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NATIONAL SCHOOL OF TROPICAL MEDICINE

Sm-TSP-2 Schistosomiasis Vaccine
Update on product and clinical development

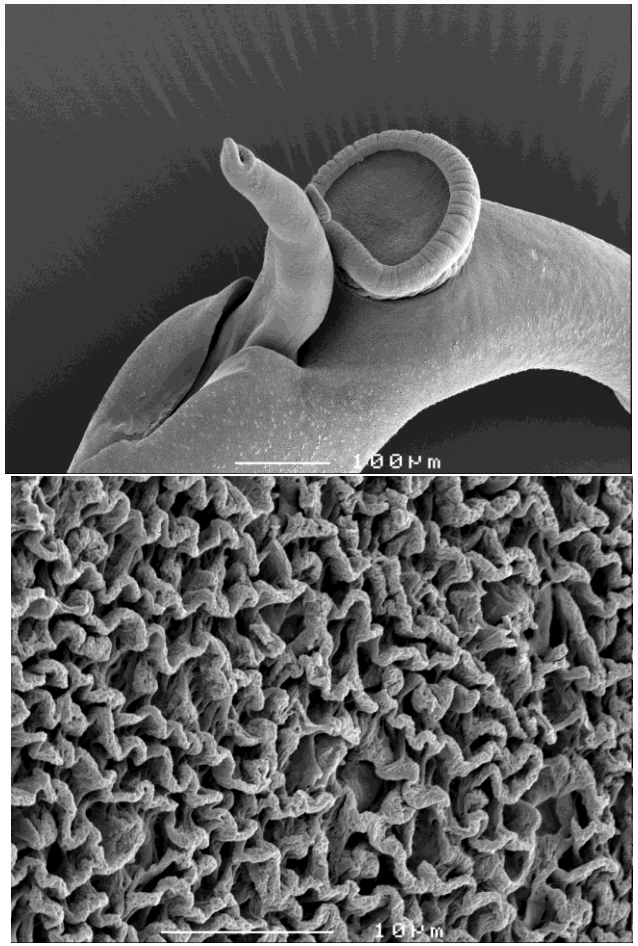
Texas Children's Hospital

Texas Children's Hospital Center for Vaccine Development

Leading the development and testing of low-cost and effective vaccines against emerging and neglected tropical diseases

