

# Novel Technologies Vaccines against Neglected Diseases

Maria Elena Bottazzi, PhD  
Deputy Director



[http://issuu.com/sabinvaccineinstitute/docs/f\\_sabin10013\\_sabcaseforinvestment-p?e=6271595/11351895](http://issuu.com/sabinvaccineinstitute/docs/f_sabin10013_sabcaseforinvestment-p?e=6271595/11351895)



# The Neglected Tropical Diseases

- 17 tropical infections:
  - Highly prevalent among the poor
  - Endemic in 149 countries primarily in rural areas of low-income countries
  - Affect more than 1.4 billion people
  - Ancient afflictions
  - Chronic
  - Disabling (growth delays, blindness or disfigurement)
  - Poverty promoting



## Immunization, Vaccines and Biologicals

### Product Development for Vaccines Advisory Committee (established April 2014)

#### Meetings, terms of reference and composition

##### Meetings

2015 PDVAC meeting including meeting materials and summary of recommendations

[2014 PDVAC meeting](#)

##### Terms of reference

The Product Development for Vaccines Advisory Committee (PDVAC) provides strategic advice and recommendations to WHO related to vaccines at the Phase 2 stage of clinical evaluation or earlier. The committee's remit is for disease areas where there is substantial disease burden in low and middle income countries, no vaccines or products currently exist, and there is some ongoing product development activity which may benefit from guidance from WHO. This committee may also have a role where first generation vaccines are licensed but development of improved second generation products is a priority for WHO. PDVAC will remain briefed on Strategic Advisory Group of Experts (SAGE) recommendations within the product development area, and be guided by SAGE on its activities.

[http://www.who.int/neglected\\_diseases/diseases/en/](http://www.who.int/neglected_diseases/diseases/en/)

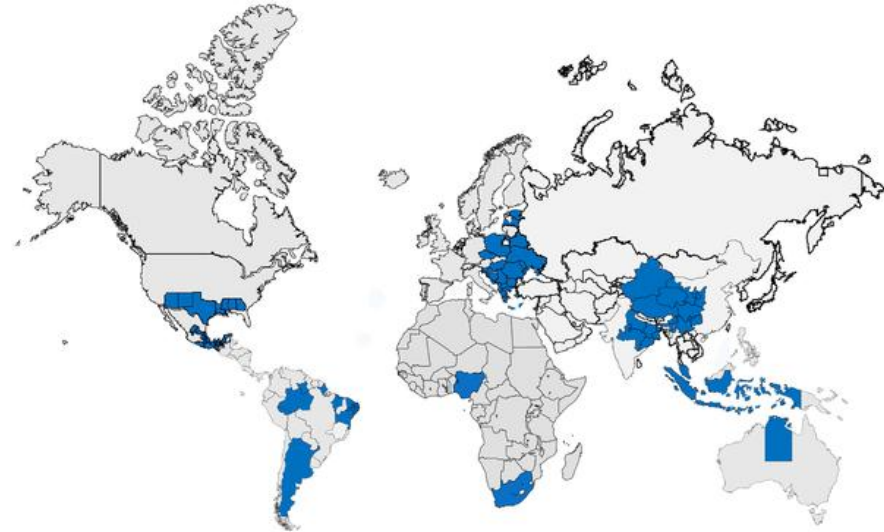
<http://www.who.int/immunization/research/committees/pdvac/en/#>



# Most of the NTDs occur among the poor in wealthy (G20) countries!!

## NTDs in the G20

- 77% Leprosy
- 71% Food-borne trematodiasis
- 67% Leishmaniasis
- 61% Dengue
- 61% Chagas disease
- 60% Lymphatic filariasis
- 50% Helminth infections



OPEN ACCESS Freely available online

PLOS NEGLECTED TROPICAL DISEASES

### Viewpoints

## NTDs V.2.0: “Blue Marble Health”—Neglected Tropical Disease Control and Elimination in a Shifting Health Policy Landscape

Peter J. Hotez<sup>1,2,3\*</sup>

<sup>1</sup>Departments of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine at Baylor College of Medicine, Houston, Texas, United States of America, <sup>2</sup>Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development, Houston, Texas, United States of America, <sup>3</sup>James A. Baker III Institute at Rice University, Houston, Texas, United States of America

Abstract: The concept of the neglected tropical diseases (NTDs)

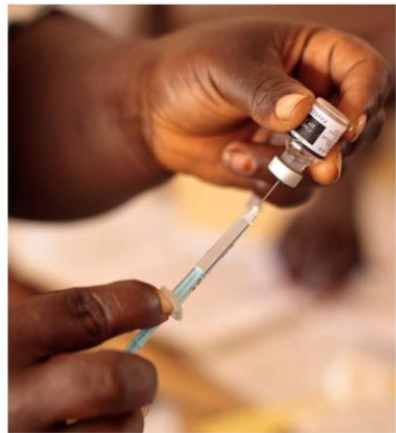
Introduction: Version 1.0

underway in at least 20 developing countries, predominantly through finan-





**Sabin PDP** focuses on translating the discovery, development, and testing of safe, effective and low-cost vaccines for neglected diseases and infections that affect more than one billion people living in poverty around the world.



