Update on plant-made VLPs

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Transient expression in N. benthamiana

DNA sequence + plants

Infiltration

Incubation

Extraction

Purification

VLP

VLPs

Influenza virus-like particle production in plants

- Influenza hemagglutinins accumulate at the plasma membrane forcing curvature of the membrane and budding of virus-like particles

No need for NA:
No sialic acid in plants

Rotavirus-like particle production in plants

- Rotavirus particle assembly
  - Multi-step process initiated in the cytosol and completed in the ER
  - Requires 4 structural antigens: VP2, VP6, VP7, VP4

Rotavirus-like particle production in plants (From Trask et al., Nature Reviews Microbiology, Volume 10: 165-177 (2012))

Clinical development overview and status update

Clinical trials – Pandemic vaccine

- Phase I H5 VLP + Alhydrogel completed in 2009
  - 48 healthy adults (18-60 years of age)
- Phase II H5 VLP + Alhydrogel completed in 2010
  - 255 healthy adults (18-60 years of age)
- Phase I H5 VLP + GLA completed in 2013 (IDRI’s trial)
  - 100 healthy adults (18-49 years of age)
  - First trial evaluating an adjuvant with intradermal administration
  - H5 VLP + Alhydrogel compared well with all other formulations
  - GLA-AL increased cross-reactivity of antibodies
- Phase II H5 VLP + GLA or Alhydrogel initiated in 2013
  - 390 healthy adults (18-60 years of age)
  - All subjects received 2 doses, no SAEs
  - Analysis of immune response ongoing
- Phase I H5 VLP + Alhydrogel initiated at beginning of 2014
  - 100 healthy adults (18-60 years of age)

Clinical trials – Seasonal vaccine

- Phase I H1 VLP completed in 2011 (non-adjuvanted)
  - 100 healthy adults (18-49 years of age)
  - 5 microgram dose met the CHMP criteria
  - Good antibody response against human viruses
- Phase III with seasonal quadrivalent launched in Oct. 2013
  - 120 healthy adults (18-49 years of age)

Findings from preclinical studies

- From preclinical trials (one dose (10 µg), no adjuvant):
  - 100% protection in mice and ferrets against H5N1 Indonesia
  - Independent NIAID heterologous challenge:
    - 100% protection against H5N1 Vietnam
    - 70% protection against H2N2 Japan
    - Rec-HA failed to protect
### Phase I/II trial with seasonal quadrivalent VLP vaccine

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Treatment Group</th>
<th>No. of Subjects</th>
<th>Dose Level</th>
<th>Administration Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal quadrivalent VLP influenza vaccine</td>
<td>Treatment Group 1 (low dose)</td>
<td>30</td>
<td>3 µg per strain, total of 12 µg HA</td>
<td>Oral</td>
</tr>
<tr>
<td>Seasonal quadrivalent VLP influenza vaccine</td>
<td>Treatment Group 2 (medium dose)</td>
<td>30</td>
<td>9 µg per strain, total of 36 µg HA</td>
<td>Oral</td>
</tr>
<tr>
<td>Seasonal quadrivalent VLP influenza vaccine</td>
<td>Treatment Group 3 (high dose)</td>
<td>30</td>
<td>15 µg per strain, total of 60 µg HA</td>
<td>Oral</td>
</tr>
<tr>
<td>100mM phosphate buffer + 150 mM NaCl + 0.01% Tween 80</td>
<td>Treatment Group 4 (placebo)</td>
<td>30</td>
<td>None</td>
<td>Oral</td>
</tr>
</tbody>
</table>

### Safety profile

**Solicited local reactions, during the first 7 days after immunization**

- H5 VLP with GLA-AF IM or ID or with alum IM meet the 3 CHMP criteria for licensure of pandemic vaccines

**Efficacy of H7 VLP after 1st dose in mice**

- 100% protection of mice immunized with one dose of 3 µg adj. H7 VLP
- 62.5% protection of mice immunized with one dose of 3 µg non-adj. H7 VLP
- 100% protection of mice immunized with 2 non-adj. doses of 3 µg (not shown)

**Phase I ongoing**

**H5 VLP clinical results**

**Trial NCT01657929**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Seroconversion rate</th>
<th>Seroprotection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 µg</td>
<td>65.0%</td>
<td>70.0%</td>
</tr>
<tr>
<td>25 µg</td>
<td>80.0%</td>
<td>85.0%</td>
</tr>
<tr>
<td>30 µg</td>
<td>52.6%</td>
<td>52.6%</td>
</tr>
<tr>
<td>35 µg</td>
<td>83.3%</td>
<td>88.9%</td>
</tr>
<tr>
<td>40 µg</td>
<td>43.8%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

- **GMT:** 135
- **Note:** H7 VLP is not significantly different from adjuvanted groups

**H5 VLP with GLA-AF IM or ID or with alum IM meet the 3 CHMP criteria for licensure of pandemic vaccines**

### Test materials

- **Test Material**: Seasonal quadrivalent VLP Influenza vaccine
- **Treatment Group**: Placebo (N=30)
- **Subjects**: 3 µg VLP Vaccine (n=30)
- **Dose**: 20 µg, 25 µg, 30 µg, 35 µg

