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Schistosomiasis Vaccine Updates

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Outline of Presentation

- Rationale for a Schistosomiasis Vaccine
  - Burden of Disease
  - Objectives and Comparative Advantages
  - Scientific and Technical Feasibility

- Current Status of R&D Efforts

- Challenges, Gaps and Opportunities
Schistosomiasis: Burden of Disease

- ~700M people in 78 countries at risk
- ~258M in need of treatment (2014)
  - 61.6M received treatment
- Tens of millions debilitating chronic morbidity
  - 3.31M Disability-Adjusted Life Year (DALY) annually

Hotez et al. PLOS NTD, 2014, July Vol. 8
http://www.who.int/mediacentre/factsheets/fs115/en/
Pathology of Schistosomiasis

- **Acute**
  - Allergic dermatitis
  - Katyama fever

- **Chronic**
  - Hepato-splenomegaly
  - Cystitis and urethritis w/ hematuria

- **Sequelae**
  - Bladder cancer
  - Female infertility
  - Risk of HIV transmission

### Affected Organs

<table>
<thead>
<tr>
<th>Affected Organs</th>
<th>Species</th>
<th>Geographical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic-Intestinal</td>
<td><em>S. mansoni</em></td>
<td>Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname</td>
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<td></td>
<td><em>S. japonicum</em></td>
<td>China, Indonesia, the Philippines</td>
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<tr>
<td>Urogenital</td>
<td><em>S. haematobium</em></td>
<td>Africa, the Middle East, Corsica (France)</td>
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Schistosomiasis Vaccines: An Identified Priority

The Most Feasible and Needed
(Science, January 2016)

- Ebola Sudan
- Chikungunya
- MERS
- Lassa fever
- Marburg
- Paratyphoid fever
- Schistosomiasis
- Rift Valley fever
- SARS
- Hookworm

The Most Important Diseases Without Vaccines
(Vaccine Nation, 14 August 2013)

- Chagas’ Disease
- Chikungunya
- Cytomegalovirus
- Dengue
- HIV
- Hookworm
- Leishmaniasis
- Malaria
- Respiratory Syncytial Virus
- Schistosomiasis
Global funding for schistosomiasis for the period 2007-2014 amounted to ~$214M.

During the same period, ~16% ($35M) of these funds were invested in vaccine R&D.
Global elimination achievable in some focal areas through MDA;

- Integrated approach with other intervention needed;
  - *e.g.*, *vaccine*

- Vaccine strategies complementary to existing control programs;

- Target to different forms of schistosomiasis.
Schistosomiasis Vaccine: Scientific Rationale

- Age-dependent concomitant immunity;
- Putative resistant individuals (endemic normals);
- Irradiated cercariae conferring up to 80% protection in animals;
- Significant efficacy with recombinant veterinary vaccines against other multicellular parasites
  - cysticercosis (*Taenia solium*)
  - cystic echinococcosis (*Echinococcus granulosus*)
Schistosoma Life Cycle & Vaccine Antigens

Candidates:
- Sh28 GST
- Sm14
- Sm-TSP2
- Sm-p80

Vaccine Targets:
- Anti-infection
- Anti-morbidity
- Transmission blocking
Sh28GST (Glutathione-S-Transferase)/Alum Vaccine for Urinary Schistosomiasis Recurrences

**Phase I (Vaccine)**
- Phase Ia
  - Healthy Adult (Europe)
  - N=24
  - Safety & Imm.
- Phase Ib
  - Healthy Children (Senegal)
  - N=24
  - Safety & Imm.

**Phase II (Vaccine+PZQ Treatment)**
- Phase IIa/b
  - Infected Adult (Senegal)
  - N=40
  - Safety & Imm.
- Phase IId
  - Infected Children (Niger)
  - N=24
  - Safety & Imm.

**Phase III (Vaccine+PZQ Treatment)**
- Phase III
  - Infected Children (Senegal)
  - N=250
  - Efficacy (delay in pathological relapses), Safety & Imm.
  - 3 year follow-up after 1st immunization

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Safety and Immunogenicity of rSh28GST Antigen in Humans: Phase 1 Randomized Clinical Study of a Vaccine Candidate against Urinary Schistosomiasis

PlosNTD, 2012

Gilles Riveau¹, Dominique Deplanque²,³, Franck Remoué¹, Anne-Marie Schacht¹, Hubert Vodouhnon², Monique Capron¹, Michel Thiry⁴, Joseph Martial⁴, Christian Libersa²,³, André Capron¹

1 Inserm – Université Lille 2, Institut Pasteur de Lille, Lille, France, 2 Inserm CIC-CRB 9301, CHRU, Lille, France, 3 Université Lille – Nord de France, Département de Pharmacologie Médicale, Faculté de Médecine, Lille, France, 4 Euregentec, Ferc Scientifique, Seraing, Belgium
Sm-14/GLA-SE Vaccine Candidate

- Fatty acid binding protein, supports fatty acid transportation;
- 65-90% protection against S.m. challenges;
- Complete protection against Fasiola hepatica challenges;
- Development path:
  - Veterinary use again liver fluke
  - Human vaccine against Schistosoma
- Phase I trial in Brazil completed: safe&immunogenic (Vaccine, 2016);
Sm Tetraspanin Vaccine: Sm-TSP2/Adjuvant

- Large extracellular domain of the Sm-TSP2, 9 kDa, expressed in *Pichia*;

- On the surface of the parasite tegument, important for parasite development and maturation;

- Response to IgG of putatively resistant individuals;

- Reducing adult worm (50-60%) and eggs (60-75%) in *S.m.* infected mouse model.

Tran et al Nat Med, 2006
Loukas et al, International J Path., 2006
Curti, et al, Hum Vac Immu 2013
Jia et al, JBC, 2014
Sm-TSP/Adjuvant Clinical Evaluation in the Field

Phase Ia
US, Adult
N=72
Fully enrolled, vaccination completed

Phase Ib
Brazil, Adult
N=60
Protocol development

Phase I, II & III. Brazil
Adult or Children
Trials
Other endemic areas
Adult or Children
The Sm-p80 Vaccine Reduced Worm Burden, Egg Shedding, and Pathology in Baboons

Calpain subunit Sm-p80

GLA-SE

>> cGMP production 4Q2017
Antigen Discovery via Differential Screening Using Samples from Endemic Areas

Whole Proteom Library Phase Display (~10^6 clones)

Protein Array (992 Proteins, 1600 Arrays)

Paravac, SchistoVac Projects (funded by EU)

NIH R01AI101274

NIH P50 AI098507
Challenges and Opportunities: Preferred Product Characteristics & Clinical Development

- Modeling is valuable in defining TPP
- Provide >75% protection against infection for 2-3 yrs
  - Parasite(s): all three parasites preferred;
  - Target population: High risk adults or school age children;
- Clinical evaluation is feasible
  - Efficacy readout: egg output (or worm burden);
  - Sensitive assays for efficacy trials need to be established;
  - Human challenge model for testing deemed not feasible at the time.
- Collaborative research & synergized effort are encouraged

Schistosomiasis Vaccine Clinical Development and Product Characteristics
Mo et al., 2015
A vaccine is needed to achieve and sustain the ultimate control and elimination;

Clinical evaluation in the field is possible;

New vaccine candidates are on the horizon;

Vaccine R&D pipeline are weak;

Collaboration and partnership are needed.
Thank You!