Update on production of plant-made influenza Virus-Like Particle (VLP) vaccine

January 25th 2013

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Vice President of Product Development

TSX: MDG
OTCQX: MDCGF
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Agenda

• Manufacturing technology
  – Background in scale-up and tech transfer

• Clinical update on influenza vaccines

• Plans forward
# Company Overview

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<th>Focus</th>
<th>Vaccines / Biosimilars</th>
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<td>Manufacturing technology</td>
<td>Transient expression in tobacco</td>
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<td>Vaccine technology</td>
<td>Virus-like particles</td>
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<td>Discovery platform</td>
<td>VLPExpress™</td>
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| Headquarters & cGMP facilities | Quebec City, Canada  
|                                | Research Triangle Park, NC, USA |

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<th>Product pipeline</th>
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<tbody>
<tr>
<td>Pandemic Flu H5 – Phase II Canada - complete</td>
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<td>Pandemic Flu H5 – Phase I USA - DARPA/IDRI</td>
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<td>Seasonal Influenza – Phase I USA – complete</td>
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<td>Rabies – GMP process and toxicology - 2012</td>
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<td>Non-influenza VLPS and Biosimilars – R&amp;D</td>
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<th>Agreements</th>
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<tbody>
<tr>
<td>Mitsubishi Tanabe Pharma – strategic alliance</td>
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<td>Philip Morris Products – licensing agreement for China</td>
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<td>DARPA Award – US$21M - completed</td>
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<td>IDRI – Phase I H5 new adjuvant, intradermal</td>
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<td>Top 10 Pharma – vaccine outside of flu</td>
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Versatile product platform: product pipeline

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<thead>
<tr>
<th></th>
<th>Research</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td><strong>Pandemic</strong></td>
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<td>Emergency Use</td>
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<td>H5 Pandemic flu VLP</td>
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<td>Moving to PI/II</td>
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<td>H5 Pandemic flu VLP (Intradermal+GLA)</td>
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<tr>
<td>H5 Pandemic flu VLP (dose ranging+GLA)</td>
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<td><strong>Seasonal</strong></td>
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<td>Quadrivalent VLP</td>
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<td>Moving to PI/II</td>
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<td><strong>Others</strong></td>
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<td>Rabies VLP</td>
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<td>Rotavirus</td>
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Manufacturing technology
Manufacturing Process

Plants & Agrobacterium preparation

Infiltration & Incubation

Extraction

Clarification

Purification

Medicago VLP

Influenza virus
Fully integrated capacity

- **Research**
  - HTP Discovery platforms

- **Development and commercial**
  - cGMP pilot
    - Pandemic, seasonal flu
  - cGMP large scale
    - Pandemic, seasonal flu

- **Commercial**

Quebec, Canada and Evry, France
Quebec, Canada
North Carolina, USA
US facility

- Research Triangle Park, North Carolina
  - 9700 m²: 2700 m² greenhouse
  - 2 batches/week – 600kg biomass/week
  - 10-20M pandemic adjuvanted doses/month
  - 70 employees to operate
  - $36M capital investment (facility and equipment)

- Milestone-based cost-sharing agreement with US Government
  - 24 months project – $21M funding from US Gov.
  - All milestones successfully completed – including production of 10M doses of H1 VLP in one month
Two Challenges That Medicago Faced

• Rapid construction of a plant-based production facility

• Short timeline for tech transfer (35X the Quebec scale)
**Timeline – DARPA Milestones**

- **$21M DARPA grant announced** (Aug)
- **US groundbreaking** (Oct)
- **2nd Milestone**
  - Preliminary equipment and facility designs (Mar)
- **3rd Milestone**
  - Scaled-up process defined (Apr)
- **US commercial facility operations begin** (Sep)
- **4th Milestone**
  - Phased commissioning and engineering (Feb)
- **Start of 5th Milestone**
  - 10M doses of H1N1 vaccine in 30 days (end of Mar)
- **5th Milestone Completed**
  - Production of >10M doses of H1N1 (Apr)
- **Completion of DARPA Project** (Aug)
- **Official Ribbon Cutting** (Nov)
- **Completion of DARPA Project** (Aug)