Schistosomiasis Vaccine Initiative

A Product Development Partnership Model

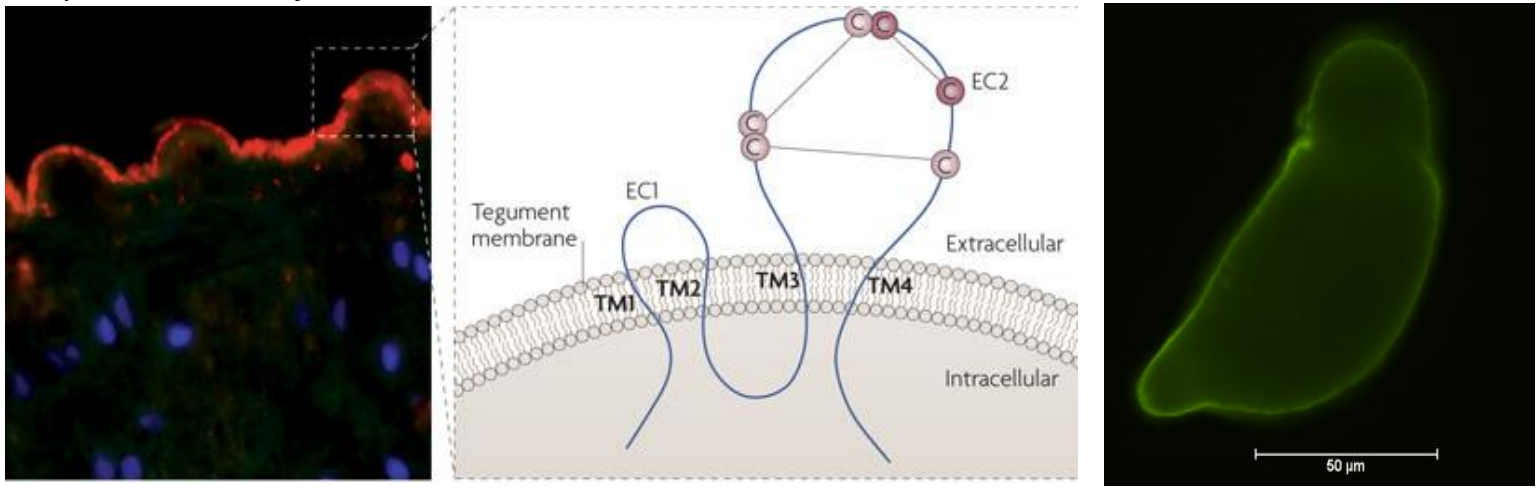


Images courtesy of M. Jones, Univ Queensland

Sm-TSP-2 protein - a vaccine target

A critical tegument protein important for the nutrient acquisition, waste excretion and immune evasion

Smyth et al., 2004, Infect Immun; Tran et al., 2006, Nature Med



sectioned adult worm

live schistosomulum

- Signal sequence trapping identified *S. mansoni* surface/secreted proteins

- *Sm*-TSP-2 (tetraspanin) identified – 4 membrane spanning protein with large extracellular loop (EC2) – same family of proteins as Sm23

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JAMES COOK UNIVERSITY AUSTRALIA

Work by Dr. Alex Loukas et al

Rationale for *Sm*-TSP-2 vaccine antigen selection

Uniquely recognized by individuals who are naturally resistant to *S. mansoni* infection

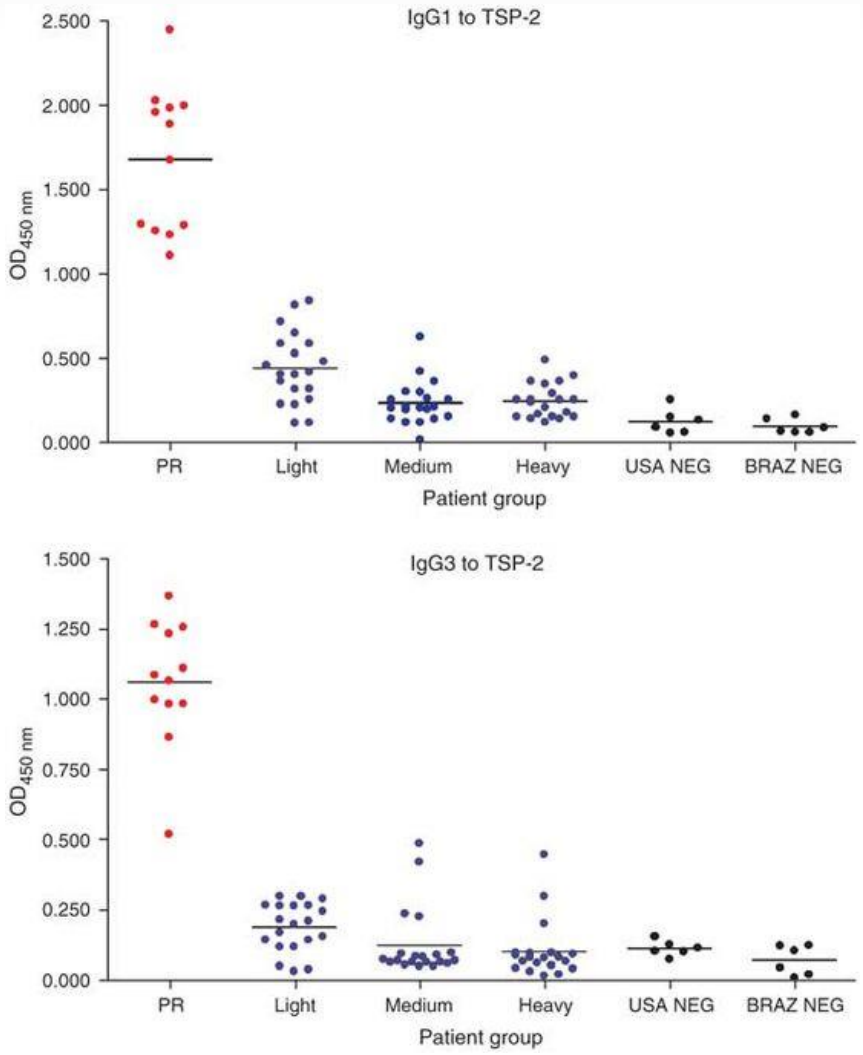
Accessible antigen on the surface of live, newly transformed schistosomula