**Dose Level**

- **100mM phosphate buffer + 150 mM NaCl + 0.01% Tween 80**
- **Form**: Oral
Phase I/II with Quadrivalent VLP vaccine
Micro-Neutralisation antibody titers 21 days post-dose (trial NCT01991587)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Criterion</th>
<th>Groups</th>
<th>3 µg/strain</th>
<th>9 µg/strain</th>
<th>15 µg/strain</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>GMT</td>
<td>93.4</td>
<td>103.1</td>
<td>153.9</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 4-fold (%)</td>
<td>44.8</td>
<td>46.7</td>
<td>55.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>H3N2</td>
<td>GMT</td>
<td>436.6</td>
<td>544.4</td>
<td>570.2</td>
<td>62.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 4-fold (%)</td>
<td>48.3</td>
<td>70.0</td>
<td>63.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B/Brisbane</td>
<td>GMT</td>
<td>24.5</td>
<td>31.0</td>
<td>57.3</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 4-fold (%)</td>
<td>20.7</td>
<td>26.7</td>
<td>40.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B/Wisconsin</td>
<td>GMT</td>
<td>69.3</td>
<td>71.3</td>
<td>107.5</td>
<td>23.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 4-fold (%)</td>
<td>34.5</td>
<td>33.3</td>
<td>44.4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B/Macao (Yamagata strain for 2012-2013 season)</td>
<td>GMT</td>
<td>27.9</td>
<td>30.6</td>
<td>62.6</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 4-fold (%)</td>
<td>13.8</td>
<td>26.7</td>
<td>53.3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Phase II/II with Quadrivalent VLP vaccine
Hemagglutination-Inhibition Antibody Titers 21 days post-dose (trial NCT01991587)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Criterion</th>
<th>Groups</th>
<th>3 µg/strain</th>
<th>9 µg/strain</th>
<th>15 µg/strain</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>GMT</td>
<td>41.4</td>
<td>50.0</td>
<td>40.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 1:40 (%)</td>
<td>79.3</td>
<td>73.3</td>
<td>81.5</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMT ≥ 2.5 (%)</td>
<td>3.6</td>
<td>4.5</td>
<td>3.7</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>H3N2</td>
<td>GMT</td>
<td>48.3</td>
<td>60.0</td>
<td>44.4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 1:40 (%)</td>
<td>79.3</td>
<td>90.0</td>
<td>81.5</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMT ≥ 2.5 (%)</td>
<td>4.7</td>
<td>7.6</td>
<td>5.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>B/Brisbane</td>
<td>GMT</td>
<td>13.8</td>
<td>43.3</td>
<td>46.1</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 1:40 (%)</td>
<td>65.5</td>
<td>70.0</td>
<td>85.6</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMT ≥ 2.5 (%)</td>
<td>2.0</td>
<td>3.9</td>
<td>3.8</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>B/Wisconsin</td>
<td>GMT</td>
<td>24.1</td>
<td>53.3</td>
<td>51.9</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 1:40 (%)</td>
<td>72.4</td>
<td>70.3</td>
<td>96.5</td>
<td>42.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMT ≥ 2.5 (%)</td>
<td>2.3</td>
<td>6.3</td>
<td>4.9</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

A single dose of H1 VLP vaccine induced polyfunctional T cell response
PBMCS collected 6 months post-vaccination, trial NCT01302990

<table>
<thead>
<tr>
<th>Peptide pool stimulation H1</th>
<th>Placebo</th>
<th>H1 VLP</th>
<th>Fluzone</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 VLP stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1 VLP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H1 VLP induces cross-reactive T cells to H5N1

PBMCs collected 6 months after vaccination, trial NCT01302990

- More CD4 & CD8 T cells cross-reactive for H5N1 compared to egg-based and placebo
- Cross-protective effects similar to those reported for H5N1 vaccines administered with oil-in-water adjuvants

Polyfunctional CD4+ T Cell response to H5

Homotypic response after vaccination with H5 VLP (21 days post-boost, trial NCT01991561)

- Cross-reactive CD4+ T cell response to HA of H2N2
  Heterotypic (group 1) response after vaccination with H5 VLP (trial NCT01991561)

- Cross-reactive CD4+ T cell response to HA of H7N9
  Heterotypic (group 2) response after vaccination with H5 VLP (trial NCT01991561)

One non-adj H5 VLP dose: 70% protection against H2N2 in mice
Conclusion

- H5 VLP pandemic vaccine
  - When formulated with alum, induce HI antibody titers that meet surrogate correlates of protection based on HI antibody titers
  - Induce polyfunctional T cell response

- H7 VLP pandemic vaccine
  - Induced a comparable or superior antibody response to H5 VLP in 2 animal models
  - Currently evaluated in humans formulated with alum

- Seasonal Quadrivalent vaccine
  - Good safety profile
  - Dosages of 9 and 15 µg per strain meets the CHMP criteria for licensure of seasonal vaccines
  - Induced a good MN antibody response cross-reactive towards other strain (B Yamagata)

Future plans

- To evaluate the alum-adjuvanted pandemic vaccine in a pivotal phase 3 trial
  - To increase the safety database
  - Will include a lot-to-lot consistency trial

- To continue the clinical evaluation of the seasonal quadrivalent VLP vaccine
  - Larger group size to evaluate CBER criteria for licensure
  - In healthy adults
  - In the elderly population

Conclusion

- Animal challenge studies and CMI results during clinical trials with plant-based VLP vaccines show potential for cross-protection
  - H5 vs. H1, H2 & H7 demonstrated to date

- CMI important for seasonal flu vaccine in terms of cross-protection
  - 2009 H1N1 pandemic: elderly protected by memory CD4 response from previous H1N1 infections (Hu et al. 2012 Int J Infect Dis)
  - Shown to protect humans in the absence of antibodies (Wilkinson 2012)
  - Characterization ongoing in current Phase I/II with seasonal VLP vaccine

- Plant-based VLPs
  - Numerous manufacturing advantages
  - Good safety and immunogenicity results in ~1,000 subjects
  - Good antibody response
  - Cross-protective effects possibly related to strong T cell response
  - Good compromise to natural infection

Merci!
Thank you!
Arigato!