Induction of broadly cross-reactive immune responses against A(H3N2) viruses: results of a phase 2 trial of a novel recombinant hemagglutinin saponin-adjuvanted nanoparticle influenza vaccine (“NanoFlu”)

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The problem with current seasonal influenza vaccines
The NanoFlu vaccine and preclinical data
The Phase 2 trial
Next steps
The problem: Available seasonal influenza vaccines are increasingly ineffective

• The core problem: effectiveness of the A/H3N2 vaccine component, especially in older adults

WHY?

• Limited breadth of response:
  • Strain-specific vaccine responses and consequent vulnerability to drift
  • Increasing A/H3N2 strain diversity
  • Early life imprinting

• Limited “strength” of response:
  • Immunosenescence
  • Weakly immunogenic vaccines – suboptimal antibody or CMI responses
  • Limited durability – late season waning

• Impaired fidelity:
  • Egg-adaptive mutations produce antigenic changes in vaccine viruses
Gaps in current seasonal influenza vaccine technologies and what “better” could look like

- Licensed vaccines address some, but not all of these deficiencies

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Problem Addressed</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Antigenic drift</td>
<td>Immunosenescence</td>
</tr>
<tr>
<td></td>
<td>Antibodies</td>
<td>T-cells</td>
</tr>
<tr>
<td>Standard Inactivated</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>High-dose inactivated</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Adjuvanted</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Cell-grown inactivated</td>
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<td>✗</td>
</tr>
<tr>
<td>Recombinant</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NanoFlu</td>
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<td>✓</td>
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</table>

- NanoFlu induces broadly cross-reactive antibodies and T-cell responses, and avoids egg-adaptive changes
The NanoFlu vaccine: The antigen

- Recombinant hemagglutinin (HA) nanoparticles
  - Produced in a Baculovirus/Sf9 insect cell system
  - Expressed as recombinant, full-length, wild-type, uncleaved HA0 that assembles into homotrimers
  - Purified homotrimers form higher order nanoparticle structures of 20-40 nm with PS-80
  - Manufactured in a rapid, high-yield, high purity, process
The NanoFlu vaccine: The adjuvant Matrix-M™

- **Recombinant hemagglutinin (HA) nanoparticle vaccine**
  - Produced in a Baculovirus/Sf9 insect cell system
  - Expressed as recombinant, full-length, wild-type, uncleaved HA0 that assemble into trypsin-resistant trimers
  - Purified into HA homotrimers to form higher order nanoparticle structures of 20-40 nm
  - Manufactured in a rapid, high-yield, high purity, process

- **Potent saponin-based Matrix-M adjuvant**
  - Extracted as saponins from bark of *Quillaja saponaria* Molina
  - Formulated with cholesterol and phospholipid, forming cage-like particles
  - Characterized by mechanisms of action that include:
    - Enhanced antigen delivery to draining lymph nodes
    - Enhancement of activated T cell, B cell, and APC populations
    - Induction of functional, and broadly cross-reactive antibodies
    - Induction of polyfunctional CD4+ T cells
  - Found to be antigen sparing in context of pandemic influenza antigens
In ferrets, NanoFlu (NIV) induced broadly cross-neutralizing immune responses to 2 decades of drifted A(H3N2) viruses, but Fluzone High Dose and Fluzone QIV did not.

Novel hemagglutinin nanoparticle influenza vaccine with Matrix-M™ adjuvant induces hemagglutination inhibition, neutralizing, and protective responses in ferrets against homologous and drifted A (H3N2) subtypes.

Phase 1: Higher Nanoflu (tNIV) wild-type HAI antibody responses (GMFRs) vs. Fluzone-High Dose (IIV3-HD) against 5 generations of antigenically drifted A(H3N2) strains

**Improved Titers against Influenza Drift Variants with a Nanoparticle Vaccine**

V Shinde, et al.
NEJM 378 (2018); 24
Phase 2: design and treatment assignments  
Various formulations of NanoFlu (qNIV) versus Fluzone-HD or FluBlok

- Dose/formulation optimization trial
- Two licensed comparators
- 1375 adults ≥65 years of age
- Randomized to 1 of 7 groups
- Single dose of test vaccine on Day 0
- 2018-19 recommended NH strains

