¿Podremos conseguir una vacuna frente a todas las cepas de la gripe?

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SEM-CIVIC
DISCLOSURES

• My laboratory has received research moneys from Pfizer, Senhwa Biosciences, Kenall Manufacturing, Avimex, Johnson & Johnson, Dynavax, 7Hills Pharma, Pharmamar, ImmunityBio, Accurius, Nanocomposix, Hexamer, N-fold LLC, Model Medicines, Atea Pharma and Merck.

• I’m a consultant for Vivaldi Biosciences, Contrafect, 7Hills Pharma, Avimex, Vaxalto, Pagoda, Accurius, Esperovax, Farmak, Applied Biological Laboratories, Pharmamar, Paratus, CureLab Oncology, CureLab Veterinary, Synairgen and Pfizer.

• I’m inventor of patents in the field of influenza virus and COVID-19 vaccines owned by the Icahn School of Medicine at Mount Sinai, New York, some of which have been licensed to Medimmune, Vivaldi and Avimex.
INFLUENZA VIRUSES

Lipid envelope derived from host cells

Non-structural proteins

PB2
PB1
PA
HA
NP
NA
M
NS

Polymerase complex

Viral RNP

NP
vRNA
PB1
PB2
PA

PAX

M1
HA
M2
INFECTIONS IN HUMANS WITH AVIAN AND SWINE INFLUENZA A VIRUSES

1918


A

H1N1

1957

H2N2

1968

H3N2

1977

H1N1

2009

H3N2v H7N9

pH1N1

B

H5N1  H9N2  H5N1  H7N7  H5N1

H5N1  H9N2
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?

In collaboration with Peter Palese and Florian Krammer
Neutralization of influenza viruses

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

3 weeks cH4/3 → 3 weeks cH5/3 → 4 weeks H3 → Shanghai (H7N9) challenge
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

3 weeks
ch4/3

3 weeks
ch5/3

4 weeks
H3

Shanghai (H7N9) challenge
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs in mice

3 weeks

cH4/3

3 weeks

cH5/3

4 weeks

H3

Shanghai (H7N9) challenge
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

TCID$_{50}$

$cH4/3 + cH5/3 + H3$

$cH4/3 + cH5/3 + cH7/3$
Hemagglutinin subtypes
cHA vaccine protects against challenge with group 1 and group 2 viruses in mice

**Influenza A group 2 immunization**

\[ \text{cH4/3} \rightarrow \text{cH5/3} \rightarrow \text{H3} \]

**Influenza A group 1 immunization**

\[ \text{cH9/1} \rightarrow \text{cH6/1} \rightarrow \text{H5/1} \]

**H7N9 challenge**

![Graph showing percent survival over days post challenge for H7N9 challenge]

- **positive control**
- **cHA vaccinated**
- **negative control**

Also protected against other group 2 viruses

**H1N1 challenge**

![Graph showing percent survival over days post challenge for H1N1 challenge]

- **positive control**
- **cHA vaccinated**
- **negative control**

Also protected against other group 1 viruses
Protection is antibody mediated

ELISA reactivity to Cal09 (pH1N1) protein

Passive transfer of serum protects from viral challenge

OD 490 nm

Reciprocal of serum dilution

Percent survival

Days post challenge

Naïve
Positive control
vector + BSA + BSA
ch9/1 + ch6/1 + ch5/1

** *, p = 0.0036
mHA influenza B vaccine protects against challenge with influenza B viruses from both lineages
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

Ferret vaccination groups (n=4)

- **“cH8/1 LAIV- cH5/1 IIV”**
  - Prime: B-cH9/1
  - Boost: cH8/1 - LAIV
  - Second Boost: cH5/1 - IIV

- **“cH5/1 IIV- cH5/1 IIV”**
  - Prime: B-cH9/1
  - Boost: cH8/1 - IIV
  - Second Boost: cH5/1 - IIV

- **“Prime-only”**
  - Prime: B-cH9/1
  - Boost: Mock
  - Second Boost: Mock

- **“TIV”**
  - Prime: TIV

- **“Naive”**
  - Prime: Mock

★ LAIV is based on the Ann Arbor backbone
Induction of HA stalk-specific antibodies (ELISA)

