Immune history and seasonal influenza virus susceptibility

Scott E. Hensley
Influenza virus

Hemagglutinin

Harris et. al. PNAS (2006) 50:19123
Humans are constantly exposed to new flu strains

- **H1N1** Spanish Flu (1918)
- **H2N2** Asian Flu (1957)
- **H3N2** Hong Kong Flu (1968)
- **H1N1** Russian Flu (1977)
- **H1N1** Swine Flu (2009)
- **H1N1** Swine Flu (2017)
HA evolution
It takes a long time to make influenza vaccines and they are not very effective.
There is something magical about childhood
We are all exposed to flu during childhood

Bodewes et al. CVI 2011
Early childhood flu exposures leave lifelong immunological imprints

Kurosaki et al, NRI 2015
Depending on our year of birth, we all have different immunological imprints!
Childhood imprinting shapes specificity of influenza virus antibody responses
Childhood imprinting shapes specificity of influenza virus antibody responses

Previous HA

X

1983 H1N1 HA

1952 H1N1 HA

2009 pH1N1 HA
An example of immune-focusing on a viral epitope encountered in childhood

1983

= focused Ab response

Li et al. *JEM* 2013
Linderman et al. *PNAS* 2014
Petrie et al. *JID* 2016
The 2009 H1N1 virus acquired a mutation in an epitope recognized by ‘middle-aged’ individuals.

Linderman et al., *PNAS* 2014
Many ‘middle-aged’ individuals were susceptible to drifted H1N1 strain in 2013-14 season

• 382 humans bled prior to 2013-2014 season
• 20 of these individuals were naturally infected with H1N1 (PCR-confirmed)
• Did these 20 people have pre-season antibody titers against vaccine strain, but not the circulating strain?

<table>
<thead>
<tr>
<th></th>
<th>A/Cal/7/09-WT</th>
<th>A/Cal/7/09-K166Q</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Petrie et al. *Journal of Infectious Disease* (2016)
Childhood imprinting affects seasonal influenza virus susceptibility
The H3N2 vaccine has only been effective in very young individuals over the past 2 years.

Is childhood imprinting involved?
Contemporary H3N2 strains possess new glycosylation site in HA

The problem of egg adaptation

A/Hong Kong/4801/2014

T160 HA

Glycosylation matches circulating strains

Zost et al. PNAS (2017)

A/Hong Kong/4801/2014

K160 HA

No antigenic site B glycosylation
Abs from ferrets infected with current H3N2 vaccine strain poorly recognize circulating H3N2

Zost et al. PNAS (2017)
What about humans?
Human influenza vaccine antigens are prepared in eggs, cell culture, and via baculovirus system.
Abs elicited by Flublok (baculovirus antigen) neutralize current circulating H3N2 strain

A. T160 HA antibody response

\[ p = 0.04 \]
\[ p = 0.01 \]
\[ \text{ns} \]

But why does the current H3N2 vaccine have such low VE in everyone except very young kids?

Hypothesis: egg-adapted H3 strain (that has K160 HA) recalled memory B cells in older children that were primed by H3N2 viruses that had K160 HA.
Summary of the past two H3N2 seasons

Prevax Ab repertoire

Individual 1
- Recognizes epitope blocked by glycan
- Recognizes epitope not blocked by glycan

Low neutralizing Ab titer against glycosylated strain

Egg-grown HA

Individual 2

Higher neutralizing Ab titer against glycosylated strain

Baculovirus HA
Can we make better influenza vaccines?

• Universal influenza vaccines based on HA stalk immunity
• mRNA-based influenza vaccines
Influenza virus

Hemagglutinin

Harris et. al. PNAS (2006) 50:19123
HA head versus HA stalk Abs
HA stalk Abs are not as great as HA head Abs (but they protect against many viral strains)

Wrammert et. al, JEM 2011
Are HA stalk Abs associated with protection in humans?

<table>
<thead>
<tr>
<th>Donors</th>
<th>Household Cohort</th>
<th>Hospitalization Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>373 healthy individuals enrolled prior to the flu season (both 2013-14 &amp; 2015-16)</td>
<td>184 patients hospitalized with severe respiratory illness symptoms were enrolled upon admission</td>
</tr>
<tr>
<td>Infection</td>
<td>Naturally acquired pH1N1 infection</td>
<td>Hospitalization with naturally acquired pH1N1 infection</td>
</tr>
<tr>
<td>Sera</td>
<td>Sera obtained prior to the season</td>
<td>Sera obtained upon hospital admission</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Influenza infection confirmed via PCR</td>
<td>Influenza infection confirmed via PCR</td>
</tr>
</tbody>
</table>
Are HA stalk Abs associated with protection in humans?

