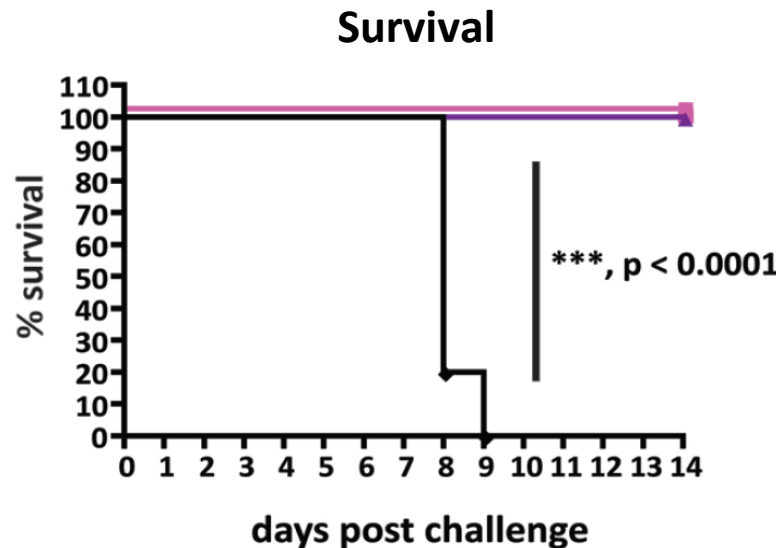
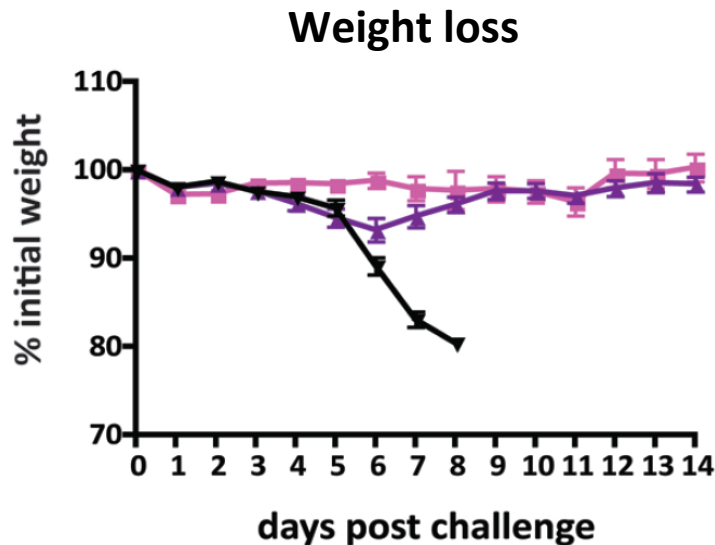
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice



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



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

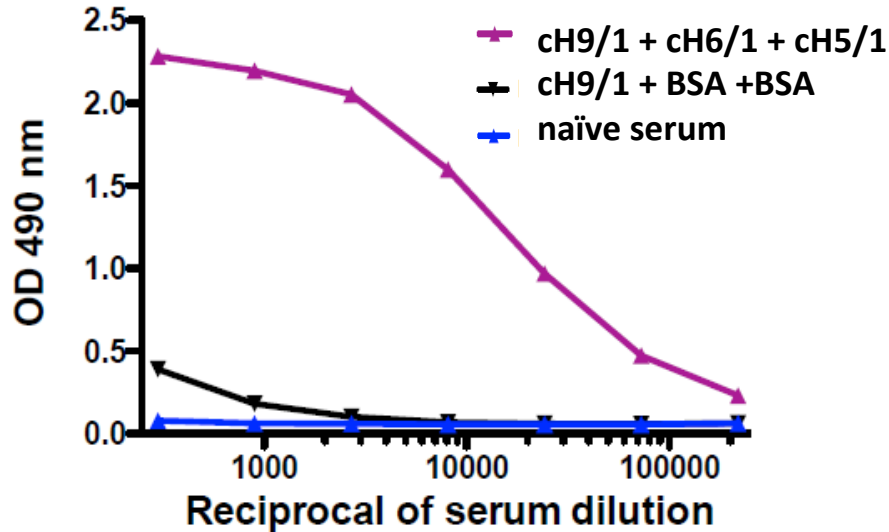


- positive control (matched inactivated)
- ▲ cH9/1 DNA + cH6/1 protein + cH5/1 protein
- ▼ cH9/1 DNA + BSA + BSA

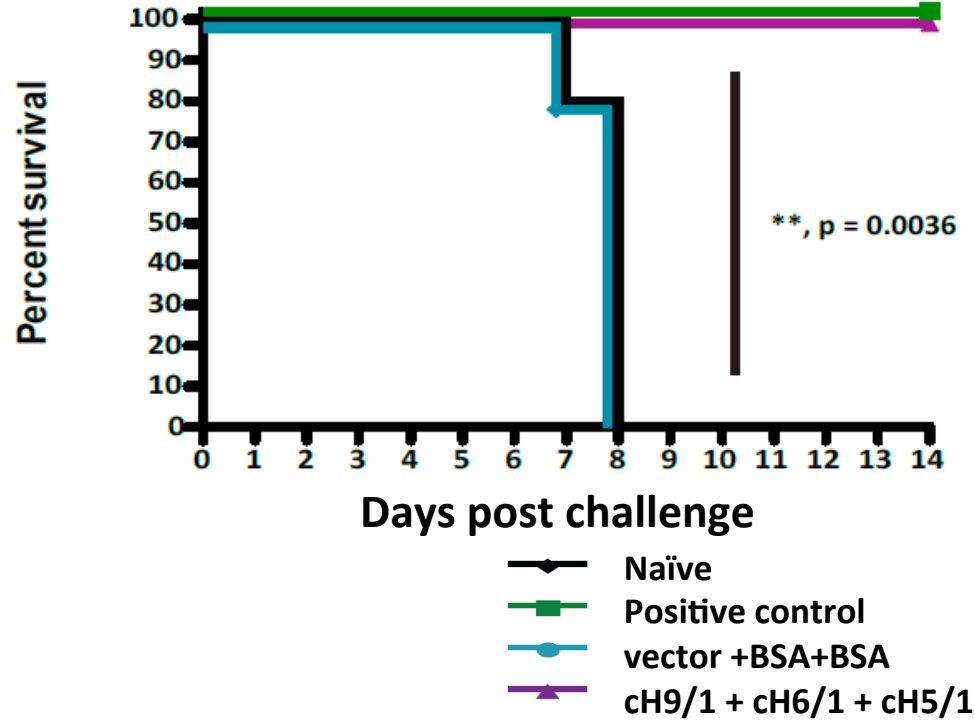
Similar results for A/PR/8/34 H1N1 and A/FM/1/47 challenges and heterosubtypic challenges with H5N1 and H6N1

