Novel Technologies

Vaccines against Neglected Diseases

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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

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 trematodiases
- 67% Leishmaniasis
- 61% Dengue
- 61% Chagas disease
- 60% Lymphatic filariasis
- 50% Helminth infections

Hotez PJ Foreign Policy March 2013
http://www.foreignpolicy.com/articles/2013/03/25/the_disease_next_door
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.
Built structure
Launched Hookworm Program

2000 to 2004

Expanded Hookworm Program
Schisto Program
Relocated to TMC

2004 to 2011

Added 7 additional programs
Expansion of capabilities

2011 to 2015

Program and Portfolio Growth
Governance and Core Competencies

VDEB
- Director and Deputy Director
- Functional Unit Leaders
- Collaborators and Partners

A unique partnership model embedded within an Academic Health Sciences Center
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

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

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 Naras Goud, Vehid Deumic, Richi Gupta, Jill Brelsford, Bin Zhan, Portia Gillespie, Jordan L. Plieskatt, Eric L. Tsao, Peter J. Hotez, Maria Elena Bottazzi

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*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

*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

- **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

Advancing a multivalent ‘Pan-anthelmintic’ vaccine against soil-transmitted nematode infections

Bin Zhan, Corleen M Beaumier, Nelline Briggs, Kathryn M Jones, Brian P Keegan, Maria Elena Bottazzi and Peter J Hotez

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, ascariosis, trichuriasis and hookworm infection. The approach builds off the current bivalent Human Hookworm Vaccine now in clinical development and would ultimately add both a single 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 Un-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 IgG among populations living in helminth-endemic regions. Here we describe a three- to 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 toxicity and preclinical evaluation, ultimately leading to Phase 1 clinical testing.

Rationale for a Pan-anthelmintic vaccine

The three major soil-transmitted nematode infections, in other words, ascariosis, trichuriasis and hookworm infections, are highly prevalent neglected tropical diseases that rank near the top of the list of most common human affections [1]. According to some estimates, approximately 180 million people are infected with the roundworm, Ascaris lumbricoides, and 600 million people with the whipworm, Trichuris trichiura, or hookworms, mostly by Necator americanus [2]. There is widespread geographical overlap of these three soil-transmitted nematode infections (also referred to as soil-transmitted helminths, intestinal helminths, intestinal nematode or gastro-intestinal 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 [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 (‘de-worming’) [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 [5]. Moreover, these 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 2018 indicate that soil-transmitted nematode infections are responsible for 5.18 million disability-adjusted life years, which leads all neglected tropical diseases [5]. In addition, ascariosis is responsible for 2,700 deaths annually [7].
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

"First in Human" Model

Success = Expansion of target pipeline

The pull

The push

Success = Licensure
NTD Vaccine Diplomacy
Impact on Foreign Policy and Areas of Conflict

Chagas Disease

Organization of Islamic Cooperation & NTDs

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

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
THANK YOU

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