Leishmaniasis: Challenges for Vaccine Development

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IDRI Goals: Leishmaniasis

• To improve existing vaccines for use in therapy and prevention.
  – Antigen Discovery
  – Vaccine Development
  – Manufacturing Process
  – Clinical Testing

• To improve existing diagnostics for VL and PKDL and develop a test(s) to demonstrate cure
Challenges to Leishmania Vaccine Development

• **PROBLEM: How to finance?**
  – Making a vaccine requires industry–type effort, **But**
  – Activity generally carried out in academic organizations
  – Solution requires creative leveraging of public/private funds

• **IDRI Solution:** Create PPP, including “Non-Profit Biotech” collaborating with industry
Funding Development of a Leishmaniasis Vaccine
Challenges to Leishmania Vaccine Development

- **Problem: How to Access Adjuvant?**
  - Academic adjuvants not practical (IL12, P. acnes- IFN)
  - Most new clinical adjuvants are in hands of industry
  - Available clinical adjuvants promote too much Th2 (alum, AS02)
  - Mouse data misleading (i.e. CpG)

- **IDRI Solution:**
  - License MPL
  - Optimize MPL formulation
  - Develop synthetic MPL substitute to lower COG
Next Generation of TLR-4 Agonists

Gluco-pyranosylphospho-Lipid A Molecules; Enhance Potency Over MPL
DC: 4h in vitro activation

Gene expression (Log2 relative to media)

IL-12p40

IL-1β

IL-6

Mouse

Human

Agonist Concentration (ng/ml)
Human PBMC IL-1β

92.3 nanomolar GLA is equivalent in potency to 57 micromolar MPL
Challenges to Leishmania Vaccine Development

• **Problem:** How to demonstrate POC

• **Solution:**
  – Perform clinical trials in multiple indications
  – Prophylactic/Therapeutic approaches
Leishmaniasis: Rationale for a Therapeutic Vaccine

• Animal Models
  – *L. major* in mice
  – *L. infantum* in dogs

• Success of immuno-chemotherapy VL trials in Brazil, India

• Clinical experience with ML/CL in Brazil and Venezuela

• PKDL studies in Sudan
Immunotherapy for Leishmaniasis

PKDL in Sudan
Leish-111f + MPL-SE
Clinical Development
Leish-111f: Recombinant Antigen Comprised of 3Linked Subunits

22KD

TSA

BamH I

62KD

LmSTI1

EcoR I

26KD

LeIF (N-term)
Leish-111f (TSA-LmSTI1-LeIF)

Figure 1 - Vaccination against Leishmaniasis using recombinant leishmanial antigens formulated in MPL-SE

BALB/c - *L. major*  
C57BL/6 - *L. infantum*
Leish-111f + MPL-SE Vaccine

Leish-111f Antigen

MPL-SE Adjuvant

Complete Vaccine
Leish-111f + MPL-SE Vaccine
Therapeutic Indications (In Progress)

- Combine vaccine with chemotherapy for treating:
  - VL
  - PKDL
  - CL
  - ML
Leish-111f + MPL-SE Vaccine
Prophylactic Indications (Planned)

• Cutaneous leishmaniasis
• Visceral leishmaniasis (prevent VL, prevent PKDL)
Completed Clinical Trials

Colombia Healthy Subjects
Phase 1 MST+/ Phase 2 MST-

Brazil CL Patients Phase 1

Peru ML Patients Phase 1

US Healthy Subjects
Phase 1
## Brazil/Peru Trial - Design

<table>
<thead>
<tr>
<th></th>
<th>Brazil Phase 1</th>
<th>Peru Phase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>CL</td>
<td>ML</td>
</tr>
<tr>
<td><strong>Vaccine Dose (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leish -111f + 25 μg MPL-SE</td>
<td>5 μg (9)</td>
<td>5 μg (12)</td>
</tr>
<tr>
<td></td>
<td>10 μg (9)</td>
<td>10 μg (12)</td>
</tr>
<tr>
<td></td>
<td>20 μg (9)</td>
<td>20 μg (12)</td>
</tr>
<tr>
<td><strong>Control (n)</strong></td>
<td>MPL-SE (8)</td>
<td>Saline (12)</td>
</tr>
<tr>
<td></td>
<td>Saline (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Antimonal</td>
<td>Antimonal</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>Safety and Tolerability Immunogenicity Clinical Evolution</td>
<td></td>
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**Infectious Disease Research Institute**

