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Plant-Made Influenza Virus-Like Particles: for Pandemic and Beyond

Nathalie Charland
Medicago

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Plant-Made Influenza Virus-Like Particles: for Pandemic and Beyond

Nathalie Charland, PhD
Director, Product Portfolio

Vaccine Technology IV
Albufeira, Portugal
May 24, 2012
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Reengineering vaccine design and production (beyond pandemic)

• Strains with pandemic potential are circulating every year; experts agree only a matter of time before a highly lethal strain develops due to strain mutations
  – Kawaoka’s & Fouchier’s studies

• Rapid response in pandemic vaccine production is needed to address rapid rates of infection & minimize deaths
  – In 2009 pandemic, time required to manufacture both egg- & cell-based vaccines resulted in “too little, too late” vaccine responses → no significant impact*

• Need for flexible technologies to respond to emerging or engineered biothreats
  – Multi-product platform

### Medicago overview

<table>
<thead>
<tr>
<th>Focus</th>
<th>Vaccines &amp; Protein-based pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing technology</td>
<td>Transient expression in Tobacco</td>
</tr>
<tr>
<td>Vaccine technology</td>
<td>Virus-like particles</td>
</tr>
<tr>
<td>Vaccine discovery platform</td>
<td>VLP Express</td>
</tr>
</tbody>
</table>
| Headquarters, laboratories & cGMP facilities | Quebec City, CANADA  
Research Triangle Park, NC, USA  
Genopole d’Evry, FRANCE |
| Agreements                | Mitsubishi Tanabe Pharma – Strategic Alliance  
DARPA Award – US$21M  
IDRI – Phase I H5 GLA, intradermal  
Pharma & U.S. Army – Vaccines outside of flu |

$35M & 12 months to build  
Capacity of 10M doses/month
# Products

<table>
<thead>
<tr>
<th>Products</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pandemic influenza</strong></td>
<td></td>
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<tr>
<td>H5</td>
<td></td>
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<tr>
<td>H5 – Intradermal+GLA</td>
<td></td>
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<tr>
<td>H1</td>
<td></td>
<td></td>
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<tr>
<td><strong>Seasonal influenza</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quadrivalent</td>
<td></td>
<td></td>
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<tr>
<td>Rabies</td>
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<tr>
<td>Undisclosed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ebola</td>
<td></td>
<td></td>
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<tr>
<td>Rotavirus</td>
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</tbody>
</table>
Protalix is paving the way...

First plant-derived pharmaceutical approved by FDA on May 1st, 2012

Drug-making plant blooms

Approval of a ‘biologic’ manufactured in plant cells may pave the way for similar products.

BY AMY MAXMEN

It was midnight when an anxious Ari Zimran finally got the phone call for which he had been waiting. The news couldn't have been better: the drug he had worked on for nearly a decade had just been approved by the US Food and Drug Administration (FDA).

Zimran, who heads the Gaucher Clinic in Jerusalem and is a member of the scientific advisory board at Protalix Biotherapeutics, a small

<table>
<thead>
<tr>
<th>PLANTS IN THE PIPELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers have begun or completed phase II clinical trials on a handful of biologics made in plants, and hope to follow Eliyso to market.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Company</th>
<th>Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locteron (interferon-α)</td>
<td>Hepatitis C</td>
<td>Biolase Therapeutics</td>
<td>Duckweed</td>
</tr>
<tr>
<td>H5N1 vaccine</td>
<td>Influenza</td>
<td>Medicago</td>
<td>Tobacco</td>
</tr>
<tr>
<td>VEN100</td>
<td>Antibiotic-associated diarrhoea</td>
<td>Ventria Bioscience</td>
<td>Rice</td>
</tr>
<tr>
<td>CaroRx</td>
<td>Dental caries</td>
<td>Planet Biotechnology</td>
<td>Tobacco</td>
</tr>
</tbody>
</table>
Medicago’s manufacturing technology

Proprietary platform for the production recombinant proteins based on a transient expression technology in plants (N. benthamiana)

- **Plants & Agrobacterium preparation**
- **Infiltration**
- **Incubation**
- **Extraction**
- **Purification**
- **Medicago VLP**
- **Influenza virus**

- 19 days to 1st lot
- Rapid lot-release:
  - HA content
  - 14-days sterility test
Characteristics of the plant-made H5 VLP vaccine

