Composite Peptide Conjugate Vaccines Induced Broadly Reactive Serum and Monoclonal Antibodies to Influenza

PRESENTED BY CLARA J. SEI
DIRECTOR, MICROBIOLOGY AND IMMUNOLOGY LABORATORY
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Background

- Emergence of influenza variants that escape vaccines and are resistant to antiviral therapeutics.
- Seasonal and pandemic influenza management challenges.
- Small composite peptide vaccines were produced utilizing conserved Hemagglutinin (HA), Neuraminidase (NA), and Matrix ectodomain (M2e) influenza proteins.
- Our preliminary studies evaluate both vaccine and therapeutic approaches against Influenza viruses.
Methods

- Mice were immunized with the composite peptide conjugate vaccines and their humoral responses evaluated in the Antisera ELISA.
- Monoclonal antibodies (mAbs) were developed from mouse spleen fusions.
- Ability of mAbs to bind across a diverse set of influenza strains was evaluated in the Binding ELISA.
- Presence of cross-neutralizing antibodies against H3N2 and H1N1 was evaluated in the Microneutralization assay.
# Peptide Conjugate Vaccines

<table>
<thead>
<tr>
<th>PEPTIDE</th>
<th>SEQUENCE</th>
<th>CONJUGATE</th>
<th>ADJUVANT</th>
<th>DOSE &amp; REGIMEN</th>
<th>MODE OF ADMIN</th>
<th>PEPTIDE SOURCE PROTEIN</th>
<th>MOUSE, MAB &amp; ISOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pep 11</td>
<td>GNLFIAPWGVIHHP HYEECSCY</td>
<td>CRM</td>
<td>TITERMAX GOLD</td>
<td>H3N2, 10⁶ Pep: 20 ug</td>
<td>H3N2: IM Pep: SQ</td>
<td>Hemagglutinin Neuraminidase</td>
<td>MS 2209 Many MABs under development</td>
</tr>
<tr>
<td>composite</td>
<td></td>
<td></td>
<td></td>
<td>D0, 14, 30, 42, 70</td>
<td></td>
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<tr>
<td>Pep 5906</td>
<td>SLLTEVETPIRNENE WGLLTEVETPIRQYIKANSKFIGITE</td>
<td>CRM</td>
<td>FREUNDS</td>
<td>50 ug D0, 21, 35, 41</td>
<td>SQ</td>
<td>Matrix Ectodomain (M2e)</td>
<td>MS 1443 MAB GA4 (IgG1)</td>
</tr>
<tr>
<td>composite</td>
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Antisera Titers from MS 2209 Primed with Flu/A Wuhan and Boosted with Flu Pep 11 on Various Influenza Antigens

- Pep 11, Composite
- Pep 10, NA
- Pep 3, HA
- Pep 6, HA
- Flu/A New Caledonia (H1N1)
- Flu/A Wuhan (H3N2)

Absorbance (OD 450nm) vs Time Interval (Days): 0, 21, 35, 42, 49, 63, 77

- Primary (Virus): D0
- Boost 1 (Virus): D14
- Boost 2 (Peptide): D30
- Boost 3 (Peptide): D42
- Boost 4 (Peptide): D70
MS 1443 Antisera Titers on Matrix (Peptide 5906)
Purified MAB GA4 Binding Activity
Cross-Neutralizing Antibodies

- MS 1441-1444 pooled sera from D63 bleed.
- MS 1443 MAB GA4

- Presence of cross-neutralizing antibodies in Serum and MAB produced from the composite matrix conjugate vaccine.

<table>
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<tr>
<th>Neutralizing Titers</th>
<th>M1441-1444 Pooled Serum</th>
<th>MS 1443 MAB GA4 (µg/mL)</th>
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</thead>
<tbody>
<tr>
<td>Flu/A Michigan, H1N1</td>
<td>81920</td>
<td>11</td>
</tr>
<tr>
<td>Flu/A Texas, H3N2</td>
<td>40960</td>
<td>22</td>
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</tbody>
</table>
Conclusions

- Composite peptide vaccines were highly immunogenic with strong humoral responses.
- Broadly reactive serum antibodies against peptide and live influenza virus were detected.
- mAbs were identified that bind to target epitopes on live influenza.
- Presence of cross-neutralizing antibodies against H3N2 and H1N1.

Current and future studies...
- Anti-influenza MABs (against HA & NA) are being characterized, in vitro.
- In vivo protection studies are being designed.
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