**Treatment assignments in Phase 2 trial:**

<table>
<thead>
<tr>
<th>Group</th>
<th>NanoFlu (qNIV) A antigen content</th>
<th>NanoFlu (qNIV) B antigen content</th>
<th>Matrix-M adjuvant content</th>
<th>Formulation</th>
<th>Subject N</th>
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<tbody>
<tr>
<td>A</td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td>In-clinic bedside mix</td>
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<tr>
<td>B</td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td>Pre-formulated (3 months)</td>
<td>310</td>
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<tr>
<td>C</td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td><strong>1.5 X increased</strong></td>
<td>Pre-formulated (3 months)</td>
<td>155</td>
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<tr>
<td>D</td>
<td>Phase 1 dose <strong>1.5 X increased</strong></td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td>Pre-formulated (3 months)</td>
<td>155</td>
</tr>
<tr>
<td>E</td>
<td>Phase 1 dose</td>
<td>Phase 1 dose</td>
<td><strong>None</strong></td>
<td>Pre-formulated (3 months)</td>
<td>310</td>
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<tr>
<td>F</td>
<td>Fluzone HD 2018-19 (trivalent)</td>
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<td></td>
<td></td>
<td>155</td>
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<tr>
<td>G</td>
<td>Flublok 2018-19 (quadrivalent)</td>
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<td></td>
<td>155</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Total</strong> 1375</td>
</tr>
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Phase 2: objectives

- Demonstrate an “adjuvant effect” (primary endpoint)

- Describe antibody and T cell responses against homologous and drifted strains:
  - Wild-type VLP hemagglutination inhibition (wt-HAI) antibody responses at Day 0, 28, 56, and 182
  - Cell mediated immunity (CMI) at Day 0 and 7: polyfunctional CD4+ T-cell responses

- Describe the safety profile through Day 182

- Post-hoc: examine antibody responses against broadly neutralizing epitopes by competitive binding assays
Phase 2: summary of topline results

- Well-tolerated, with a reactogenicity and safety profile comparable to Fluzone HD and FluBlok
- Met primary endpoint, adjuvant effect shown for 5 of 6 strains tested
- Demonstrated that a stable adjuvant co-formulation was feasible with a quadrivalent vaccine
- Higher A/H3N2 *wild-type* VLP HAI antibody responses compared to Fluzone HD which spanned multiple currently-circulating subclades; and, similar *wild-type* VLP HAI antibody responses compared to FluBlok
- Substantially better competitive antibody responses against conserved, head- and stem- broadly neutralizing epitopes than either Fluzone HD or FluBlok (POSTER 11007)
- Substantially better polyfunctional CD4+ T cell responses than either Fluzone HD or FluBlok
Phase 2: NanoFlu *wt*-HAI responses comparable to FluBlok; but greater than Fluzone on three A/H3N2 viruses Day 0 and 28 GMTs against vaccine homologous and drifted A/H3N2 viruses
Phase 2: NanoFlu had greater wt-HAI responses against A/H3N2 than Fluzone HD Day 0 and 28 GMTs against homologous and drifted viruses
Influenza HA bnMAbs: epitope binding site of 2 Novavax broadly neutralizing monoclonal antibodies (bnMAbs) isolated from mice following vaccination with NanoFlu (A/HK/4801/2014); and 1 J&J stem bnMAb

- Novavax receptor binding domain (RBD) bnMAb: A2.91.3
- Novavax vestigial esterase (VE) bnMAb: A2.4.1
- J&J stem bnMAb: CR8020
Phase 2: NanoFlu had highest competitive antibody responses to multiple conserved epitopes: Receptor binding domain (RBD) mAb, vestigial esterase (VE) mAb, and stem mAb competitive antibody equivalents (CAE)
Phase 2: higher adjuvant dose (group C) induced best antigen-specific polyfunctional T cell responses

Day 0 and 7 boxplot of log10 counts of double cytokine+ CD4+ T cells (all strains pooled)

Cytokines stained: IL-2, IFN-γ, and TNF-α;
Double cytokine+: at least 2 of 3 cytokine+ on ICCS
**Phase 2**: higher adjuvant dose (group C) induced best antigen-specific polyfunctional T cell responses

Day 0 and 7 boxplot of log10 **counts** of double cytokine+ CD4+ T cells (all strains pooled)

Cytokines stained: IL-2, IFN-γ, and TNF-α;
Double cytokine+: at least 2 of 3 cytokine+ on ICCS
Phase 2: higher adjuvant dose (group C) has lowest level of non-response

Day 0 and 7 boxplot of log10 counts of double cytokine+ CD4+ T cells (all strains pooled)

Cytokines stained: IL-2, IFN-γ, and TNF-α;
Double cytokine+: at least 2 of 3 cytokine+ on ICCS
Phase 2: summary of topline results

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• Substantially better polyfunctional CD4+ T cell responses than either Fluzone HD or FluBlok
Next Steps