Protection is antibody mediated

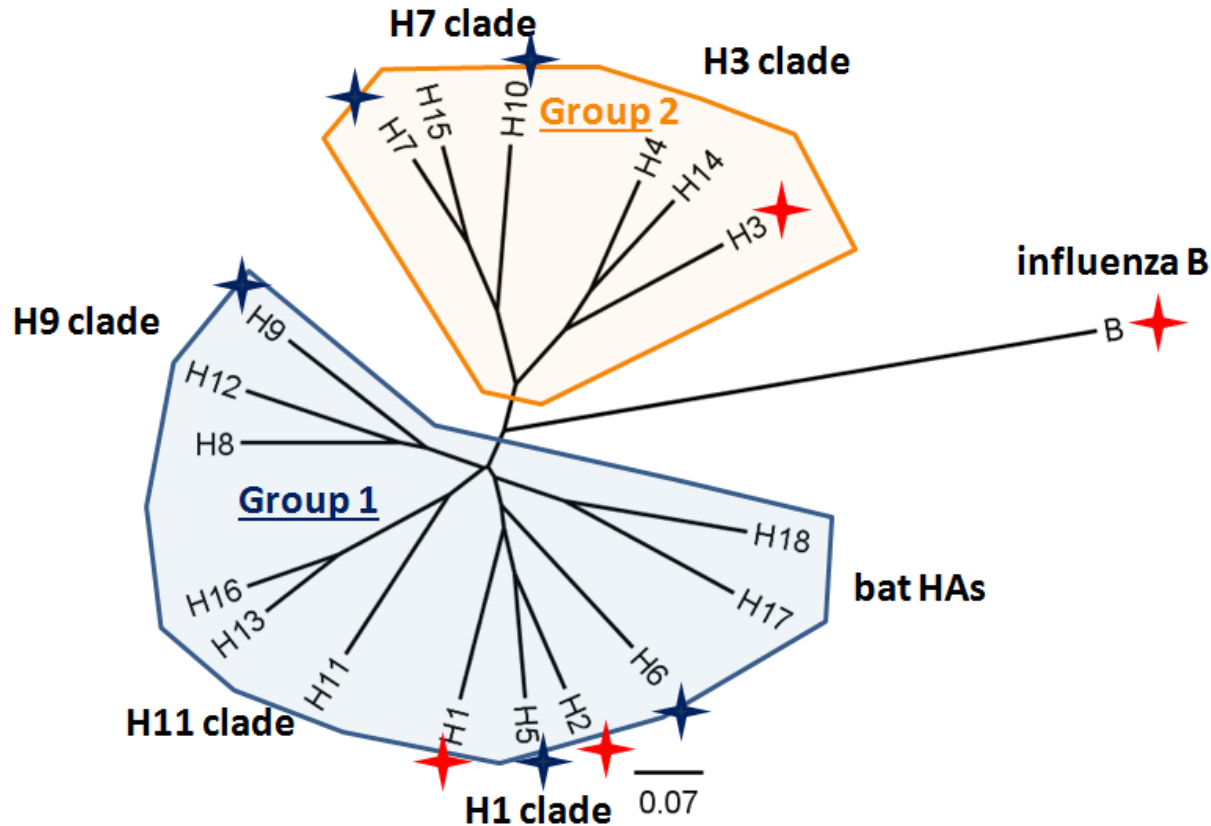
ELISA reactivity to Cal09 (pH1N1) protein



Passive transfer of serum protects from viral challenge

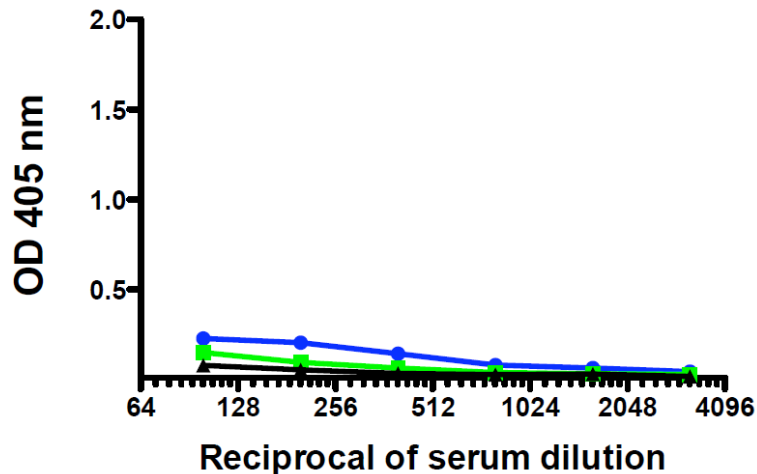


Cross-protection against group 2 viruses?



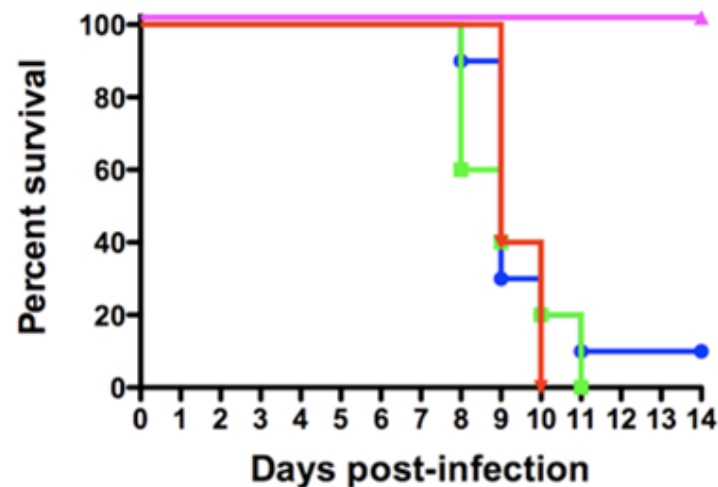
Group 1-group 2 cross-reactivity is not sufficient to protect from virus challenge