Suppression of *Sm*-TSP-2 RNA expression results in malformed tegument

Protects different strains of mice (C57BL6 and CBA/J) in vaccine trials via reduced adult worm, liver egg and fecal egg burdens compared to controls

Protects mice when formulated with various adjuvants, including aluminum hydroxide

Strongly recognized by sera from resistant rats but not chronically infected mice



Nature Medicine **12:** 835–840, 2006

Sm-TSP-2 Schistosomiasis Vaccine

Vaccine	Sm-TSP-2	
Pathogen	*Schistosoma mansoni*	
Antigen	Tetraspanin 2	
Proposed function	Integrity of Tegument	
Molecular Weight (kDa)	9 (8.8)	
Expression System	Pichia pink	
cGMP scale	20 L scale	
Vaccine Lots	11-69F-003	1975
Yield	2.1 mg/mL (1.1 g)	2.1 mg/mL (1.1 g)
Stability (to date)	72 months	24 months
Potency Release	ED_{50} (95% FL) 4.82 (3.52-6.7) µg	
Drug Product Formulation	0.1 mg Sm-TSP-2 absorbed to 0.8 mg/mL Alhydrogel® in 10 mM imidazole, 15% sucrose, 2 mM phosphate, pH 7.4 buffer	
Immuno-stimulant (POI)	Glucopyranosylphospho-Lipid A (IDRI), Aqueous Formulation	
GLP Toxicology Study	CD® IGS rats	

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Clinical Development

- ✓ Trial sites: United States, Brazil, Uganda
- ✓ To date safety/immunogenicity shown in 72/60 healthy adult volunteers, respectively
- ✓ Number of trials: 1 completed, 1 ongoing, 1 planned

DMID 13-0009: A **Phase I** Study of the Safety, Reactogenicity, and Immunogenicity of Sm-TSP-2/Alhydrogel® With or Without GLA-AF for Intestinal Schistosomiasis in Healthy Adults

NCT02337855

DMID 14-0100: A **Phase Ib** Study of the Safety, Reactogenicity, and Immunogenicity of Sm-TSP-2/Alhydrogel® with or without AP 10-701 for Intestinal Schistosomiasis in Healthy Exposed Adults

NCT03110757

TSP-18-03 : Phase I/IIb

Part I: Randomized, double-blind Phase 1 trial in 90 healthy adults aged 18-45 years, vaccinated in a staggered, dose-escalating fashion.