Our goal is to  
bring vaccines  
to market  
**for less than  
US\$ 1–2  
per dose.**



# Program and Portfolio Growth

**2000  
to  
2004**

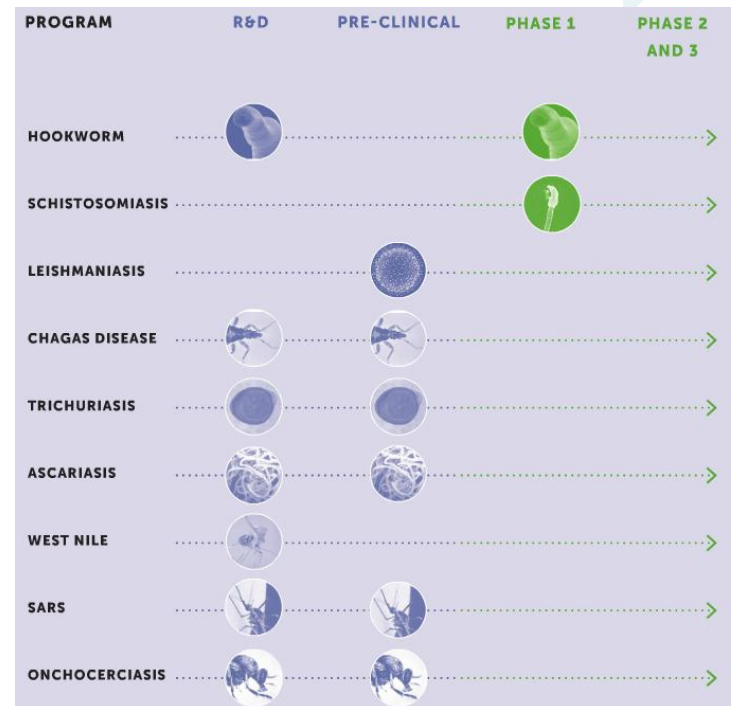
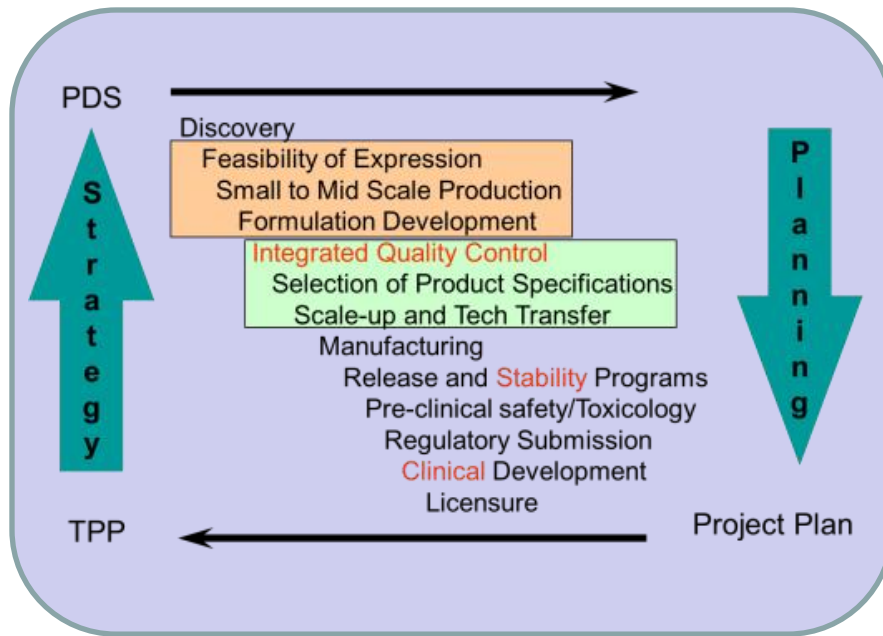
- Built structure
- Launched Hookworm Program