Brazil/Peru trial design details include the following:

- **Population**: Brazil CL vs. Peru ML
- **Vaccine Dose (n)**: Different doses for each phase, with Brazil having 5, 10, and 20 μg, and Peru having 5, 10, and 20 μg as well.
- **Control (n)**: Brazil and Peru both use saline as control.
- **Chemotherapy**: Both use antimonial.
- **Endpoints**: Safety, tolerability, immunogenicity, and clinical evolution are the main endpoints.

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This table and diagram provide a clear overview of the trial design, including the different phases, populations, vaccine doses, controls, chemotherapies, and endpoints.
Brazil CL Therapeutic Trial Results

Clinical Status at Study Day 336

- **5 μg Vaccine**: 89% Cured, 11% Relapsed
- **10 μg Vaccine**: 100% Cured
- **20 μg Vaccine**: 78% Cured, 22% Relapsed
- **MPL-SE**: 75% Cured, 25% Relapsed
- **Saline**: 67% Cured, 33% Relapsed

Number of Patients
Summary

The Leish-111f + MPL-SE vaccine:

- Safe and well tolerated
- Immunogenic
- Does not exacerbate disease when given with chemotherapy to CL and ML patients
Vaccine Development; Sub-unit vaccines

• **Selective:**
  – Use only relevant antigens
  – Use adjuvants with desired qualities

• **Versatile:** Antigens can be used alone, in combination, as fusions

• **Manufacturing options greatly increased**
Next Generation Vaccine: SMT plus MPL-SE

- Wk 0
- 3
- 6
- 9
- 13

C57BL/6 mice

Immunizations
Challenge with *L. infantum*
Parasite burden

**Spleen**
- Parasite number (log_{10})
- Saline
- MPL-SE
- SMT + MPL-SE

**Liver**
- Parasite number (log_{10})
- Saline
- MPL-SE
- SMT + MPL-SE

* indicates statistical significance.
Sterol 24-c-methyltransferase (SMT): A Potent Leishmaniasis Vaccine Candidate

SMT is involved in the biosynthesis of ergosterol; target of amphotericin B

*Leishmania* SMT is highly conserved among species (>96%), and is homologous to those of *Trypanosoma* (66%) and *Candida* (39%), but no homologous protein found in humans.
Challenges to Leishmania Vaccine Development

• **PROBLEM:** Who will manufacture the vaccine?

• **Solution:**
  – Reduce risk for Pharma (keep cost low, finalize POC studies, define market potential)
  – Leverage canine market
Challenges to Leishmania Vaccine Development

• **PROBLEM**: Sustainability

• **Solution**:
  – Incentives for Pharma
  – Exclusive vs. Non-Exclusive (include diligence requirements)
  – Multiple Indications
  – Vaccine registration in Europe, U.S., etc.
Summary: The Ideal Leishmania Vaccine

- Safe
- Induces effective T cell response against appropriate antigens
- Induces long-term immunity
- Prophylactic and therapeutic activity
- Effective against more than one form of leishmaniasis
- Cost-effective
- Reproducible, transferable manufacturing process
Leishmaniasis Vaccine Development: Future Directions

- Finalize Antigen Selection
- BUT Antigen ≠ Vaccine
- MPL-SE is Effective, but, COG is an Issue
- Animal Studies, Mice, Hamsters, Dogs (combine with rabies)
- Obtain POC in Clinic
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