Part II: Randomized, double-blind Phase IIb trial in 200 adults aged 18-45 years Vaccinations with *Sm*-TSP-2/Alhydrogel® with or without AP 10-701 vs. a comparator vaccine

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DMID 13-0009: First-in-Human Dose Escalation Study of *Sm*-TSP-2 Healthy Adults in a Non-Endemic Area

Schematic of Study Design:

Cohort	Group	Study Product	Number
1*	A	10ug ***Sm*-TSP-2/Alhydrogel®**	10
	B	10ug ***Sm*-TSP-2/Alhydrogel®/GLA-AF**	10
	C	Placebo†	4
2*	D	30ug ***Sm*-TSP-2/Alhydrogel®**	10
	E	30ug ***Sm*-TSP-2/Alhydrogel®/GLA-AF**	10
	F	Placebo†	4
3	G	100ug ***Sm*-TSP-2/Alhydrogel®**	10
	H	100ug ***Sm*-TSP-2/Alhydrogel®/GLA-AF**	10
	I	Placebo†	4
Total			72

Treatment assignments will be randomized within each cohort in a 10:10:4 ratio and double-blinded (i.e., neither the subject nor the investigator will be aware of the formulation assigned: Alhydrogel® only, Alhydrogel®/GLA-AF, or placebo). All subjects will receive a total of 3 doses of the assigned study product (Days 1, 57 and 113).

*Escalation decisions (i.e., the decision to proceed with the next dose cohort) will be made within 2 weeks after the last subject in the current cohort completes the 7 day post dose 1 visit (Visit 3).

† Placebo will be normal saline (0.9% NaCl)

Safety/Reactogenicity Results

Vaccine was safe and well tolerated

Tenderness and pain at the injection site, and headache and fatigue were the most common vaccine-related reactogenicity events

No SAEs related to vaccination reported

No significant differences in frequencies of injection site or systemic reactions between placebo and vaccine recipients within each cohort, and no significant differences when vaccine groups were compared with each other, but the numbers are small.

Three subjects (all given vaccine + GLA-AF) reported 4 episodes of mild fever during the week after vaccination

No significant clinical laboratory abnormalities were noted

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SEROCONVERSION RATES AFTER 3 DOSES OF VACCINE (Day 127) ≥4-fold rise; Per protocol population

Vaccine Dose Group	Number/Total	Percent
10mcg TSP-2	0/8	0
10mcg TSP-2 + GLA-AF	3/10	30
30mcg TSP-2	0/8	0
30mcg TSP-2 + GLA-AF	4/8	50
100mcg TSP-2	2/8	25
100mcg TSP-2 + GLA-AF	8/9	89
Placebo	0/10	0

Immunogenicity Summary

Peak levels of antibody were observed after the third dose of vaccine, with the exception of the 10mcg dose group. No placebo recipients seroconverted.

Groups given GLA-AF tended to develop higher levels of antibody (p=NS).

The proportions of subjects seroconverting were highest in the 30mcg with GLA-AF and 100mcg with GLA-AF; these groups had significantly higher frequencies of seroconversion than did placebo recipients.

Dose-response relationships for vaccine antigen when formulated with GLA-AF were significant when anchoring with placebo seroconversion rates (0, 30%, 50% and 89%; p=0.0001; chi-square for linear trend).

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Ongoing Dose Escalation Study of *Sm*-TSP-2 in Healthy Adults from *S. mansoni* Endemic Area in Brazil

Cohort	Group	Study Product	Number
1*	A	10mcg *Sm*-TSP-2/Alhydrogel®	8
	B	10mcg *Sm*-TSP-2/Alhydrogel®/ AP 10-701	8
	C	Euvax B Hepatitis B vaccine†	4
2*	D	30mcg *Sm*-TSP-2/Alhydrogel®	8
	E	30mcg *Sm*-TSP-2/Alhydrogel®/ AP 10-701	8
	F	Euvax B Hepatitis B vaccine†	4
3	G	100mcg *Sm*-TSP-2/Alhydrogel®	8
	H	100mcg *Sm*-TSP-2/Alhydrogel®/ AP 10-701	8
	I	Euvax B Hepatitis B vaccine†	4
Total			60