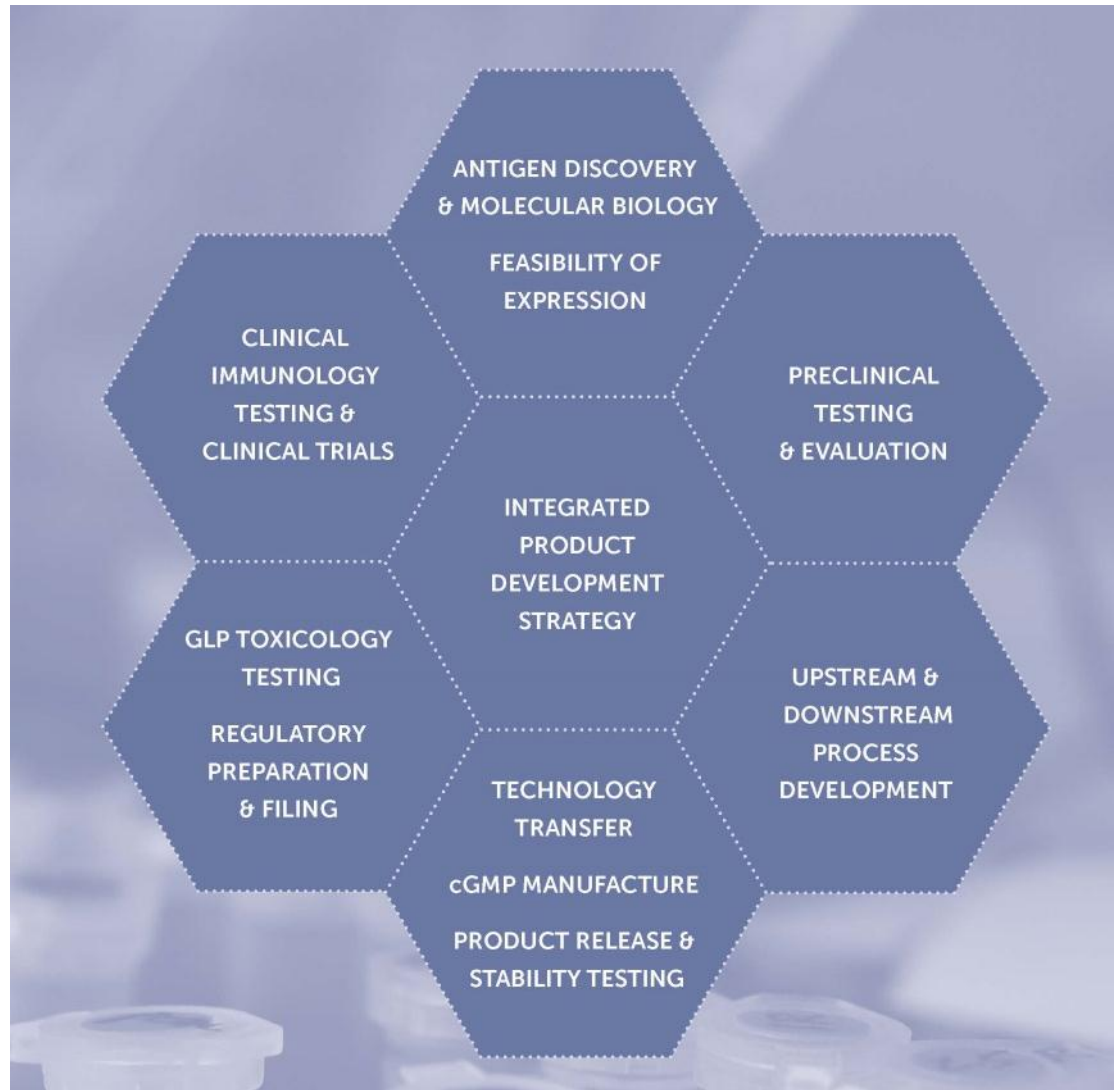
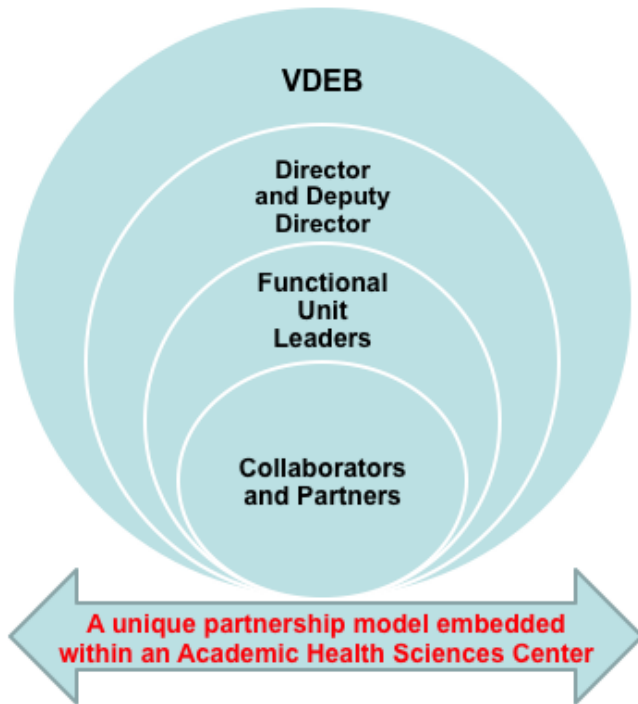
**2004  
to  
2011**

- Expanded Hookworm Program
- Schisto Program
- Relocated to TMC

**2011  
to  
2015**

- Added 7 additional programs
- Expansion of capabilities



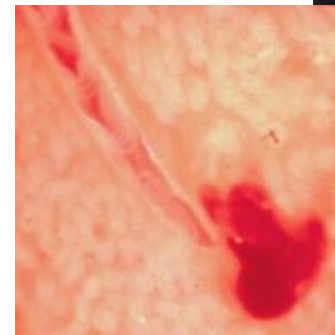
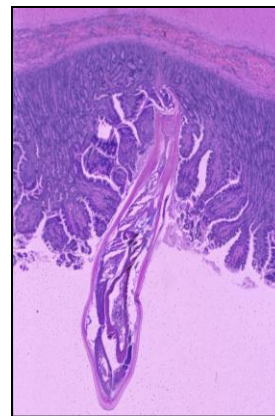
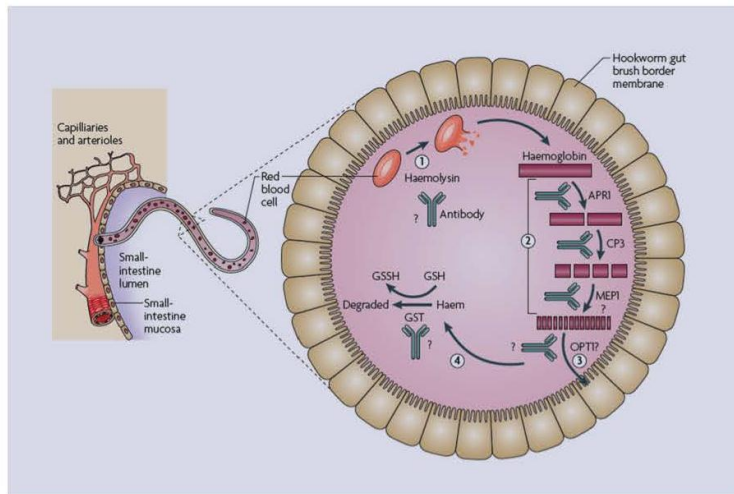
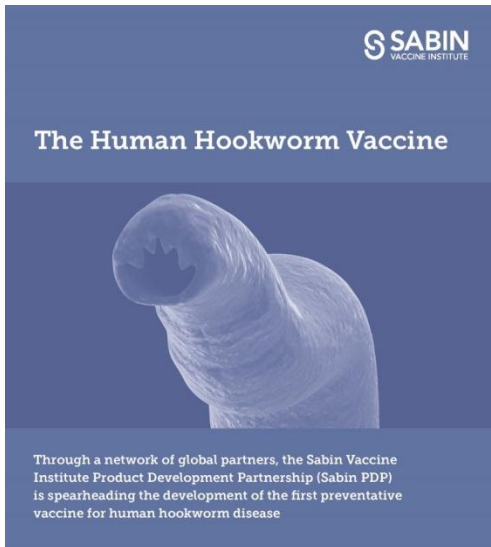