Phil82 (H3N2) ELISA



- CH9/1_{PR8}-CH6/1_{PR8}-CH2/1_{PR8}
- CH9/1_{PR8}-BSA-BSA
- ▲ Naive

Phil82 (H3N2) challenge

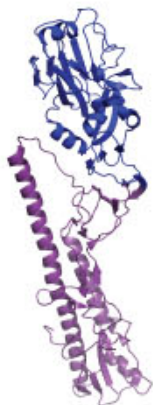


- CH9/1_{PR8}-CH6/1_{PR8}-CH2/1_{PR8}
- CH9/1_{PR8}-BSA-BSA
- ▲ Positive control
- Negative control

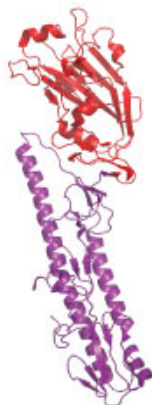
Group 2 proof of concept



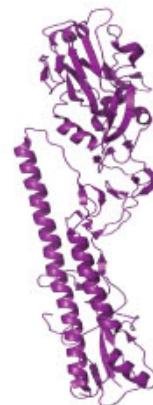
3 weeks



3 weeks



4 weeks



CH4/3 DNA

**CH5/3 protein
boost**

**CH7/3 protein
boost
(H3 protein for the
H7 challenge)**

**ma Phil82 (H3)
ma X31 (H3)
Rhea (H7)
H7N9
challenge**

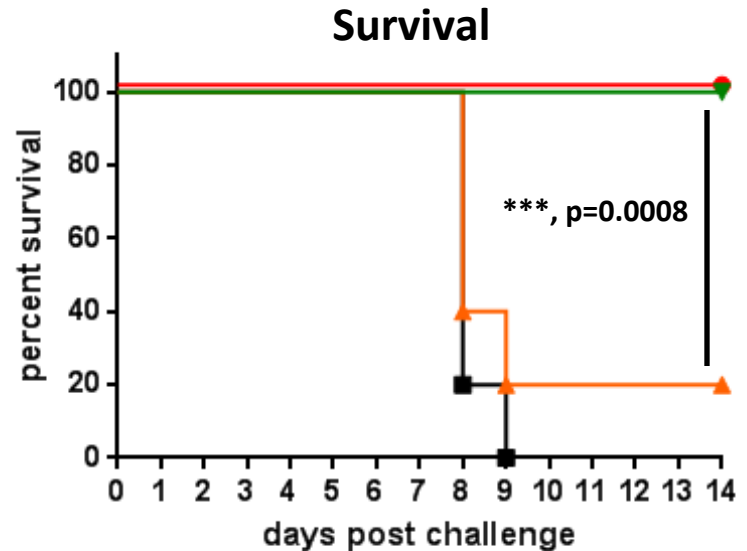
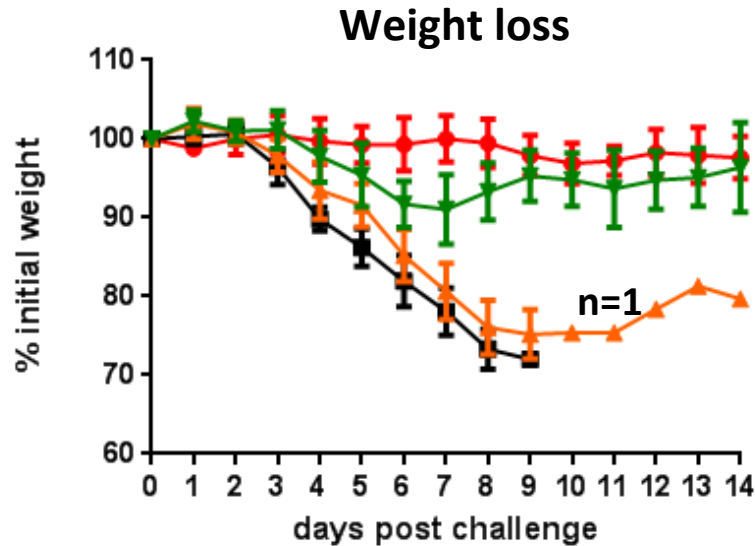
Control groups:

