SCHISTOSOMIASIS VACCINATION: WHAT ARE THE BEST APPROACHES?

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VIC Global Health Vaccine - May 10, 2017
Activities of the National Reference Centre for Parasitology (NRCP)

**RANGE OF TESTS: DISEASES**
- Malaria
- Chagas disease
- Hum. African Trypanosomiasis
- Leishmaniasis
- Babesia
- Filariasis
- Cysticercosis
- Fascioliasis
- Hydatid disease
- Trichinellosis
- Gnathostomiasis
- Toxoplasmosis
- Schistosomiasis
- Toxocariasis
- Strongyloidiasis
- Paragonomiasis
- Baylisascariasis
- Amoebiasis
- Giardiasis
- Cryptosporidiosis

**BLOOD**

**FOOD**

**WATER**

**MODELS**

**DRUG SCREENING**
- Trypanosoma cruzi
- Trypanosoma brucei
- Leishmania spp. (VL and CL)
- Giardia lamblia
- Cryptosporidium parvum: KO IFNg model

**BIOMARKERS DISCOVERY**
- Chagas disease: Transgenic and KO ApoA1
- Babesiosis
- Malaria
- Leishmaniasis (CL and CL)
- Dengue (US CDC collaboration)
- Clostridium difficile infection (US DoD)

**ANTIGENS USED FOR**

**VACCINE**
- Schistosomiasis
- Chagas disease
- Leishmaniasis (CL and VL)
- Cryptosporidiosis
IN VIVO MODELS: CRYPTOSPORIDIOSIS
Cryptosporidium Oocysts can survive through this process.
• Causes of diarrheal outbreaks
• Most at risk: Children, Elderly and immunosuppressed

❖ 1987  Carrollton, Georgia. 13,000 people infected - Water supply
❖ 1993  South-Eastern Wisconsin, USA. ~ 403,000 people infected. ~ 4,400 people hospitalized. >100 people died. Municipality Water supply
❖ 1995  Torbay in Devon, UK, 575 cases.
❖ 1996  Cranbrook, British Columbia, Canada, 2,000 cases. Weeks later, Cranbrook, British Columbia, Canada, 10,000 to 15,000 cases.
❖ 2001  North Battleford, Saskatchewan, Canada. 1907 cases
❖ 2002  Glasgow, Scotland  floods led to 140,000 cases.
❖ 2007  Utah, USA, 1302 cases. Public pools were the cause.
❖ 2008  Northampton, UK, about 250,000 cases. Tap water.
❖ 2010  Östersund, Sweden, over 4000 cases.
C. parvum and cryptosporidiosis: an interview with Dr. Momar Ndao, McGill University

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Interview conducted by April Cashin-Garbrett, BA Hons (Cantab)

What is Cryptosporidium parvum and where is it found?

Cryptosporidium parvum is one of the most common enteropathogens to affect humans in the world. The protozoan parasite causes a gut infection referred to as cryptosporidiosis.
Oleylphosphocholine (OIPC) arrests *Cryptosporidium parvum* growth *in vitro* and prevents lethal infection in interferon gamma receptor knock-out mice


Karine Sonzogni-Desautels, Axel E. Renteria, Fabio V. Camargo,
Thomas Z. Di Lenardo, Alexandre Mikhail,
Michael J. Arrowood, Anny Fortin,
and Momar Ndao.
BIOMARKERS DISCOVERY: CHAGAS DISEASE
Chagas Disease: Epidemiology

• Infection caused by a protozoan parasite, spread by kissing bugs. Endemic to Central & South America, Mexico
• Estimated that 16-18 million people are infected
• ~50,000 people die annually from Chagas disease
• Also spread by blood transfusion, organ transplants, mother-child (transplacental), and from contaminated food.
Estimated Number of Immigrants with *T. cruzi* Infection in Non-Endemic Countries

The Lancet 2010, 375:1388
Identification of Novel Diagnostic Serum Biomarkers for Chagas’ Disease in Asymptomatic Subjects by Mass Spectrometric Profiling

Momar Ndao,1,2* Terry W. Spithill,2,3,4 Rebecca Caffrey,5 Hongshan Li,6 Vladimir N. Podust,7 Regis Perichon,8 Cynthia Santamaria,3 Alberto Ache,9 Mark Duncan,10 Malcolm R. Powell,11,12 and Brian J. Ward1,2
Biomarkers, Genomics, Proteomics, and Gene Regulation

Apolipoprotein A-I Truncations in Chagas Disease Are Caused by Cruzipain, the Major Cysteine Protease of Trypanosoma cruzi

Qianqian Miao,*,† Cynthia Santamaria,* Dana Bailey,* Jacques Genest,‡ Brian J. Ward,*† and Momar Ndao*†

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SCHISTOSOMIASIS VACCINE:
CLASSICAL APPROACHES

https://www.emaze.com/@ACQRRIQW/Schistosomiasis
Epidemiology

- 700 million people at risk
- Over 200 million people infected
- 750,000 deaths per year
- Most important human helminth infection
- Important public health impact

*S. mansoni*  
*S. haematobium*  
*S. japonicum*  
*S. mekongi*  
*S. intercalatum*
Schistosoma mansoni Cathepsin B

- Most abundant cysteine peptidase in parasite gut
- Involved in hemoglobin digestion
- Needed for parasite development

Modified from Kasny (2009) Adv Paraitol
Sm-CB + CpG Challenge: Worm & Egg Burden

- **59% worms burden reduction**
- **56% Eggs burden reduction in liver**
- **54% Eggs burden reduction in intestine**