Stalk-titer (cH6/1 HA)

*No detectable HI titers following vaccination
Viral titers in tissues following H1N1 challenge infection, day 4

- **Trachea**
  - Naive
  - TIV
  - Prime-only
  - cH8/1 IIV - cH5/1 IIV
  - cH8/1 LAIV - cH5/1 IIV

- **Nasal turbinates**
  - Naive
  - TIV
  - Prime-only
  - cH8/1 IIV - cH5/1 IIV
  - cH8/1 LAIV - cH5/1 IIV

- **Bronchus**
  - Naive
  - TIV
  - Prime-only
  - cH8/1 IIV - cH5/1 IIV
  - cH8/1 LAIV - cH5/1 IIV
HA stalk-specific antibodies are long-lived in ferrets
Initial clinical trial outline for phase I trial (CVIA 057)
Study start date: December 2017

Group 1
- Prime: cH8/1N1 LAIV
- Boost: cH5/1N1 IIV +AS03

Group 2
- Prime: cH8/1N1 LAIV
- Boost: cH5/1N1 IIV

Group 3
- Placebo

Group 4
- cH8/1N1 IIV +AS03

Group 5
- Placebo

LAIV: Live-attenuated influenza virus vaccine (Leningrad backbone)
IIV: Inactivated influenza virus vaccine → split vaccine
AS03: Adjuvant
**Trial design overview**

- Prospective, randomized, controlled, observer-blind, phase 1 trial
- Healthy male and female adults 18 through 39 years of age
- 65 subjects (39 Duke, 26 CCHMC) randomized to one of five groups
- Median age 29 years; 40 female, 25 male

<table>
<thead>
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<th>Study Groups</th>
<th>Number of Subjects</th>
<th>Dose 1</th>
<th>Dose 2</th>
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<tbody>
<tr>
<td></td>
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<td>Treatment</td>
<td>Route</td>
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<tr>
<td>1</td>
<td>20</td>
<td>cH8/1N1 LAIV</td>
<td>Intranasal</td>
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<tr>
<td>2</td>
<td>15</td>
<td>cH8/1N1 LAIV</td>
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<td>5</td>
<td>Normal Saline</td>
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<td>cH8/1N1 IIV + AS03&lt;sub&gt;A&lt;/sub&gt;</td>
<td>Intramuscular</td>
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<tr>
<td>5</td>
<td>10</td>
<td>PBS</td>
<td>Intramuscular</td>
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Serum IgG stalk responses

ch6/1 serum IgG ELISA
mean - EU

ELISA units

day 1  day 29  day 85  day 113  day 252  day 420

LAIV8-IIIV5/AS03
LAIV8-IIIV5
IIIV/AS03-IIIV5/AS03
placebo

Performed by NEOMED labs (CRO)
Serum IgG stalk responses – fold induction

**cH6/1 serum IgG ELISA**
Mean induction over baseline

- **LAIV8-IIV5/AS03**
- **LAIV8-IIV5**
- **IIV8/AS03-IIV5/AS03**
- **placebo**

Performed by NEOMED labs (CRO)
Binding breadth - induction

cH6/1 serum IgG ELISA
mean induction over baseline

H2 serum IgG ELISA
mean induction over baseline

H9 serum IgG ELISA
mean induction over baseline

H18 serum IgG ELISA
mean induction over baseline

Performed by NEOMED labs (CRO)
Passive transfer of serum from cHA vaccinated individuals protects mice against heterosubtypic influenza virus challenge

cH6/1N5 virus challenge
CONCLUSIONS

VACUNACION SECUENCIAL CON VACUNAS DE GRIPE BASADAS EN PROTEINAS HA QUIMERICAS INDUCEN ANTICUERPOS CONTRA EL TALLO DE LA HA CAPACES DE PROTEGER CONTRA GRIPE SEVERA CON HOMOLOGOS Y HETEROLOGOS VIRUS DE LA GRIPE
THANKS

...and let’s get vaccinated.