CH4/3 DNA + BSA + BSA

naïve (neg. contr.)

matched vaccine (pos. contr.)

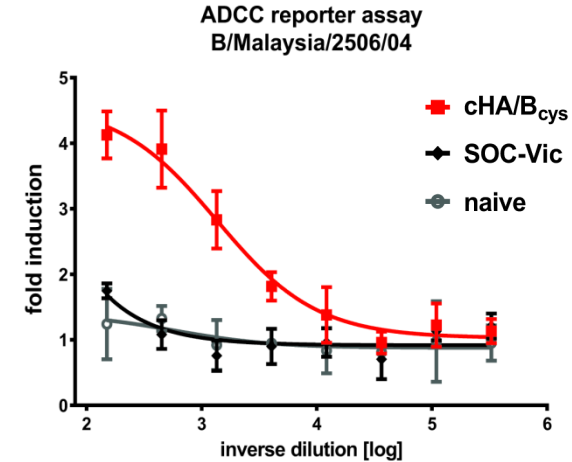
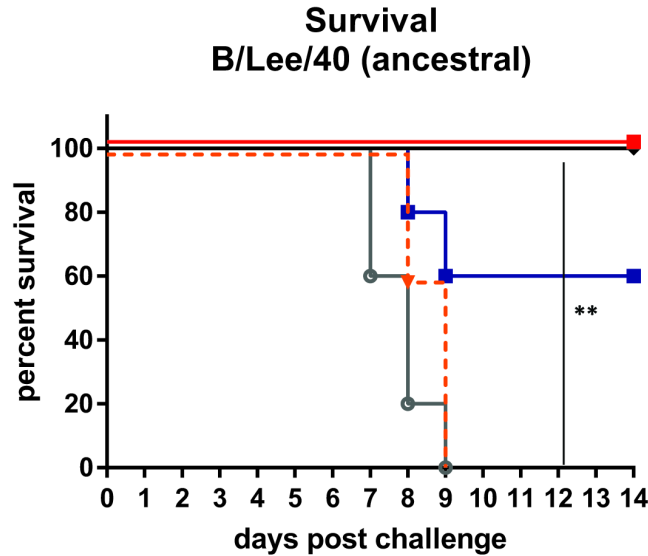
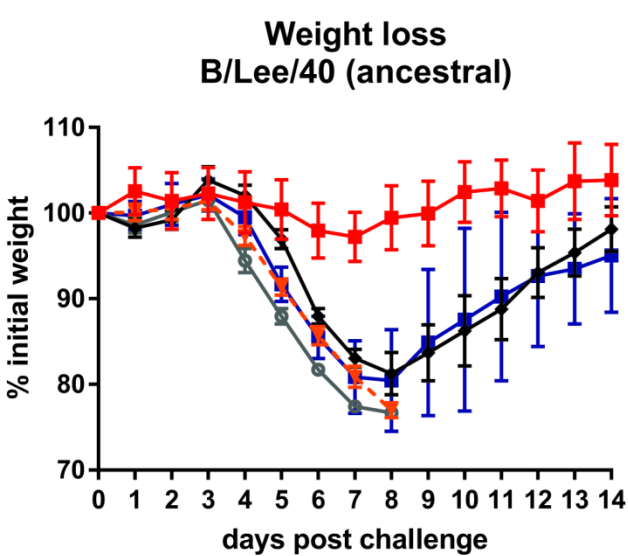
A/Philippines/2/82 H3N2 challenge



- cH4/3 DNA + cH5/3 protein + cH7/3 protein
- cH4/3 DNA + BSA + BSA
- Naive
- Positive control

Similar results for other H3N2 viruses and heterosubtypic challenges with H7N1 and H7N9 (cH7/3 protein was replaced by full length H3 protein for the H7 challenge group).

