Influenza Universal Vaccines

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EPIDEMIOLOGY OF HUMAN INFLUENZA VIRUSES

A

H2N2
1957

H1N1
1918

B

H1N1
1918

H3N2
1968

Yamagata

Victoria

pH1N1
2009
Evolution and spread of flu viruses
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

Hemagglutinin subtypes

[Diagram showing the classification of hemagglutinin subtypes into clusters: H1a, H1b, H9 Cluster, H3 Cluster, and H7 Cluster.]
Strategies to overcome HA-head immunodominance

1. Use of headless constructs

Impagliazzo et al. (2015). Science
Yassine et al. (2015). Nat Med 21, 1065-1070
2. Repeated vaccination with influenza virus chimeric HA vaccines induce protective antibodies against multiple subtypes of influenza virus.
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

Proof of principle

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

cH4/3 DNA

3 weeks

cH5/3 protein boost

4 weeks

H3 protein boost

Shanghai (H7N9) challenge
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

Control groups:
ch4/3 DNA + BSA + BSA
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

H10N7

H3N2v

WyoH3

cH4/3 DNA + cH5/3 protein + H3 protein
cH4/3 DNA + cH5/3 protein + cH7/3 protein
Abs mediate protection

Passive transfer (Phil82) H3N2

- BcH7/3 + cH5/3 protein + cH4/3 protein
- BcH7/3 + BSA + BSA
- Bwt+ BSA + BSA
- Naive
- Positive control

% survival

Days post challenge

**, p<0.026
Targeting group 1 HA viruses
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

Proof of principle

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

PR8 H1N1
FM1 H1N1
pH1N1
H5N1
H6N1
challenge
Vaccination with cHA constructs protects from pH1N1 (A/Netherlands/602/09) challenge

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

% survival

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

days post 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

- cH9/1 + cH6/1 + cH5/1
- cH9/1 + BSA + BSA
- naïve serum

- Passive transfer of serum protects from viral challenge

Graphs show:
- OD 490 nm vs Reciprocal of serum dilution
- Percent survival vs Days post challenge
Prime–Boost cHA vaccines based in LAIV and IIV platforms

Florian Krammer, Raffael Nachbagauer, Adolfo García-Sastre, Peter Palese and Randy A. Albrecht
Prime–Boost cHA vaccines based in LAIV and IIV platforms

“cH8/1 LAIV- cH5/1 IIV”

Prime: B-cH9/1  
Boost: cH8/1 - LAIV  
Boost: cH5/1 - IIV

“cH5/1 IIV- cH5/1 IIV”

Prime: B-cH9/1  
Boost: cH8/1 - IIV  
Boost: cH5/1 - IIV

“Prime-only”

Prime: B-cH9/1  
Boost: Mock  
Boost: Mock

“TIV”

Boost: TIV

“Naive”

Boost: 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