# The Human Hookworm Vaccine Initiative

- Highly prevalent neglected tropical disease – 440 million people
- 3.2 million DALYs
- A leading cause of maternal and childhood anemia in low- and middle-income countries

25 Necator worms = 1 ml blood loss = 0.55 mg Fe = Child's daily iron intake

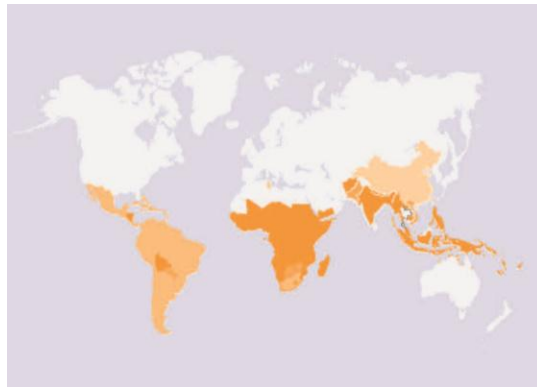




# Key Technical Partners



Remko van Leeuwen



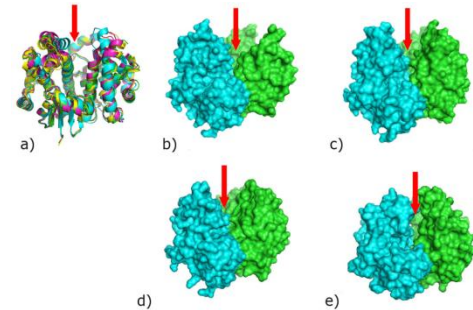
- Amsterdam Institute Global Health and Development (AIGHD)
- Albert Schweitzer Hospital
- Centre de Recherches Medicales de Lambarene
- Center of Excellence Baden-Wurttemberg
- Eberhard Karls University
- FIOCRUZ/FUNDEP
- George Washington University
- Pharmidex
- Q-Biologicals
- Tübingen Institute of Tropical Medicine
- University of Amsterdam
- University of Leiden



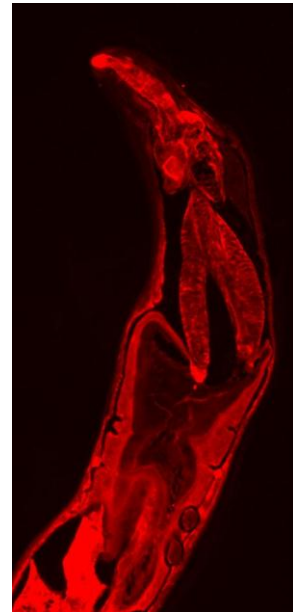


# Na-GST-1 Hookworm Vaccine

- **Platform:** *P. pastoris*
- **Insert:** FL-wild type; no tags
- **Amino Acids:** 1-206
- **Fermentation Yield:** 0.7-1.2 g/L
- **Purification Process Recovery\*:** 55% (0.445 g/L)
- **Formulation:** 0.1 mg/mL Na-GST-1 with 0.8 mg/mL Alhydrogel® in a buffer containing 10% (D)-glucose, 10 mM imidazole, pH 7.4
- **DP cGMP MFG:** Aeras November 13, 2009



**3-D  
Structure  
24 kDa  
Homodimers**



**Immuno-  
Localization  
of *Na-GST-1***



Contents lists available at SciVerse ScienceDirect

Protein Expression and Purification

Journal homepage: [www.elsevier.com/locate/ypro](http://www.elsevier.com/locate/ypro)

Expression, purification, and molecular analysis of the *Necator americanus* glutathione S-transferase 1 (*Na-GST-1*): A production process developed for a lead candidate recombinant hookworm vaccine antigen

Gaddam Narsa Goud<sup>a</sup>, Vehid Deumic<sup>a</sup>, Richi Gupta<sup>a</sup>, Jill Brelsford<sup>a</sup>, Bin Zhan<sup>a,1</sup>, Portia Gillespie<sup>a,1</sup>, Jordan L. Plieskatt<sup>a</sup>, Eric I. Tsao<sup>c</sup>, Peter J. Hotez<sup>a,b,\*,1</sup>, Maria Elena Bottazzi<sup>a,\*,1</sup>

<sup>a</sup> Department of Microbiology, Immunology & Tropical Medicine, George Washington University Medical Center, Washington, DC, USA

\*UF/DF – Q-XL –Butyl-HP – SEC75; >98% purity



# Na-APR-1(M74) Hookworm Vaccine

- **Platform:** *N. benthamiana*
- **Insert:** Double mutant; His-tagged
- **Amino Acids:** 74-446
- **Production Yield:** 5-15mg/Kg
- **Formulation:** 0.1 mg/mL Na-APR-1(M74) with 0.8 mg/mL Alhydrogel® in a buffer containing 10mM Imidazole/150mM NaCl/0.3% Empigen pH 7.4
- **DP cGMP MFG:** FH/WRAIR  
June 16, 2011



## Human Vaccines & Immunotherapeutics

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/khvi20>

Expression, purification, and characterization of the *Necator americanus* aspartic protease-1 (Na-APR-1 (M74)) antigen, a component of the bivalent human hookworm vaccine