<table>
<thead>
<tr>
<th></th>
<th>Household Cohort</th>
<th>Hospitalization Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors</td>
<td>373 healthy individuals enrolled prior to the flu season (both 2013-14 &amp; 2015-16)</td>
<td>184 patients hospitalized with severe respiratory illness symptoms were enrolled upon admission</td>
</tr>
<tr>
<td>Infection</td>
<td>Naturally acquired pH1N1 infection</td>
<td>Hospitalization with naturally acquired pH1N1 infection</td>
</tr>
<tr>
<td>Sera</td>
<td>Sera obtained prior to the season</td>
<td>Sera obtained upon hospital admission</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Influenza infection confirmed via PCR</td>
<td>Influenza infection confirmed via PCR</td>
</tr>
</tbody>
</table>
HA head Abs are associated with protection in the 2015-16 ‘household’ study

Barbour et al. *manuscript in prep*
HA stalk Abs are not associated with protection in the 2015-16 ‘household’ study

Barbour et al. *manuscript in prep*
# Are HA stalk Abs associated with protection in humans?

<table>
<thead>
<tr>
<th></th>
<th>Household Cohort</th>
<th>Hospitalization Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donors</strong></td>
<td>373 healthy individuals enrolled prior to the flu season (both 2013-14 &amp; 2015-16)</td>
<td>184 patients hospitalized with severe respiratory illness symptoms were enrolled upon admission</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>Naturally acquired pH1N1 infection</td>
<td>Hospitalization with naturally acquired pH1N1 infection</td>
</tr>
<tr>
<td><strong>Sera</strong></td>
<td>Sera obtained prior to the season</td>
<td>Sera obtained upon hospital admission</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Influenza infection confirmed via PCR</td>
<td>Influenza infection confirmed via PCR</td>
</tr>
</tbody>
</table>
HA head Abs are associated with protection in the 2015-16 ‘hospitalization’ study

Barbour et al. *manuscript in prep*
HA stalk Abs are not associated with protection in the 2015-16 ‘hospitalization’ study

Barbour et al. *manuscript in prep*
HA stalk Abs are not independently associated with protection in the 2015-16 ‘hospitalization’ study.

<table>
<thead>
<tr>
<th></th>
<th>Log2 HAI titer OR (95% CI)</th>
<th>Log2 stalk titer OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAI only</td>
<td>0.75 (0.60, 0.94)</td>
<td></td>
</tr>
<tr>
<td>Stalk only</td>
<td></td>
<td>0.87 (0.75, 1.00)</td>
</tr>
<tr>
<td>HAI + Stalk</td>
<td>0.78 (0.63, 0.97)</td>
<td>0.91 (0.79, 1.06)</td>
</tr>
</tbody>
</table>

Controls: n = 116  Cases: n = 63
HA stalk-based vaccines will need to elicit high levels of Abs.

The same data shows levels required for mouse protection.
Nucleoside-modified, purified mRNA formulated in LNP is highly expressed and stimulates potent immune responses.
mRNA-based ZIKV vaccine protects rhesus macaques

Pardi et al. Nature 2017
mRNA vaccine elicits a long-lasting antibody response

Pardi et al. *unpublished*
mRNA vaccine elicits a protective immune response

Pardi et al. *unpublished*
mRNA vaccine elicits HA head and HA stalk Abs


Pardi et al. *unpublished*
mRNA vaccine protects against homologous and drifted influenza virus strains

Pardi et al. unpublished
Main points

- Early childhood immunological imprints shape the specificity of antibody responses against new influenza virus strains
  - This is clearly the case with H1N1 viruses
  - This appears to be the case with H3N2 viruses
- Egg-adaptive mutations likely led to low vaccine effectiveness last year
- HA stalk Abs are not at sufficiently high levels in most individuals to protect against seasonal influenza virus
- mRNA vaccines might be a good alternative to conventional influenza vaccines—it is unclear why they elicit such high levels of Abs
Acknowledgements

Collaborators
Drew Weissman—U. Penn
Sara Cobey—U. of Chicago
Arnold Monto -- U. Michigan
Josh Petrie -- U. Michigan
Emily Toth Martin-- U. Michigan
Aubree Gordon-- U. Michigan
Patrick Wilson -- U. of Chicago
John Treanor -- U. of Rochester
Jesse Bloom – Fred Hutch
Florian Krammer – Mt Sinai

Tyler Garretson
Theresa Eilola
Sigrid Gouma
Seth Zost
Elinor Willis
Amy Davis
Kaela Parkhouse
Shannon Barbour
Megan Gumina
Claudia Arevalo

Yang Li
Susi Linderman
Ben Chambers

National Institute of Allergy and Infectious Diseases
Burroughs Wellcome Fund
CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance