Sm-p80-based schistosomiasis vaccine: Preparation for human clinical trials

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Science ranked schistosomiasis vaccine as one of the top 10 vaccines that need to be urgently developed
(January 1, 2016, 351:16-19)

- Reliance on repeated treatment with praziquantel not adequate, infection rates continue to be high
- Development of drug resistance by the parasite?
- Durable reduction in the disease spectrum and transmission via vaccination linked with chemotherapy?
- A vaccine would contribute to the reduction of schistosomiasis morbidity through induced immune responses

1. Neglected Tropical Diseases: Defining Opportunities to Accelerate Translational Research. NIAID/NIH, Bethesda, MD (March 9-11, 2011)
### Preferred product characteristics, NIAID/NIH, Bethesda, MD

| Acceptable features for a prophylactic schistosomiasis vaccine
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<td><strong>Indication</strong></td>
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| **Target Populations** | Population in endemic countries
- Adults (18-59 years of age) in high-risk occupations or areas
- High risk school age children (3-12 years of age) |
| **Efficacy** | Reduce at least 75% infection by one of the schistosome species
(Efficacy readout: egg output and/or worm burden) |
| **Duration of Protection** | 2-3 years after last dosing |
| **Dosage and Cost** | Parenteral administration, 2 doses administration
Less than $1/dose |
| **Product Criteria** | • The vaccine antigen should not react to IgE from target population
• Can be co-administered with local MDA/other interventions |
| **Manufacturing** | Suitability for human trials: purity > 90% (Yield ∼ 50 mg/L) Endotoxin levels < 50 EU/mg |
Vaccination strategies using Sm-p80

Sm-p80 has been tested for its prophylactic efficacy in different vaccine formulations and approaches

- DNA
- Recombinant protein/adjuvant
- Prime/boost

Sm-p80-based vaccine formulations have been tested in three experimental animal models of infection and disease

- Mouse
- Hamster
- Baboon
Sm-p80-based schistosomiasis vaccine: double-blind preclinical trial in baboons demonstrates comprehensive prophylactic and parasite transmission-blocking efficacy

A typical prophylactic vaccine efficacy protocol

Control groups of baboons:
- Received only the delivery vehicle and no antigen
- Were challenged with the same number of larvae

Week 0: Primary immunization
Week 4: First boost
Week 8: Second boost
Week 12: Challenge with schistosome cercariae
Week 20-24: Necropsy

Number of worms recorded and compared with controls and % reduction in number of worms was determined

Reduction in the number of eggs in tissues (liver and intestine) and egg hatching ability was determined
Efficacy of Sm-p80/GLA-SE Vaccine

**Worm Reduction**

- 65.90% Protection
  - p<0.0001
- 43.49% Protection
  - p<0.0001
- 93.45% Protection
  - p<0.0001

**Egg Reduction in Feces**

- GLA-SE (n=20)
  - Trial 1
  - Trial 2
  - Trial 3
  - Trial 4
- rSm-p80+GLA-SE (n=20)
  - Trial 1
  - Trial 2
  - Trial 3
  - Trial 4

**Egg Reduction in Tissues**

- 91.3% Reduction
  - p<0.0001
- 88.50% Reduction
  - p<0.0002
- 89.95% Reduction
  - p<0.0001

**Reduction in Egg Hatching**

- 81.51% Reduction
  - p<0.001

**Analysis**

- Number of Worms Recovered (Mean ± SE): Worm Pairs, Male Worms, Female Worms
- Eggs Recovered in Feces (Gram, Mean ± SE)
- Number of Egg/Grain Tissue (Mean ± SE): Liver, Small Intestine, Large Intestine, Gross
Modeling Studies Using Our Sm-p80/GLA-SE Data

Imperial College: Sir Roy Anderson

Mathematical model for the evaluation of the potential impact of a partially efficacious vaccine on the transmission dynamics of Schistosoma mansoni in human communities (Parasites & Vectors 201710:294).

- Vaccine efficacy of 60% will interrupt transmission in communities with low and moderate transmission.
- For high transmission settings, higher vaccine efficacies are required to interrupt transmission or multiple booster vaccine doses each year may be necessary.
- Vaccine that impacts either on worm establishment, worm fecundity or adult parasite survival in the human host is almost equally beneficial [all of theses are targeted by Sm-p80-based vaccine].
- Model shows that breaking transmission in even low intensity transmission areas, may take 18 years or more.

The impact of the transmission setting, $R_0$, for Model 1 on the temporal trend in the mean worm burden $M$, with 80% vaccine efficacy on parasite establishment only, i.e. $v_1 = 0$, $v_2 = 0$, $v_3 = 0.80$, for (a) $p = 70\%$ and (b) $p = 85\%$. The starting value for the mean worm burden is $M_0 = 100$ per host and the vaccine protection is assumed to be lifelong, i.e. $\omega = 0$.
Deployment of Sm-p80-based vaccine

• **Approach:** Mass Drug/Vaccine Administration or MDVA
Schematic representation of experimental design mimicking natural conditions of schistosomiasis in field conditions

Vaccine efficacy in simulated conditions of endemic areas

**Egg Reduction in Tissues**

- Cpg-ODN (n=5) vs Sm-p80+ CpG-ODN (n=4)
- 49.37% Reduction, p<0.001
- 49.33% Reduction, p<0.005

**Reduction in Egg Hatching**

- Cpg-ODN (n=5) vs Sm-p80+ CpG-ODN (n=4)
- 87.84% Reduction, p<0.001
- 82.29% Reduction, p<0.001

**Weekly Egg Burden**

- Liver
  - Control (Cpg-ODN) n=5, Experimental (Sm-p80+Cpg-ODN) n=4
  - 26.1% Reduction, p=0.02
- Small Intestine
  - Control (Cpg-ODN) n=5, Experimental (Sm-p80+Cpg-ODN) n=4
  - 64.5% Reduction, p<0.001
- Large Intestine
- Gross

- Urine
  - Control (Cpg-ODN) n=5, Experimental (Sm-p80+Cpg-ODN) n=4
  - 64.5% Reduction, p<0.001

**Trickle challenge infection**

Eggs per Gram in Feces

**Chronic disease**

**PZQ treatment**

**Vaccination**

**Boilus challenge infection/ Necropsy**

**CAA Levels in Urine (log/ml)**

Roadmap for Sm-p80/GLA-SE Vaccine (SchistoShield®)
(U.S. Patent No. 9,248,169; India Patent No. 10079/DELNP; Chinese Patent No. 201080035900X; Brazilian Patent No. 1015136-2)

1991 – 2019
Discovery Phase; Proof of Concept; Non-Clinical Development
[NIH / NIAID, Thrasher Foundation and Bill & Melinda Gates Foundation]

2017
Vaccine Licensed to PAI Life Sciences for Phase I Trials in USA

2018 - 2019
Bovine Sm-p80/Sj-p80 Vaccine
[NIH / NIAID SBIR Phase I]

2019 – 2021
Clinical Trials in USA
[NIH / NIAID / VTEUs: Clinical Trial Concept under review]

2015 – 2019
Pre-Clinical Development
[NIH / NIAID SBIR Phase I/II]

2018
Toxicology
[NIH / NIAID/ Battelle]

2019 – 2022
Clinical Trials in Africa
Funding Explored

Licensing / Marketing of Vaccine