- Lot-release assays include purity, potency by SRID, lipid and protein content, residual DNA, endotoxins, nicotine and anabasine content, sterility
- Additional characterization such as SEC, NTA, MFI, PDI, glycans
- Product purity 98% (HA0, HA1, HA2)
General safety profile
*Phase 1 H1 VLP and Phase 2 part A H5 VLP*

Similar profiles were observed for systemic AEs
# Safety

**IgE to plant glycans**

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Group</th>
<th>Number of subjects with IgEs ≥ grade 1 to bromelain at screening</th>
<th>Number of subjects that showed an IgE increase after vaccination</th>
<th>Number of subjects that showed detectable IgEs 6 months after vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1 with H1 VLP (one dose)</strong></td>
<td>Non-adjuvanted VLP (n=58)</td>
<td>3.5% (2/57)</td>
<td>0% (0/57)</td>
<td>1.8% (1/56)</td>
</tr>
<tr>
<td></td>
<td>Fluzone (trivalent, n=20)</td>
<td>0% (0/20)</td>
<td>0% (0/20)</td>
<td>0% (0/20)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=20)</td>
<td>0% (0/20)</td>
<td>0% (0/20)</td>
<td>0% (0/20)</td>
</tr>
<tr>
<td><strong>Phase 2 with H5 VLP (two doses)</strong></td>
<td>Adjuvanted VLP (n=192)</td>
<td>3% (6/191)</td>
<td>0% (0/188)</td>
<td>3% (6/191)</td>
</tr>
<tr>
<td></td>
<td>Non-adjuvanted VLP (n=29)</td>
<td>7% (2/29)</td>
<td>0% (0/29)</td>
<td>4% (1/27)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=27)</td>
<td>0% (0/28)</td>
<td>0% (0/28)</td>
<td>0% (0/28)</td>
</tr>
</tbody>
</table>

- No onset of allergic reactions correlating with *in vitro* assay ([manuscript in preparation](#))
Antibody response – H5 VLP  
_HI test_  

Seroconversion rate after two doses of H5 VLP (18-64 years of age)

<table>
<thead>
<tr>
<th>H5 VLP Vaccine</th>
<th>5 µg +Al</th>
<th>10 µg +Al</th>
<th>20 µg +Al</th>
<th>30 µg +Al</th>
<th>45 µg +Al</th>
<th>45 µg +Al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I</strong> (groups of 12 subj.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.7 (0.02-0.48)</td>
<td>25.0 (0.06-0.57)</td>
<td>58.3 (0.28-0.85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase II</strong> (part A, groups of 30 subj)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>58.6 (0.39-0.77)</td>
<td>53.6 (0.34-0.73)</td>
<td>46.7 (0.28-0.66)</td>
<td>21.4 (0.08-0.41)</td>
<td></td>
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</tr>
</tbody>
</table>

*Preclinical and Clinical Development of Plant-Made Virus-Like Particle Vaccine against Avian H5N1 Influenza*

Nathalie Leduc1, Brian J. Ward2, Sonia Triepienier3, Emanuele Mentonoli4, Michele Dargis3, Giulia Lapini2, Louis P. Vezina1

1 Medicago Inc., Galilee, Canada, 2Newman Institute of the McGill University Health Center, Montreal General Hospital, Montreal, Canada, 3Ministero della Sanità, Rome, Italy, 4Istituto Superiore di Sanità, Rome, Italy
Antibody response – H5 VLP

*Phase II trial part B*

*Seroconversion rates after two doses*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>H5 VLP Vaccine, 20 µg dose + alum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-29 n=23</td>
</tr>
<tr>
<td></td>
<td>30-39 n=22</td>
</tr>
<tr>
<td></td>
<td>40-49 n=26</td>
</tr>
<tr>
<td></td>
<td>50-60 n=26</td>
</tr>
<tr>
<td>HI test</td>
<td>56.5%</td>
</tr>
<tr>
<td>SRH test</td>
<td>52.2%</td>
</tr>
<tr>
<td>MN test</td>
<td>52.2%</td>
</tr>
</tbody>
</table>

All vaccine doses statistically different from placebo

**H5 VLP vaccine equally immunogenic in young and older adults**
Duration of antibody response – H5 VLP
HI titers for homologous strain

