Flunisyn: Advanced development of a synthetic universal influenza t-cell vaccine

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Flunisyn: Advanced Development of a Synthetic Universal Influenza T-cell Vaccine

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Immune Targeting Systems

London based biotech company developing vaccines for mutating viruses and cancer

Lead Program: Universal Flu vaccine (Flunisyn™)

- 2nd Phase-I study complete (Flunisyn +/- Adjuvant) - Phase 2a initiation H2-2012
- Existing flu vaccines – poorly effective & don’t deliver T-cell correlates of protection

Pipeline extension offers unique targeted product profiles

- Universal Hepatitis B therapeutic vaccine – targets antiviral treatment cessation (7MM/Asia)
- Cancer vaccine platform – Maximising immunogenicity whilst eliminating HLA screening

Investors:
## Mutating Viruses: Disease protection requires T-cell immunity

<table>
<thead>
<tr>
<th>Performance Parameter</th>
<th>Benefit</th>
<th>Flunisyn™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-use capability (Booster effect) *</td>
<td>Single vaccine regimen (Avoids heterologous prime-boost strategy)</td>
<td>✓</td>
</tr>
<tr>
<td>Responder frequency</td>
<td>High % respond to vaccination (Eliminates HLA typing of human subjects)</td>
<td>✓</td>
</tr>
<tr>
<td>Breadth of response</td>
<td>Improved antiviral activity</td>
<td>✓</td>
</tr>
<tr>
<td>Magnitude &amp; Quality of response</td>
<td>Improved antiviral activity</td>
<td>✓</td>
</tr>
<tr>
<td>Broad cross reactive T-cell immunity</td>
<td>All viral strains / genotypes</td>
<td>✓</td>
</tr>
</tbody>
</table>

Historical T-cell vaccine pipeline failures highlight rate limiting immunological performance parameters

**Improved vaccines must address full correlates of protection** (unachieved by adjuvants alone)
DepoVaccine™ Promotes a Short Term Antigen Depot

DepoVaccines promote an antigen depot \( (↑ T_{1/2}) \)
Depot forming adjuvant boosts immunogenicity

Synthetic: Scalable, Stable & Characterisable

<table>
<thead>
<tr>
<th>Selection Parameters</th>
<th>Typical High Density Antigen Sequence Profile (35 amino Acid Reading Frame)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird</td>
<td>Species</td>
</tr>
<tr>
<td>H1N1</td>
<td>Human</td>
</tr>
<tr>
<td>H1N2</td>
<td>Avian</td>
</tr>
<tr>
<td>H2N2</td>
<td>Avian</td>
</tr>
<tr>
<td>H3N2</td>
<td>Avian</td>
</tr>
<tr>
<td>H5N1</td>
<td>Avian</td>
</tr>
<tr>
<td>H7N7</td>
<td>Avian</td>
</tr>
</tbody>
</table>

Densigen™

- 35aa conserved immunoprevalent antigen
- Non-envelop viral protein hydrophobic cores

Freeze Dried Nanoparticle Formulation
Flunisyn – contains 6 different Densigens

Summary

Company

DepoVaccine Platform

Flunisyn™
HBV
Oncology

IMMUNE TARGETING SYSTEMS
Flunisyn™: First Time in Human Study

**Objective:** Dose escalation study to establish initial data set with prototype formulation of Flunisyn (non-adjuvanted) – double blind and placebo controlled

1. Safety & immunogenicity (dose response)
2. Quality of immune response
   a) T cell phenotype (cytokine expression, CD4/CD8)
   b) X-reactivity to disparate influenza strains

**Study design:**

<table>
<thead>
<tr>
<th>Group (n = 12 per cohort)</th>
<th>Injections</th>
<th>Blood samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Day 1, 29 &amp; 99</td>
<td>Day -7. 1, 8, 15, 29, 36, 53, 99, 106, 113, 279</td>
</tr>
<tr>
<td>Flunisyn (50µg/peptide)</td>
<td>Day 1, 29 &amp; 99</td>
<td>Day -7. 1, 8, 15, 29, 36, 53, 99, 106, 113, 279</td>
</tr>
<tr>
<td>Flunisyn (150µg/peptide)</td>
<td>Day 1, 29 &amp; 99</td>
<td>Day -7. 1, 8, 15, 29, 36, 53, 99, 106, 113, 279</td>
</tr>
<tr>
<td>Flunisyn (500µg/peptide)</td>
<td>Day 1, 29 &amp; 99</td>
<td>Day -7. 1, 8, 15, 29, 36, 53, 99, 106, 113, 279</td>
</tr>
</tbody>
</table>
Flunisyn™ Phase-I Clinical Summary