- TDR/WHO committee established threshold: 40%
- CathB + CpG: 59% reduction worm number; 56% & 54% reductions in liver and intestinal eggs, respectively
Sm-Cathepsin B + CpG: Antibody Production

- The formulation generated robust CathB-specific total IgG endpoint titers (>120,000 at week 9)
- IgG2c greater than IgG1
- This may be a marker of the immune environment pre-challenge
Th1 cytokines (IFNγ & TNFα) were increased in the experimental group
Th1 responses are believed to be crucial for protection
Sm-CB + CpG: Th1 biased response
A vaccine consisting of *Schistosoma mansoni* cathepsin B formulated in Montanide ISA 720 VG induces high level protection against murine schistosomiasis

Alessandra Ricciardi¹, Kittipos Visitsunthom¹, John P. Dalton²,³ and Momar Ndao¹,⁴*

- CathB + Mont: 60% reduction worm number; 62% & 56% reductions in liver and intestinal eggs respectively
- The formulation generated robust CathB-specific total IgG endpoint titers (>120,000 at week 9)
- IgG1 greater than IgG2c
- Th1 (IFN\(\gamma\) & TNF\(\alpha\)) and Th2 (IL-4 & IL-5) cytokines were increased in the experimental group
- Sm-CB + Mont: Mixed Th1/Th2 response
In vitro parasite killing assay

- Plate 60 schistosomula
- Add the various combinations*
- Incubate 24 hours at 37°C
- Assess viability
- Supernatant collection

*Combinations
1) Media
2) Sera
3) Lung cells
4) Lung cells + pre-immune sera
5) Lung cells + immune sera
Immune Mechanisms Involved in Sm-cathepsin B + Montanide Mediated Protection in mice

- Highest parasite killing (63%) in the presence of lung cells and immune serum from experimental animals
- Suggesting an antibody dependant effect

- CD4 depletion reduced parasite killing from 63% to 36% in experimental group
- Addition of immune serum did not contribute to a significant change in parasite killing

- NK cell depletion reduced parasite killing from 63% to 34% in Exp. group
- Addition of immune serum did not contribute to a significant change in parasite killing
- Killing maintained after CD8⁺ or F4/80⁺ cell depletion
SCHISTOSOMIASIS VACCINE: NEW APPROACHES

Repurposing an Attenuated Salmonella typhimurium YS1646 Strain to Develop a Novel Mucosal Schistosomiasis Vaccine
Oral Delivery of the Sj23LHD-GST Antigen by *Salmonella typhimurium* Type III Secretion System Protects against *Schistosoma japonicum* Infection in Mice

Guo Chen¹, Yang Dai², Jianxiang Chen¹, Xiaoting Wang², Bo Tang¹, Yinchang Zhu²*, Zichun Hua¹,³*

*S. japonicum* burden in mice immunized with heterologous prime-boost vaccination.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mice (n)</th>
<th>Worms (n, % reduction)</th>
<th>Eggs (n, % reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>31±2</td>
<td>122533±22535</td>
</tr>
<tr>
<td>Vector</td>
<td>11</td>
<td>28±3 (10.37)</td>
<td>100797±9131 (17.74)</td>
</tr>
<tr>
<td>Protein</td>
<td>12</td>
<td>24±3 (21.62*)</td>
<td>83402±11364 (31.93*)</td>
</tr>
<tr>
<td>nirB</td>
<td>10</td>
<td>19±4 (42.73**)</td>
<td>62205±14557 (53.23***)</td>
</tr>
<tr>
<td>nirB prime-boost</td>
<td>11</td>
<td>15±3 (51.35***,†)</td>
<td>45842±8810 (62.59***,†)</td>
</tr>
<tr>
<td>Vector prime-boost</td>
<td>9</td>
<td>26±3 (14.59)</td>
<td>92878±23881 (24.20)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, n=9-12; *P<0.05 and ***P<0.001 compared with vector; †P<0.05 compared with nirB group.
doi:10.1371/journal.pntd.0001313.t003
OUTCOMES
Weight loss
Behavioral changes
Adult worm burden
Eggs/gram of liver-intestine
Humoral and cellular responses

S. mansoni Cat B-YS1646

Sm-Cath B -YS1646

Colonic Epithelium

Dendritic Cell

Pro-inflammatory Cytokines

Plasma cells

Memory T cells

Effector & Helper T cells

B cells

Memory B cells
• lac-sopE2-SmCathepsin B → LEC;
lac-sspH1-SmCathepsin B → LHC
• nirB-sopE2-SmCathepsin B → NEC;
nirB-sspH1-SmCathepsin B → NHC
• pagC-sopE2-SmCathepsin B → PEC;
pagC-sspH1-SmCathepsin B → PHC
Immunogenicity and Challenge Studies

**Oral Doses**

- Sm-Cath B -YS1646

**Challenge**

- 150 Cercaria

**SAC**

- 10 weeks

Day 0         2        6

- 3 weeks
- 6 weeks
Prime-Boost Model

Oral Doses

Sm-Cath B -YS1646

Day 0 2 4

IM

Challenge

SAC

3 weeks 3 weeks 6 weeks

20 μg Recomb. CatB 150 Cercaria

10⁹ CFUs

13 weeks
Prime-Boost Model

IM

Oral Doses

Challenge

SAC

Day 0

21 23 25

13 weeks

Sm-Cath B - YS1646

20 μg Recomb. CatB

3 weeks

3 weeks

6 weeks

150 Cercaria

$10^9$ CFUs

13 weeks

$20 \mu g$ Recomb. CatB
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