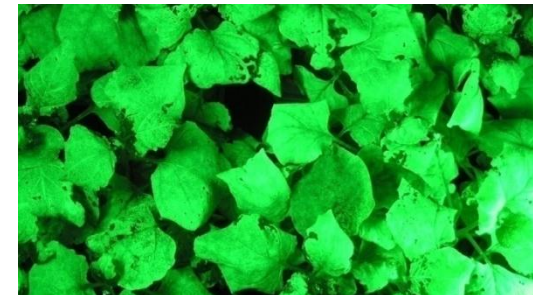


## Human Vaccines & Immunotherapeutics

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/khvi20>

New tools for NTD vaccines: A case study of quality control assays for product development of the human hookworm vaccine Na-APR-1<sub>M74</sub>



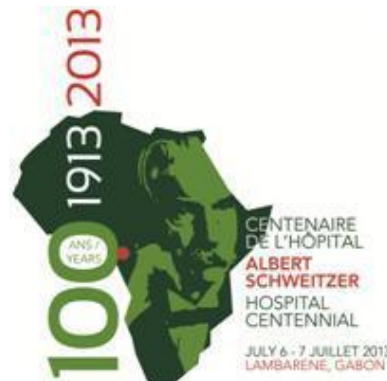
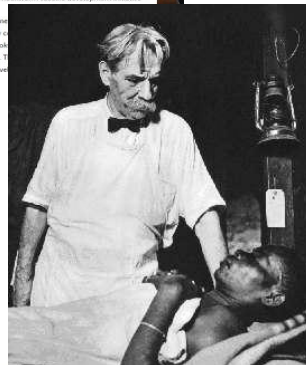
Expression of GFP 4 days following agroinfiltration

\*IAMC - Q-FF – SEC 200; >95% purity





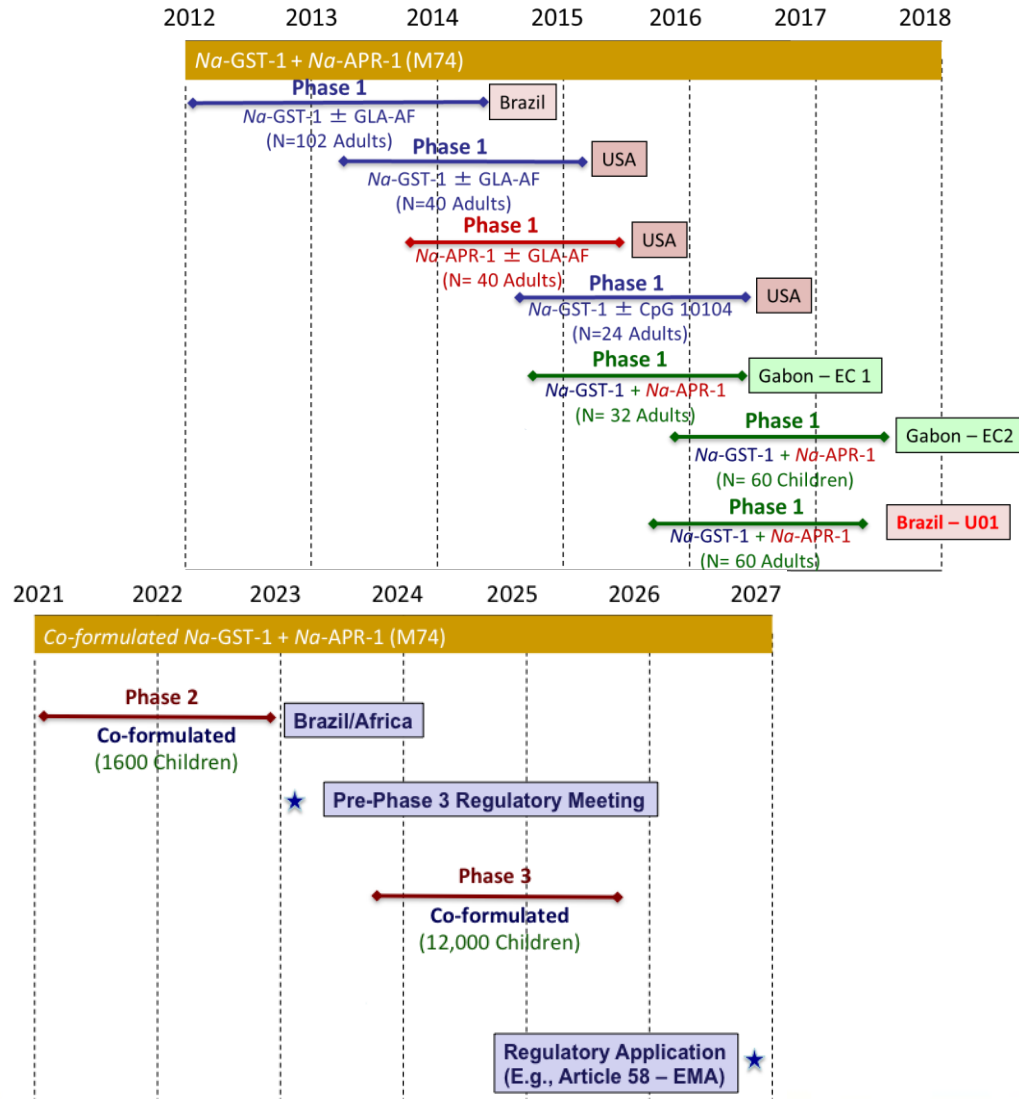
# Clinical and Field Sites Brazil and Gabon



Americaninhas  
Minas Gerais  
Brazil







## TARGET PRODUCT PROFILE FOR HUMAN HOOKWORM VACCINE

**An injectable single or bivalent recombinant protein-based vaccine**

1 or 2 recombinant antigens + 1-2 adjuvants  
1 or 2 doses

**Targets moderate and heavy infections by *Necator americanus***

Prevention of hookworm-related iron-deficiency anemia & related sequelae

**Pre-school and school-aged children (< 10 years)**

*N. americanus* endemic regions  
Latin America, Caribbean, sub-Saharan Africa and Southeast Asia