Flunisyn is safe and well tolerated at all doses tested

**Immunogenicity:**

**Magnitude & booster amplification**

- Increases in both CD4+ and CD8+ T cells post vaccination (day 36)

*Flunisyn boosts low levels of memory T-cells*

**Increases in both CD4+ and CD8+ T cells post vaccination (day 36)**

- Flunisyn-specific T cell response (n=11)
- measured by intracellular cytokine staining

Summary Company DepoVaccine Platform

Flunisyn™ HBV Oncology

IMMUNE TARGETING SYSTEMS
No difference in HLA-restriction between vaccine responders and overall HLA prevalence

<table>
<thead>
<tr>
<th>HLA-supertype</th>
<th>Responder</th>
<th>Overall Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>n / 21</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>HLA-A01</td>
<td>8</td>
<td>38%</td>
</tr>
<tr>
<td>HLA-A02</td>
<td>11</td>
<td>52%</td>
</tr>
<tr>
<td>HLA-A03</td>
<td>12</td>
<td>57%</td>
</tr>
<tr>
<td>HLA-A24</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>HLA-B07</td>
<td>14</td>
<td>67%</td>
</tr>
<tr>
<td>HLA-B08</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>4</td>
<td>19%</td>
</tr>
<tr>
<td>HLA-B44</td>
<td>8</td>
<td>38%</td>
</tr>
<tr>
<td>HLA-B58</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>HLA-B62</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>HLA-DR1</td>
<td>5</td>
<td>24%</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>4</td>
<td>19%</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>HLA-DR7</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>HLA-DR11</td>
<td>4</td>
<td>19%</td>
</tr>
<tr>
<td>HLA-DR13</td>
<td>4</td>
<td>19%</td>
</tr>
<tr>
<td>HLA-DR15</td>
<td>5</td>
<td>24%</td>
</tr>
</tbody>
</table>

Flunisyn specific T-cells recognise cells infected with different influenza A virus strains

Cross-reactivity correlated with degree of hepatoma cell line infectivity

* Cross-reactivity correlated with degree of hepatoma cell line infectivity
Flunisyn™: Key Performance Parameters

Immunologically optimum dose – highlights its best-in-class potential:

- **Responder frequency**: 10/12 subjects met responder criteria (without HLA screening)
- **Booster amplification**: confirmed (at 1\textsuperscript{st} & 2\textsuperscript{nd} booster)
- **Breadth**: mean 4.5 / 6 antigens (incl. multi-epitopic CD4 & 8 / antigen)
- **Magnitude**: significant increase over base line
- **Cross reactivity**: all potential seasonal & pandemic flu strains
Advax Significantly Enhances T-cell Immunogenicity (non Clinical)

Advax (microparticulate Inulin) enhances Flunisyn & functional antibody responses to hemagglutinin (Rats)

- Magnitude of response (20X)
- Breadth of response (>50% include multi-epitopic / peptide responses)
- CD8 profile (30-40% of total response)
- Antiviral cytokines (500X)
- HAI antibody titres (8X or 1:320)
Improved Influenza Disease Protection

- Adds back missing T-cell correlates
  - All potential influenza-A strains
  - Annual prime vaccination

- Boosts antibody performance
  - Improved HAI titres
  - Improved cross reactivity

Counteracting Immunosenescence mechanisms
Regulatory “Risk : Benefit” justification

Lead indication: Improved Elderly seasonal flu vaccine – Flunisyn / MP-Inulin + TIV

Established seroprotection surrogate end-points are not correlated with clinical disease protection
  - Clinical studies highlight T-cell immunity drives influenza disease protection
  - Current seasonal flu vaccine does not deliver T-cell immunity
Developing Unique Products and Platform

Flunisyn Programme:

• Start First in Elderly study Q2 2012
• Live virus challenge study H1 2013

Universal Hepatitis B vaccine (Hepsyn) Programme:

• Pre-clinical GxP 2012/2013
• Phase 1b H2 2013

Oncology Programme:

• PoC Q3 2012
• Target selection Q3 2012