Americaninhas
Minas Gerais

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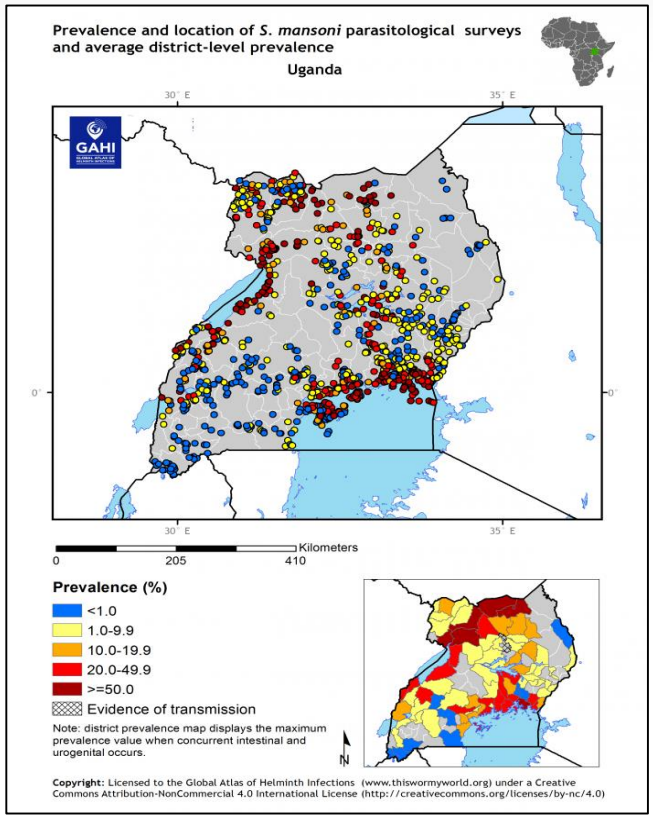
Phase I/IIb clinical trial in Uganda

MAKERERE UNIVERSITY
WALTER REED PROJECT
(MUWRP)

PI: Hannah Kibuuka



Schematic of Study Design:

Start Date: Jan. 2019

Part A

Cohort	Group	Study Product	Number
1*	A	10mcg *Sm*-TSP-2/Alhydrogel®	12
	B	10mcg *Sm*-TSP-2/Alhydrogel®/ AP 10-701	12
	C	Hepatitis B vaccine†	6
2*	D	30mcg *Sm*-TSP-2/Alhydrogel®	12
	E	30mcg *Sm*-TSP-2/Alhydrogel®/ AP 10-701	12
	F	Hepatitis B vaccine†	6
3	G	100mcg *Sm*-TSP-2/Alhydrogel®	12
	H	100mcg *Sm*-TSP-2/Alhydrogel®/ AP 10-701	12
	I	Hepatitis B vaccine†	6
Total			90

Vaccine formulation assignments will be randomized within each cohort in an 12:12:6 ratio and double-blinded (i.e., neither the subject nor the investigator will be aware of the formulation assigned: Alhydrogel® only, Alhydrogel®/ AP 10-701, or Hepatitis B vaccine). All subjects will receive a total of 3 doses of the assigned study product (Days 0, 56 and 112).

*Escalation decisions (i.e., the decision to proceed with the next dose cohort) will be made within about 2 weeks after the last subject in the current cohort completes the 7 day post dose 1 visit (Visit 03).

† Comparator arm will be Hepatitis B vaccine

Part B

Cohort	Group	Study Product	Number
4	G	*Sm*-TSP-2/Alhydrogel®	100
	H	Hepatitis B vaccine†	100
Total			200

Vaccine assignments will be randomized in a 1:1 ratio and double-blinded (i.e., neither the subject nor the investigator will be aware of the formulation assigned: Alhydrogel® only, Alhydrogel®/ AP 10-701, or Hepatitis B vaccine). All subjects will receive a total of 3 doses of the assigned study product (Days 0, 56 and 112).

† Comparator arm will be Hepatitis B vaccine

18-month Follow-up

Endpoints: EPG and CAA

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MHRP
U.S. MILITARY HIV RESEARCH PROGRAM

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