**Pediatric population**

Iron deficiency anemia caused by chronic moderate and heavy infections  
Severe growth, developmental, and cognitive impairments

**Vaccinations incorporated into existing mass drug administration programs**



# Demand Forecasting Assumptions

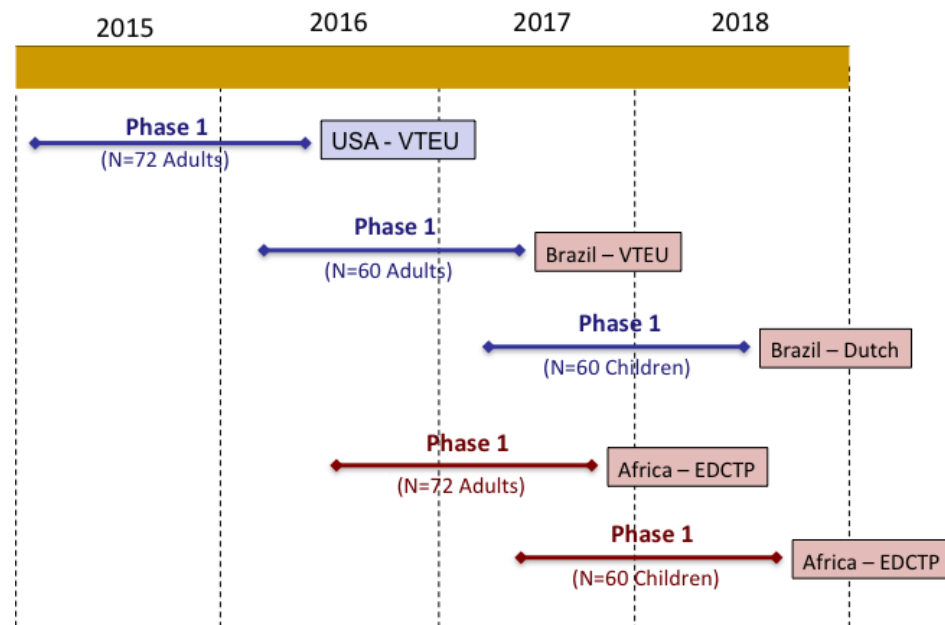
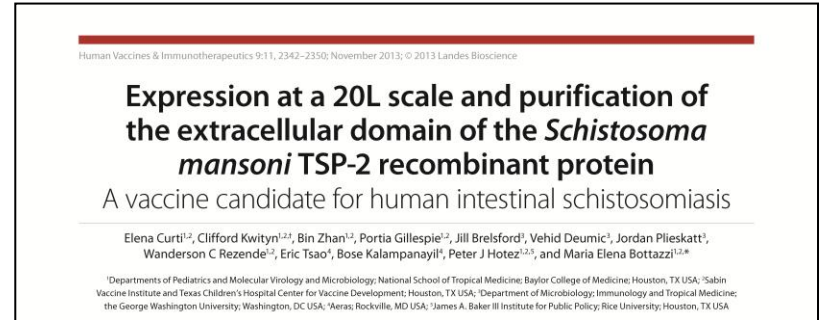
- **Target Population**
  - 876.2 million pre-school and school-age children who currently require preventive chemotherapy for STH infections worldwide
  - [http://www.who.int/gho/neglected\\_diseases/soil\\_transmitted\\_helminthiases/en/](http://www.who.int/gho/neglected_diseases/soil_transmitted_helminthiases/en/)
- **Three doses per child**
  - 10 micrograms per dose (for lowest dose quantity)
  - 100 micrograms per dose (for highest dose quantity)
- **A single age new cohort is immunized each year, approximately 100 million children worldwide**
- **Required production of each antigen**
  - 26,286 grams of each antigen (low dose quantity)
  - 144,573 grams of each antigen (mean dose quantity)
  - 262,860 grams of each antigen (high dose quantity)
- **Required doses**
  - 3 billion doses of vaccine (single vial formulation) over 3-years
- **Worldwide Mean** approximate total manufacturing cost per dose estimated to be \$0.24 (2010 US Dollars)



# Sm-TSP-2 Schistosomiasis Vaccine

## Targeting Hookworm and Schistosomiasis Co-Infections

- **Platform:** *Pichia* PINK
- **Insert:** wild type fragment; no tags
- **Amino Acids:** 107-184
- **Production yields:** 1.2 g/10L
- **Formulation:** 0.1 mg/mL Sm-TSP-2 with 0.8 mg/mL Alhydrogel® in a buffer containing 15% Sucrose, 10 mM imidazole, 2mM Phosphate, pH 7.4
- **DP cGMP MFG:** Aeras  
December 17, 2011





# Pan-Helminthic Vaccine under Development

Review

EXPERT  
REVIEWS

## Advancing a multivalent 'Pan-anthelmintic' vaccine against soil-transmitted nematode infections

Expert Rev. Vaccines Early online, 1–11 (2014)

Bin Zhan<sup>1\*</sup>,  
Coreen M Beaumier<sup>1,2\*</sup>,  
Neima Briggs<sup>1,2\*</sup>,  
Kathryn M Jones<sup>1</sup>,  
Brian P Keegan<sup>1</sup>,  
Maria Elena Bottazzi<sup>1\*</sup>  
and Peter J Hotez<sup>1\*</sup>

<sup>1</sup>Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX, USA  
<sup>2</sup>Medical School/Graduate School of Biomedical Sciences, University of Texas Health Science Center (UTHealth), Houston, TX, USA