Proof of concept for influenza B virus



- cHA/B_{cys}
- ▽- prime-only_{cys}
- ◆ SOC-Vic
- naive
- SOC-Yam

Similar results for other influenza B viruses from the B/Yamagata, B/Victoria and ancestral lineage.

Pre-clinical testing in the ferret model

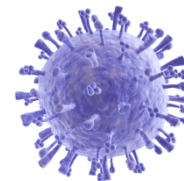


Heterologous prime-boost experiment with cHA vaccines in ferrets

cH8/1N1 LAIV



cH5/1N1 IIV



cH8/1N1 IIV



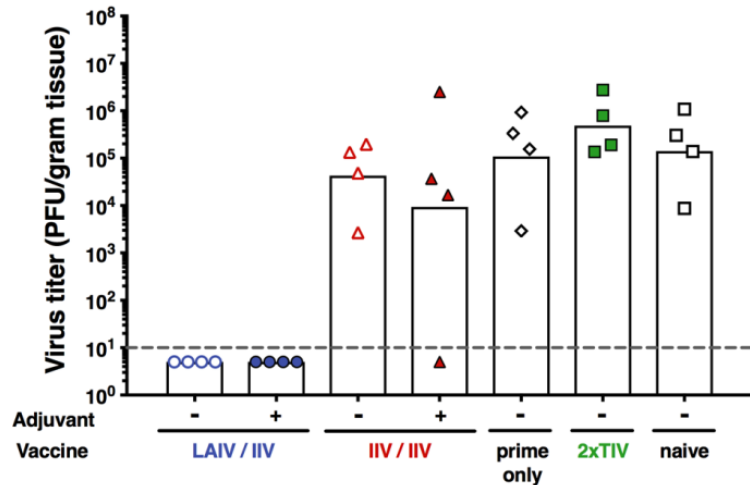
cH5/1N1 IIV



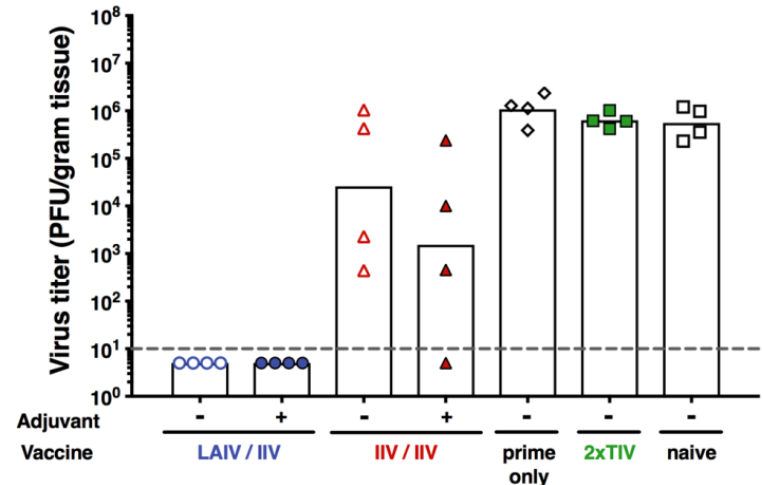
**pH1N1
challenge**

cHA based vaccines protect ferrets from pandemic H1N1 challenge

Trachea virus titers



Lung virus titers

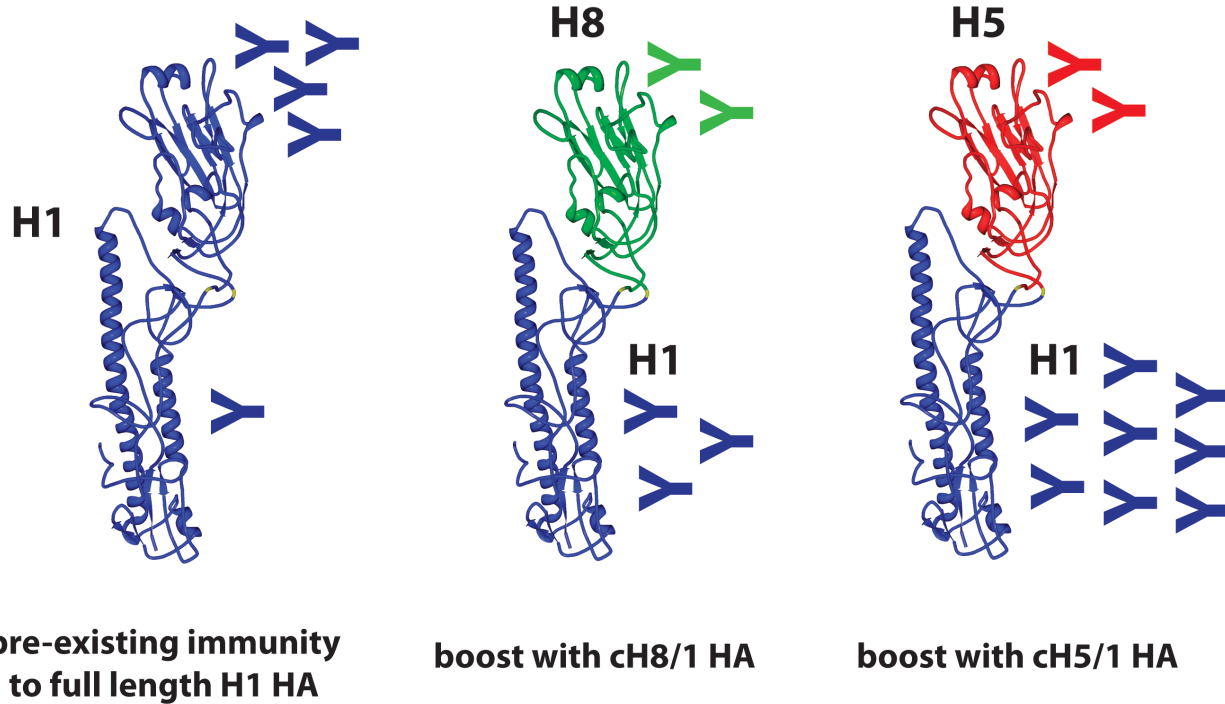


Lessons learned from pre-clinical studies

- Chimeric HA constructs induce broadly reactive anti-stalk antibodies and protect mice and ferrets from challenge with heterologous and/or heterosubtypic virus strains
- Chimeric HA vaccination impacts on transmission and is long-lasting
- The observed protection is antibody mediated
- Good protection against emerging viruses (H5, H6, H7, H10 etc.)
- Works well as inactivated split vaccine
- A trivalent vaccine with an group 1, group 2 and influenza B stalk component will be needed

(Krammer and Pica *et al.*, JVI, 2013; Margine and Krammer *et al.*, JVI, 2013, Krammer *et al.*, JVI 2013, Krammer *et al.*, JVI, 2014, Nachbagauer *et al.*, JVI, 2015, Ryder *et al.*, JVI, 2015, Nachbagauer *et al.*, NPJ Vaccines, 2016, Ermler *et al.*, JVI, 2017, Nachbagauer *et al.*, NPJ Vaccines, 2017, Isakova-Sivak *et al.*, Virology, 2018, Nachbagauer *et al.*, Vaccines, 2018)

Concept for a human universal influenza virus vaccine



Krammer and Palese, Nat. Immunol., 2013

Trivalent vaccine with group 1, group 2 and influenza B stalk component necessary

Conclusions – cHA vaccine

- **Chimeric hemagglutinin (cHA) vaccine constructs protect from heterologous and heterosubtypic challenge in animal models**
- **H5N1 vaccination induces high levels of stalk-reactive antibodies in humans providing support for a cHA based vaccine**
- **cHA-based vaccines are currently tested in Phase I/II clinical trials** (clinicaltrials.gov ID NCT03300050 and NCT02275200)

Acknowledgements

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BILL & MELINDA
GATES *foundation*



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