Adjuvant Technology for Pandemic Influenza Vaccines

Christopher Fox
5th WHO International Partners Meeting
Belgrade, Serbia, March 27-29, 2012
Who We Are

• Infectious Disease Research Institute (IDRI)
• Founded in 1993 by Steve Reed
• Over 100 employees, ~40 w/advanced, ~90 in R&D
• Funders include BARDA, NIH, BMGF, DARPA, PATH, WHO, M.J. Murdock Charitable Trust, Eli Lilly & Co., American Leprosy Missions, GSK, and other Public Private Partnerships.
• Annual budget for 2011 ~$25 million

60,000 square foot facility with state-of-the-art laboratories and instrumentation.
### IDRI’s Emphasis & Capabilities

#### Areas of Emphasis
- Adjuvants
- Tuberculosis
- Leishmaniasis
- Leprosy
- Diagnostics
- Compound Screening

#### Capabilities
- Adjuvants and Formulations
- Vaccinology & Antigen Discovery
- Process Sciences
- GMP Manufacturing
- Clinical/Regulatory/QA/QC
- Diagnostics Development
- Drug Discovery
IDRI’s Accomplishments

• Developed next generation of adjuvants
  – Defined ligands: TLRs (1/2/6, 4, 7/8, 9) and non-TLRs (QS21)
  – Formulations: Emulsions, aqueous suspensions, alum, liposomes, solid lipid nanoparticles, hydrogels, creams

• First molecularly defined TB vaccine (in clinic)

• Most comprehensive and largest collection of TB antigens

• First defined leishmaniasis vaccine (in clinic)

• Diagnostic antigens on the market
  - Leishmaniasis
  - Chagas Disease
Benefits of Adjuvants

- *Increase antibody titers, cell-mediated immunity*
- *Shape immune response* (e.g. Th1/Th2)
- *Response broadening*
- *Enable immunization in weakened immune system* (e.g. geriatric)
- *Reduce antigen dose, number of doses*

Adjuvant access, formulation/manufacturing know-how difficult to obtain

IDRI provides public sector solution through adjuvant access and formulation technology transfer
# Clinical Trials

<table>
<thead>
<tr>
<th>Collaborator</th>
<th>Disease Area</th>
<th>Adjuvant Formulation</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Design</td>
<td>Seasonal influenza</td>
<td>GLA-SE</td>
<td>Complete</td>
</tr>
<tr>
<td>Immune Design/Protein Sciences</td>
<td>Pandemic influenza</td>
<td>GLA-SE</td>
<td>Complete</td>
</tr>
<tr>
<td>Fiocruz</td>
<td>Schistosomiasis</td>
<td>GLA-SE</td>
<td>Active: Subjects in follow-up</td>
</tr>
<tr>
<td>Rockefeller University</td>
<td>Adjuvant</td>
<td>GLA-SE, GLA-AF, SE</td>
<td>Active: Subjects in follow-up</td>
</tr>
<tr>
<td>Imperial College, London</td>
<td>HIV</td>
<td>GLA-AF</td>
<td>Active: Enrolling</td>
</tr>
<tr>
<td>Sabin Vaccine Institute</td>
<td>Hookworm</td>
<td>GLA-AF</td>
<td>Active: Enrolling</td>
</tr>
<tr>
<td>IDRI - LEISH-F3</td>
<td>Leishmaniasis</td>
<td>GLA-SE</td>
<td>Active: Enrolling</td>
</tr>
<tr>
<td>WRAIR (CelTOS)</td>
<td>Malaria</td>
<td>GLA-SE</td>
<td>Active: Recruiting</td>
</tr>
</tbody>
</table>
# Planned Clinical Trials

<table>
<thead>
<tr>
<th>Collaborator</th>
<th>Disease Area</th>
<th>Adjuvant Formulation</th>
<th>Anticipated Start Date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH/LMIV</td>
<td>Malaria</td>
<td>GLA-SE</td>
<td>TBD</td>
<td>Pending: Scientific rational for use of GLA under review at MVI</td>
</tr>
<tr>
<td>European Vaccine Initiative (p27A)</td>
<td>Malaria</td>
<td>GLA-SE</td>
<td>Q2 2012</td>
<td>Pending: Sponsor selection in progress</td>
</tr>
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</tr>
<tr>
<td>Imperial College, London</td>
<td>HIV</td>
<td>GLA-AF</td>
<td>Q2 2012</td>
<td>Pending: Manufacturing in March 2012</td>
</tr>
<tr>
<td>Imperial College, London (TaMoVac)</td>
<td>HIV</td>
<td>GLA-AF</td>
<td>Q2 2012</td>
<td>Pending: Sponsor selection in progress</td>
</tr>
<tr>
<td>IDRI – MtblID93</td>
<td>Tuberculosis</td>
<td>GLA-SE</td>
<td>Q2 2012</td>
<td>Pending: Pre-IND meeting on March 5th</td>
</tr>
</tbody>
</table>
Response Broadening

GLA increases and broadens HAI antibody responses to Fluzone (mice)
Technology to be Transferred: Squalene Nanoemulsion

- Manufactured by high pressure homogenization
- Homogeneous, metabolizable ~100 nm droplets

Table 2. SE Release Test Methods and Specifications (4% v/v oil)