\*Authors for correspondence:  
hotez@bcm.edu  
bottazzi@bcm.edu

<sup>†</sup>Authors contributed equally

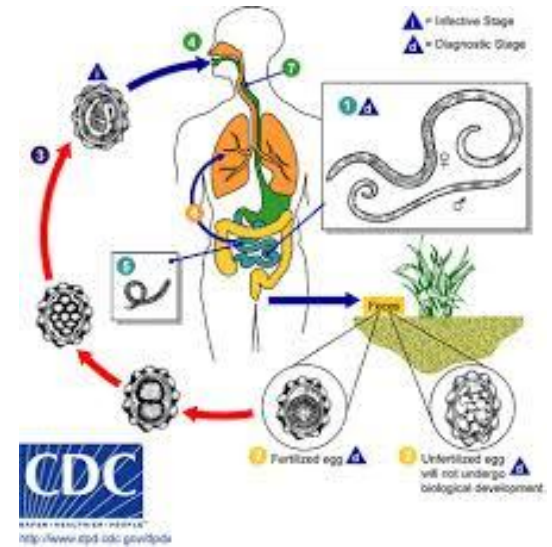
The Sabin Vaccine Institute Product Development Partnership is developing a Pan-anthelmintic vaccine that simultaneously targets the major soil-transmitted nematode infections, in other words, ascariasis, trichuriasis and hookworm infection. The approach builds off the current bivalent Human Hookworm Vaccine now in clinical development and would ultimately add both a larval *Ascaris lumbricoides* antigen and an adult-stage *Trichuris trichiura* antigen from the parasite stichosome. Each selected antigen would partially reproduce the protective immunity afforded by UV-attenuated *Ascaris* eggs and *Trichuris* stichosome extracts, respectively. Final antigen selection will apply a ranking system that includes the evaluation of expression yields and solubility, feasibility of process development and the absence of circulating antigen-specific IgE among populations living in helminth-endemic regions. Here we describe a five year roadmap for the antigen discovery, feasibility and antigen selection, which will ultimately lead to the scale-up expression, process development, manufacture, good laboratory practices toxicology and preclinical evaluation, ultimately leading to Phase 1 clinical testing.

**Keywords:** *Ascaris lumbricoides* • *Ascaris suum*, deworming • geohelminth • hookworm • intestinal helminth • *Necator americanus* • Pan-anthelmintic vaccine • soil-transmitted helminth • soil-transmitted nematode • *Trichinella spiralis* • *Trichuris muris* • *Trichuris trichiura*

### Rationale for a Pan-anthelmintic vaccine

The three major soil-transmitted nematode infections, in other words, ascariasis, trichuriasis and hookworm infections, are highly prevalent neglected tropical diseases that rank near the top of the list of most common human afflictions [1]. According to some estimates, approximately 800 million people are infected with the roundworm, *Ascaris lumbricoides*, and 600 million people with the whipworm, *Trichuris trichiura* or hookworms, mostly by *Necator americanus* [1,2]. There is widespread geographical overlap of these three soil-transmitted nematode infections (also referred to as soil-transmitted helminth, intestinal helminth, intestinal nematode or geohelminth infections) in impoverished areas of sub-Saharan Africa, East Asia and South Asia and tropical regions of Central and South America [3]. Coinfections with two or even all three

soil-transmitted nematode infections are extremely common in children [2,3]. The WHO currently estimates that 874.5 million children are infected or exposed to *A. lumbricoides*, *T. trichiura* and hookworms, and therefore, require regular and periodic anthelmintic treatment ('deworming') (Table 1) [4]. Such children are often chronically infected and suffer from long-term disabling consequences including growth stunting, reductions in physical fitness, and cognitive and intellectual delays [2]. Moreover, there are millions of pregnant women in developing countries with soil-transmitted nematode infections, especially hookworm infection [5]. Recent estimates from the Global Burden of Disease Study 2010 indicate that soil-transmitted nematode infections are responsible for 5.18 million disability-adjusted life years, which leads all neglected tropical diseases [6]. In addition, ascariasis is responsible for 2,700 deaths annually [7].

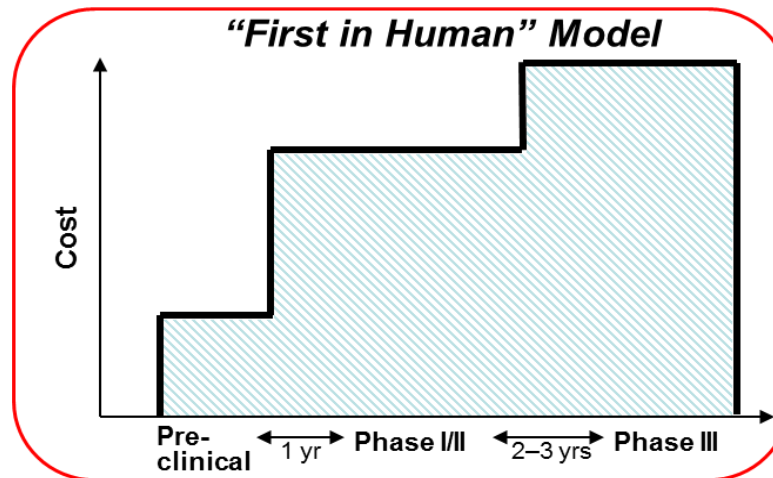


Trichuris stichosome



# Key Strategies for Global Access

- Complete business case for the human hookworm vaccine
- Engage in partnership discussions with **DCVM Network**
- Discussions with potential Phase 2/3 funders, including grant funding, private investment and loan financing
- Advance WHO/GAVI discussions to encourage prioritization of NTD vaccine uptake