<table>
<thead>
<tr>
<th>Dose of H5 VLP (µg)</th>
<th>% of subjects with positive antibody response (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-vaccination</td>
</tr>
<tr>
<td>20 + alum</td>
<td>0</td>
</tr>
<tr>
<td>30 + alum</td>
<td>0</td>
</tr>
<tr>
<td>45 + alum</td>
<td>0</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
</tbody>
</table>

Alum showed benefit on the antibody level for the H5 VLP vaccine although formulation not optimized at high vaccine dosages
Antibody response – H1 VLP

*HI test*

Seroconversion rate after one single non-adjuvanted dose of H1 VLP (18-49 years of age)

<table>
<thead>
<tr>
<th>H1 VLP Vaccine (groups of 20 subj.)</th>
<th>5 µg</th>
<th>13 µg</th>
<th>28 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61.1</td>
<td>63.2</td>
<td>82.4</td>
</tr>
<tr>
<td></td>
<td>(0.36-0.83)</td>
<td>(0.38-0.84)</td>
<td>(0.60-0.97)</td>
</tr>
</tbody>
</table>
H1 VLP Vaccine Induced a Long Lasting Memory Multifunctional T cell Response

Memory CD4^+ T Cells

Memory CD8^+ T Cells

H1 (VLP) Response

Polyfunctional T cells
H1 VLP Vaccine Induces Cross-Reactive CD4⁺ T cell Responses against HA (H5N1)

Total CD4⁺ T cell response against HA (H1N1):
- PBMC at +6 month post-vaccine
- In vitro stimulation with H5 VLP and cytokine detection

* P<0.05 (Mann-Whitney)
Main conclusions from clinical trials

• Safety
  – Safe and well tolerated
  – More than 400 subjects dosed
  – 1 or 2 doses
  – With or without alum
  – Dosages up to 45 µg
  – No onset of allergic reactions

• Immunogenicity
  – The HA-VLP vaccine induces durable antibody response
  – Durable, poly-functional and cross-reactive T Cell responses to influenza HA antigens
  – Strong innate immune response induced (data not shown)
Expanding the applications of the manufacturing and vaccine platforms

- Can the manufacturing and vaccine platforms also produce VLPs presenting non-influenza antigens?
  - different genomic organization (RNA, DNA, polyprotein…)
  - different envelope proteins structure
  - different budding sites and requirements
VLP Express: Accelerating the discovery of VLP-based vaccines

- Scale-down of manufacturing technology
  - HT cloning (96 DNA constructs in 10 days)
  - Automated HT infiltration (50 expression strategies/days)
  - HT monitoring of viral protein and VLP accumulation
  - Generic purification method

- Screening
  - Capacity improved 10X
  - Time to identification 10X faster
Flexibility:

Broadening applications of manufacturing & vaccine platforms

• Throughput of VLP Express enables running multiple projects in parallel

• In 2011, the discovery team has tested >2,000 engineering approaches and identified those driving the assembly of VLPs for 7 different families of viruses:
  – Influenza (including 20 sub-types)
  – Rabies
  – Proprietary undisclosed enveloped VLP
  – Ebolavirus
  – Varicella-zoster virus
  – HIV
  – Partnered undisclosed capsid VLP

• Advantages
  – Testing of multiple expression vectors in parallel
  – Comparing different protein engineering strategies
  – Co-expressing various proteins using separate Agrobacteria
  – Rapid optimization of expression conditions
  – Allow development of vaccines with "built-in" efficacy and manufacturing readiness
Advantages of Medicago’s plant-based technology

• Pandemic
  – Target any HA sequence including wild-type
  – Induce strong antibody responses
  – Induce a balanced immune response
    • Strong CD4+ and CD8+ memory
    • Cross-reactive for other strains
  – More durable strain-specific immunity
  – Superior cross-reactivity
  – Possible role in the elderly

• Other emerging threats
  – Many features of plant-made influenza VLPs vaccines applicable to other indications (natural or man-made)
  – Flexibility, speed, scale-up & cost advantages
Acknowledgements

At Medicago
Research and Innovation team
Product Development team
Manufacturing and QA teams

Collaborators

GLA adjuvanted vaccine
From IDRI: Darrick Carter Patti Hon Anthony Desbiens
Steve Reed Rhea Coler
Susan Baldwin Chris Fox

From CSU (animal studies): Richard Bowen

Cell-mediated Immune response
ImmuneCarta: David Favre
McGill University: Brian J. Ward’s team

Sponsors

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