**Years:**
- 2010
- 2011
- 2012
Construction, Automation and Start-up in RTP, USA

- **September 2010**: Construction
- **January 2011**: Construction
- **March 2011**: Construction
- **August 2011**: Start-up
- **September 2011**: Start-up
- **February 2012**: Start-up
Influenza vaccines
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 for id administration with GLA (ongoing)
    • 100 healthy adults (18-49 years of age)

• Seasonal vaccine
  – **Phase I** H1 VLP completed in 2011 (non-adjuvanted)
    • 100 healthy adults (18-49 years of age)
Type I hypersensitivity reactions

Degranulation of mast cells require the binding of at least two epitopes to two adjacent IgE antibody molecules. This cross-linking may be achieved by two peptide epitopes, by one glycan and one peptide epitope, but also two glycan epitopes.
Cross-reactive glycans found in plant allergens

Complex N-glycan not associated with allergy

(Altmann F. 2007)
N-glycans found in HA VLP vaccines

N-glycans found in H1 VLP vaccine (lot PDD-20101108A)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Relative abundance</th>
</tr>
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<tbody>
<tr>
<td>Gn2M3FGn2</td>
<td>21.4%</td>
</tr>
<tr>
<td>GnM3FGn2</td>
<td>9.6%</td>
</tr>
<tr>
<td>Gn2M3XFGn2</td>
<td>43.5%</td>
</tr>
<tr>
<td>GnM3XFGn2</td>
<td>9.2%</td>
</tr>
<tr>
<td>GnM4XGn2</td>
<td>8.6%</td>
</tr>
<tr>
<td>Lewis and alike</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

- Glycan structures confirmed by 3 laboratories: Medicago, Univ. Of Rouen, Proteodynamics
- Glycans in H5 VLP vaccine are of similar structure (data not shown) but relative abundance not assessed
## 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>Phase 1 with H1 VLP (one dose)</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>Phase 2 with H5 VLP (two doses)</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)*
Clinical trials with H5 VLP

- 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>90 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I (groups of 12 subj.)</td>
<td>16.7 (0.02-0.48)</td>
<td>25.0 (0.06-0.57)</td>
<td>58.3 (0.28-0.85)</td>
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<tr>
<td>Phase II (part A, groups of 30 subj)</td>
<td></td>
<td></td>
<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></td>
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<tr>
<td>Sanofi H5 Licensed vaccine</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>44 (0.28-0.66)</td>
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</table>
H1 VLP

- Phase I: H1 VLP met all CHMP criteria after a single 5µg dose (no adjuvant)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>5µg</th>
<th>13µg</th>
<th>28µg</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>n=19</td>
<td>n=18</td>
<td>n=19</td>
<td>n=19</td>
</tr>
<tr>
<td>Seroprotection rate (95%CI)</td>
<td>15.8(3.4;39.6)</td>
<td>22.2(6.4;47.6)</td>
<td>21.1(6.1;45.6)</td>
<td>10.5(1.3;33.1)</td>
</tr>
<tr>
<td>Geometric mean titer (95%CI)</td>
<td>12.4(7.9;19.7)</td>
<td>11.9(7.0;20.1)</td>
<td>12.0(7.3;19.6)</td>
<td>7.7(5.3;11.4)</td>
</tr>
<tr>
<td><strong>21 days after vaccination</strong></td>
<td></td>
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<tr>
<td>Seroprotection rate (95%CI)</td>
<td>26.3(9.1;51.2)</td>
<td>83.3(58.6;96.4)</td>
<td>73.7(48.8;90.9)</td>
<td>84.2(60.4;96.6)</td>
</tr>
<tr>
<td>Seroconversion ratea (%)</td>
<td>5.3(0.1;26.0)</td>
<td>61.1(35.7;82.7)</td>
<td>63.2(38.4;83.7)</td>
<td>84.2(60.4;96.6)</td>
</tr>
<tr>
<td>Geometric mean titer (95%CI)</td>
<td>13.4(7.8;23.0)</td>
<td>132.0(60.6;287.4)</td>
<td>84.5(47.6;150.0)</td>
<td>210.2(88.6;498.8)</td>
</tr>
<tr>
<td>Mean geometric increase (95%CI)</td>
<td>1.1(0.8;1.5)</td>
<td>11.1(4.1;29.8)</td>
<td>7.0(4.1;12.1)</td>
<td>27.2(10.8;68.5)</td>
</tr>
</tbody>
</table>
H1 VLP induces long-term CD4+ T cells