- Phase 3 non-inferiority immunogenicity trial to start Q3 2019
  - Demonstrate immunologic non-inferiority to licensed seasonal influenza vaccine on 4 homologous vaccine strains
  - Establish pivotal clinical trial dataset to support filing of BLA via accelerated approval pathway
End - Thank You
Backups
IN TERMS OF:

• Solicited AEs (reactogenicity) in the 7 days post-treatment
  • Severe solicited AEs: 1.3—2.3%
  • Reactogenicity of adjuvanted vaccine was not notably different than either licensed comparator

• Unsolicited AEs through Day 28
  • Severe unsolicited AEs: 0.7—2.3%

• Serious adverse events (SAEs) were infrequent through Day 28, and none were deemed treatment-related by the investigators
  • 0—2.3%
Phase 2: an adjuvant effect was demonstrated

Ratio of baseline adjusted Day 28 wt-HAI GMTs (adjuvanted NanoFlu (B) / unadjuvanted NanoFlu (E))

A/Sing H3N2: p = 0.002, Ratio >1 favors adjuvant
A/Switz H3N2: p < 0.001, Ratio >1 favors adjuvant
A/Wis H3N2: p = 0.005, Ratio >1 favors adjuvant
A/Mich H1N1: p = 0.002, Ratio >1 favors adjuvant
B/Col (VIC): p = 0.002, Ratio >1 favors adjuvant
B/Phu (YAM): p = 0.003, Ratio >1 favors adjuvant

Success criterion for demonstration of adjuvant effect: show statistically significant ratio of (adj. / non-adj.) > 1 for at least 2 of 6 strains.
Influenza HA: which epitopes make a good vaccine target? Neutralizing epitopes, their neutralizing potential, and potential vaccine targets

Epitopes
- Receptor binding domain (RBD)
- Vestigial esterase subdomain (VE)
- Stem

Neutralizing potential

Hemagglutinin

Viral attachment & membrane
Fusion

Membrane
Fusion
Confirm the Phase 1/2 safety and immunogenicity results

Establish a clinical data set that:

- Demonstrates an adjuvant effect
- Confirms feasibility of a co-formulated quadrivalent vaccine
- Selects the optimal does/formulation for a Phase 3 clinical trial
- Compares Nanoflu responses to licensed comparators
- Supports discussion of accelerated approval pathway with the FDA
Phase 2: demographics

- Median age: 70-72 years
- % Female: 49-65%
- % White: 86-91%
- % received prior year influenza vaccine: 85-89%
- % received any influenza vaccine in the past 3 years: 90-94%
Phase 2: safety profile was comparable between NanoFlu, Fluzone HD, and FluBlok

Safety outcomes through Day 28

IN TERMS OF:

• Solicited AEs (reactogenicity) in the 7 days post-treatment: 27—38%
  • Severe solicited AEs: 1.3—2.3%

• Unsolicited AEs through Day 28: 13.5—23.6%
  • Severe unsolicited AEs: 0.7—2.3%

• Medically attended adverse events (MAEs) through Day 28: 6—10.6%

• Serious adverse events (SAEs) were infrequent through Day 28: 0—2.3%
Phase 2: why use wild-type virus-like-particle (VLP) HAI assay instead of the classical HAI assay?

- Major problems with classical HAI assay in terms of:
  - Performance: limited ability to interrogate HAI responses to contemporary A/H3N2 viruses
  - Relevance: reliance on egg-adapted HAI reagents may yield biased/clinically irrelevant results
  - Unintended consequences: creates barrier to entry for next generation recombinant vaccine technologies

- We developed a wild-type VLP HAI assay to overcome these issues:
  - The assay employs:
    - VLPs expressing wild-type sequenced HAs as the agglutinating agent
    - Human type-O RBCs as the indicator particle
  - Rehabilitates assay performance and restores its clinical relevance
  - We validated assay performance using CDC historical reference ferret antisera

- FDA requires vaccine developers use the classical egg-based HAI assay to establish non-inferiority versus licensed comparators; we will do so in the upcoming phase 3 non-inferiority immunogenicity trial

- For purposes of understanding the performance of NanoFlu versus licensed comparators, we will show you wild-type VLP HAI data hereafter, which we believe is the more unbiased and clinically relevant
Phase 1/2: egg-adapted reagents may give a misleading/clinically irrelevant result

MN responses (GMFRs) against egg-adapted vs. wild-type A/Singapore H3N2

NanoFlu induced improved neutralization responses against wild-type vs. egg-adapted A/Singapore H3N2 viruses underscoring the problem of egg-adaptive mutations

Neutralization antibody responses against wild-type circulating viruses are the most clinically relevant