**Success** = Expansion of target pipeline



**Success** = Licensure



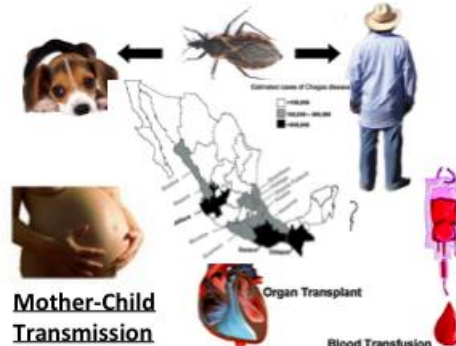
# NTD Vaccine Diplomacy

## Impact on Foreign Policy and Areas of Conflict

Siete razones por las que Europa debe ocuparse del Chagas



### Chagas Disease



“Aleppo Evil” قرحة حلب  
: The Ulcer, the Boil,  
the Sand-fly, and the  
Conflict

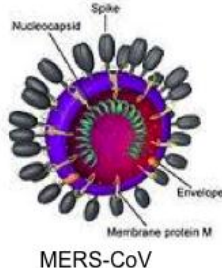
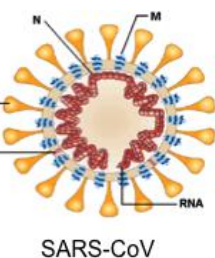


### Organization of Islamic Cooperation & NTDs

#### Yeast-expressed recombinant protein of the receptor-binding domain in SARS-CoV spike protein with deglycosylated forms as a SARS vaccine candidate

Wen-Hsiang Chen<sup>1,2</sup>, Lanying Du<sup>1,2</sup>, Shirali M Chag<sup>1</sup>, Cuiqing Ma<sup>1</sup>, Nancy Tricoche<sup>1</sup>, Xinrong Tao<sup>1</sup>, Christopher A Seid<sup>1</sup>, Elissa M Hudspeth<sup>1</sup>, Sara Lustigman<sup>1</sup>, Chien-Te K Tseng<sup>1</sup>, Maria Elena Bottazzi<sup>1</sup>, Peter J Hotez<sup>1,2</sup>, Bin Zhan<sup>3,4</sup>, and Shibo Jiang<sup>1,2,3,4</sup>

<sup>1</sup>Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX, USA; <sup>2</sup>Yankee F. Medical Research Institute, New York Blood Center, New York, NY, USA; <sup>3</sup>Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX, USA; <sup>4</sup>Key Laboratory of Medical Molecular Biology of MOE, Shanghai Medical College and Institute of Medical Microbiology, Fudan University, Shanghai, PRC



Disease Targeted (Approximate Number of People Affected)	Affected Geographic Areas of Interest to US Foreign Policy Interests	Stage of Development
Human hookworm infection (400 million)	OIC countries in Africa, the Middle East, and Asia India and China	Phase 1
Schistosomiasis (250 million)	OIC countries in Africa and the Middle East	Completed current good m manufacture
Ascariasis and Trichuriasis (>800 million)	OIC countries in Africa, the Middle East, and Asia India and China	Preclinical
Leishmaniasis (10 million)	Areas of conflict in the Middle East and North Africa, including OIC countries	Preclinical
Chagas disease (7-8 million)	Venezuela, Ecuador, Bolivia	Preclinical
SARS (None currently)	China	Preclinical

Hotez PJ (2014) “Vaccine Diplomacy”: Historical Perspectives and Future Directions. PLoS Negl Trop Dis 8(6): e2808.  
doi:10.1371/journal.pntd.0002808 <http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0002808>





# Current Funding Streams

- NIAID, NIH
- European Union
- Dutch Ministry of Foreign Affairs
- Gates Foundation
- Carlos Slim Foundation
- SWEEMRI
- Kleberg Foundation
- HNW Individuals: Gary Michelson, Len Blavatnik, Chao Foundation
- Brighton Biotech Inc.
- University of Malaysia
- Texas Children's Hospital



National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
U.S. Department of Health and Human Services  
[www.niaid.nih.gov](http://www.niaid.nih.gov)



Ministry of Foreign Affairs



FUNDACIÓN  
*Carlos Slim*



Robert J. Kleberg, Jr.

and

Helen C. Kleberg Foundation



# THANK YOU

## Contact Information

**Sabin Vaccine Institute**  
2000 Pennsylvania Ave, NW  
Suite 7100  
Washington, DC 20006  
+1 (202) 842-5025

**Sabin Vaccine Institute Product  
Development Partnership**  
1102 Bates Ave  
Suite 1470  
Houston, TX 77030

[www.sabin.org](http://www.sabin.org)  
[@SabinVaccine](https://twitter.com/SabinVaccine)

**Dr. Peter J. Hotez**  
President  
Director, Sabin PDP  
[hotez@bcm.edu](mailto:hotez@bcm.edu)  
+1 (713) 798-1199

**Dr. Maria Elena Bottazzi**  
Deputy Director, Sabin PDP  
Director, Product Development  
[bottazzi@bcm.edu](mailto:bottazzi@bcm.edu)  
+1 (832) 824-0510

**Dr. David Diemert**  
Director, Clinical Trials  
[ddiemert@gwu.edu](mailto:ddiemert@gwu.edu)  
+1 (202) 994-2909

**Dr. Jeffrey Bethony**  
Director, Clinical Immunology  
[jbethony@gwu.edu](mailto:jbethony@gwu.edu)  
+1 (202) 994-3535

**Tara Hayward**  
Director, Resource Development  
[tara.hayward@sabin.org](mailto:tara.hayward@sabin.org)  
+1 (202) 683-1881



Twitter: @mebottazzi

@sabinvaccine

Email: [bottazzi@bcm.edu](mailto:bottazzi@bcm.edu)