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance (visual)</td>
<td>Milky-white liquid</td>
</tr>
<tr>
<td>Squalene quantitation (GC)</td>
<td>27.5 - 41.2 mg/mL</td>
</tr>
<tr>
<td>Osmolality (vapor pressure)</td>
<td>250 - 350 mmol/kg</td>
</tr>
<tr>
<td>pH</td>
<td>5.0 - 6.5</td>
</tr>
<tr>
<td>Particle size (dynamic light scattering)</td>
<td>120 ± 40 nm</td>
</tr>
</tbody>
</table>
Emulsion Process Diagram

- **Squalene**
- **PC**
- **Oil Phase**
- **Aqueous Phase**

**Silverson Mixer**
- 10,000RPM

- **Crude Emulsion, Particle Size: >1µm**

- **Microfluidizer**
  - 30,000PSI, 16 Passes

- **Final Emulsion, Particle Size: ~100nm**

- **Sterile Filtration**
  - 0.2µm Filter

- **Ready for Use Sterile Filtration Sonication**

- **25mM Ammonium Phosphate Buffer**
- **Pluronic F68**
- **Glycerol**
Pilot Batch Manufacture and QC

Photos courtesy of Adrian Onu
**Emulsion Quality Control**

<table>
<thead>
<tr>
<th>Batch</th>
<th>CI Visual Appearance</th>
<th>IDRI Visual Appearance</th>
<th>CI Particle Size (Z-avg, nm)</th>
<th>IDRI Particle Size (Z-avg, nm)</th>
<th>CI Squalene (mg/ml)</th>
<th>IDRI Squalene (mg/ml)</th>
<th>CI Osmolality (mmol/kg)</th>
<th>IDRI Osmolality (mmol/kg)</th>
<th>CI pH</th>
<th>IDRI pH</th>
<th>CI Pass/Fail</th>
<th>IDRI Pass/Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Milky-white liquid</td>
<td>Milky-white liquid</td>
<td>101.1</td>
<td>101.1</td>
<td>34.3</td>
<td>33.6</td>
<td>310</td>
<td>306</td>
<td>5.6</td>
<td>5.7</td>
<td>Pass</td>
<td>Pass</td>
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<tr>
<td>2</td>
<td>Milky-white liquid</td>
<td>Milky-white liquid</td>
<td>100.6</td>
<td>100.6</td>
<td>35.4</td>
<td>34.1</td>
<td>299</td>
<td>299</td>
<td>5.6</td>
<td>5.7</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>3</td>
<td>Milky-white liquid</td>
<td>Milky-white liquid</td>
<td>101.2</td>
<td>102.5</td>
<td>35.3</td>
<td>34.9</td>
<td>309</td>
<td>310</td>
<td>5.6</td>
<td>5.7</td>
<td>Pass</td>
<td>Pass</td>
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**Adjuvant-Antigen Compatibility**

<table>
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<tr>
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<th>Particle Size T=24hrs (Z-avg, nm)</th>
<th>HA content T=0 (µg/ml)</th>
<th>HA content T=8hrs (µg/ml)</th>
<th>HA content T=24hrs (µg/ml)</th>
<th>pH antigen</th>
<th>pH antigen-adjuvant mix</th>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Antigen alone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>36.4</td>
<td>35.5</td>
<td>37.7</td>
<td>7.2</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>106.2</td>
<td>105.7</td>
<td>105.9</td>
<td>37.9</td>
<td>36.4</td>
<td>40.3</td>
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<tr>
<td>2</td>
<td>109.7</td>
<td>105.7</td>
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<tr>
<td>3</td>
<td>107.2</td>
<td>107.4</td>
<td>108.4</td>
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# Antigen-Adjuvant Compatibility

![Image of vaccine and vaccine with adjuvant](image)

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Adjuvant Training Course

Photos courtesy of Patty Hon
Key Elements of Training Program

- Identify appropriate adjuvant formulation
- Site visit at recipient prior to equipment installation
- Acquire equipment/supplies
- Training visit at IDRI (watch, do, teach)
- Translation of SOPs
- Site visit at recipient site for pilot batch production
- Present one-day adjuvant course
- Independent production of adjuvant at recipient site; verification at IDRI
- Regular communication (biweekly teleconf, emails)
Other Technology Transfer Projects

• **India**
  • Adjuvant and antigen tech transfer (Gennova, Pune)
    • Multiple antigens and adjuvants
    • Construction of new 44,000 ft$^2$ vaccine formulation center
  • 1st and 2nd Advanced Vaccinology Courses (CMC, Vellore)

• **Brazil**
  • Antigen and adjuvant tech transfer (Instituto Butantan and Ourofino, São Paulo)

• **Mexico and Central America**
  • Latin American Diploma on Vaccinology (Instituto Carlos Slim de Salud, Mexico City)
Conclusions

• **IDRI-CI adjuvant technology transfer accomplished with modest budget (~$800,000) and accelerated timeline (10 months)**
• *Project is now in second phase: preclinical evaluation of adjuvanted vaccine*
• **IDRI-CI have developed a working model of adjuvant tech transfer that can be applied to other institutes; results and lessons learned will be published**
• *Technology transfer efforts further IDRI’s reach in the developing world and help fulfill our mission*
Acknowledgments

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- Regie Castro
- Jeralyn Roco
- Karen Kinch
- Laura Shoemaker
- Anna Marie Beckmann
- Zack Sagawa

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