PBMCs collected 6 months after vaccination

Overall responses in total CD4+ T cells stimulated with H1 peptide pool (A) or H1 VLP (B) (H1 cohort, N=88 subjects): data are derived from SPICE-based functional analysis of ICS results on background-subtracted values from non-stimulated samples that are summed-up and presented as “total” response to H1 VLP stimulation per million CD4+ T cells. Placebo group (black dot) is compared to H1 VLP groups (5, 13, 28µg, no adjuvant, orange square) and to the Fluzone comparator group (red triangle). “*” indicates statistically significant differences between two-group analysis by Mann-Whitney test (P≤0.05).
H5 VLP induces long-term CD4+ T cells

PBMCs collected 6 months after vaccination

**Overall responses in total CD4+ T cells stimulated with H5 VLP (H5 cohort, N=53 subjects):**

A) Data are derived from SPICE-based functional analysis of ICS results on background-subtracted values from non-stimulated samples that are summed-up and presented as “total” H5 VLP response per million CD4+ T cells. Placebo group (black dot) is compared to H5 VLP groups (20, 30, 45µg) with adjuvant (orange square) and to H5 VLP 40µg group with no adjuvant (red triangle). * indicates statistically significant differences between two groups by Mann-Whitney non-parametric test. The lower grey rectangle on the lower of the graph indicates a putative threshold of biologically significant CMI based on ROC analysis (data not shown), assuming that negative placebo (6/8) should have negative CMI responses.

B) Correlation between H5 VLP stimulation and peptide stimulation.
Functionality of T cells induced by H1 VLP

Distribution of functional responses in total CD4+ (A) and CD8+ (B) T cells stimulated with H1 VLP (H1 cohort, N=88 subjects): data are derived from SPICE-based functional analysis of ICS results on background-subtracted values from non-stimulated samples that are summed-up and presented as the distribution of “total” functional responses in color-coded pie charts. Each functional signature is indicated on the legend, with arcs representing the different functional markers as indicated by the legend on functional markers. Placebo group (1) is compared to H1 VLP groups (5, 13, 28µg, no adjuvant, 2) and to the Fluzone comparator group (3). A permutation analysis (SPICE software) is presented on the bottom with P values resulting from the comparison between the distributions of averaged functional responses from each group.
H1 VLP induces cross-reactive T cells to H5N1

*PBMCs collected 6 months after vaccination*

Overall cross-reactive responses in total CD4+ (left) CD8+ T cells (right) stimulated with H5 VLP in the H1 cohort (N=88 subjects): H1 VLP group (5, 13, and 28 µg, no adjuvant) (orange square) is compared to the placebo group (black dot) and the Fluzone comparator (red triangle). * indicates statistically significant differences between two groups by Mann-Whitney non-parametric test.
Summary of CMI findings with VLPs

• Protection despite low to undetectable functional antibody titers for the challenge strain shown in two animal models (mucosal antibodies – CMI)

• Plant-made VLPs are strong inducers of
  – Innate immunity
  – Long-lasting memory T cells
  – Strong polyfunctional memory CD4 T response

• H1 VLP induced more CD4 T cells cross-reactive for H5N1 compared to egg-based and placebo
  – To our knowledge, this is a first demonstration of such an effect with an H1 vaccine

• Similar cross-protective effects reported for H5N1 vaccines administered with oil-in-water adjuvants
Possible implications of CMI

• Pandemic
  – Speed and scale-up advantages obvious

• Seasonal
  – More durable strain-specific immunity
  – Superior cross-reactivity
  – Possible role in the elderly
  – Better efficacy in case of mismatch
    • Capacity to respond to mismatch never met
    • Important medical costs of mismatch (e.g.: 1997/98 H3N2)
    • Few cost estimates but at least 5-fold increase in $$

Current plans with influenza vaccines

• Phase II trial with H5 VLP mixed with GLA-based adjuvants and/or Alhydrogel (Canada)

• Phase I/II trial with seasonal vaccine

• In addition to safety, evaluation of the humoral and cell-based immune response
Thank you!