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Schistosomiasis Vaccine Updates

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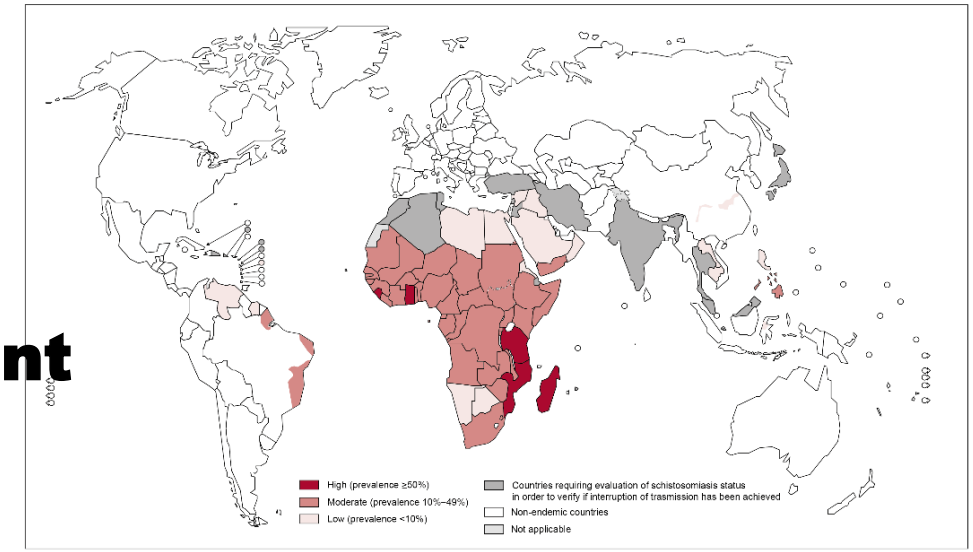
Outline of Presentation

- **Rationale for a Schistosomiasis Vaccine**
  - ***Burden of Disease***
  - ***Objectives and Comparative Advantages***
  - ***Scientific and Technical Feasibility***
- **Current Status of R&D Efforts**
- **Challenges, Gaps and Opportunities**

Schistosomiasis: Burden of Disease

- ~700M people in 78 countries at risk
- ~258M in need of treatment (2014)
  - 61.6M received treatment
- Tens of millions debilitating chronic morbidity
  - 3.31M Disability-Adjusted Life Year (DALY) annually

Distribution of schistosomiasis, worldwide, 2011



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Hotez et al. PLOS NTD, 2014, July Vol. 8
http://www.who.int/mediacentre/factsheets/fs115/en/

Pathology of Schistosomiasis

- **Acute**
  - ***Allergic dermatitis***
  - ***Katyama fever***
- **Chronic**
  - ***Hepato-splenomegaly***
  - ***Cystitis and urethritis w/ hematuria***
- **Sequelae**
  - ***Bladder cancer***
  - ***Female infertility***
  - ***Risk of HIV transmission ↑***

Affected Organs	Species	Geographical distribution
Hepatic-Intestinal	*S. mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	S. japonicum	China, Indonesia, the Philippines
Urogenital	*S. haematobium*	Africa, the Middle East, Corsica (France)

Schistosomiasis Vaccines: An Identified Priority

The Most Feasible and Needed

(*Science, January 2016)*

- Ebola Sudan
- Chikungunya
- MERS
- Lassa fever
- Marburg
- Paratyphoid fever
- Schistosomiasis
- Rift Valley fever
- SARS
- Hookworm

The Most Important Diseases Without Vaccines

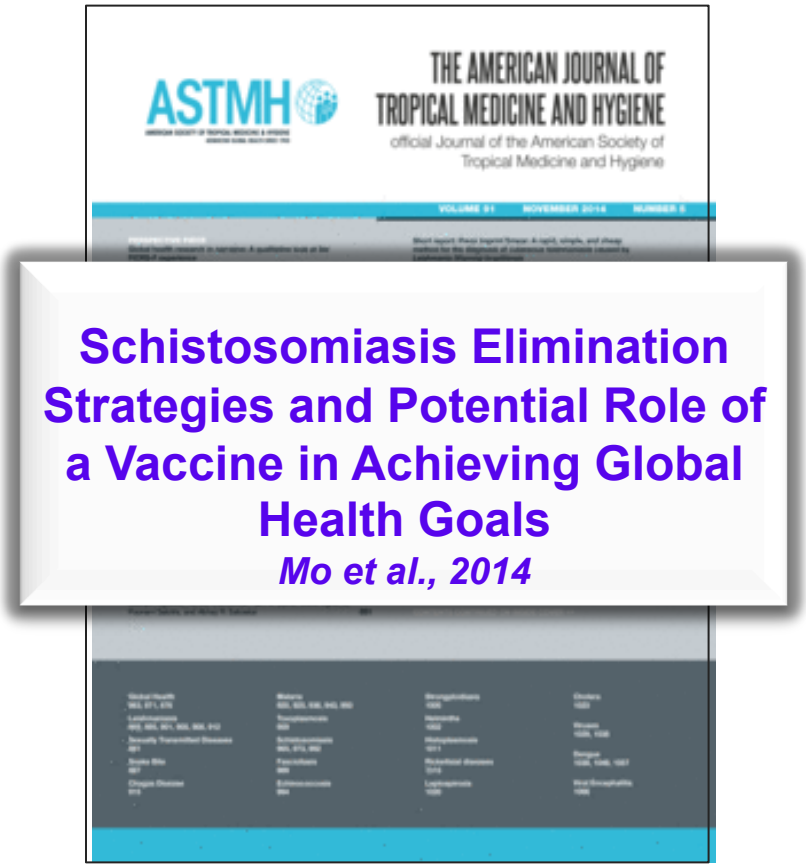
(Vaccine Nation, 14 August 2013)

- Chagas' Disease
- Chikungunya
- Cytomegalovirus
- Dengue
- HIV
- Hookworm
- Leishmaniasis
- Malaria
- Respiratory Syncytial Virus
- Schistosomiasis

Global Funding for Schistosomiasis R&D

- Global funding for schistosomiasis for the period 2007-2014 amounted to ~$214M.
- During the same period, ~16% ($35M) of these funds were invested in vaccine R&D.

Role of Schistosomiasis Vaccines

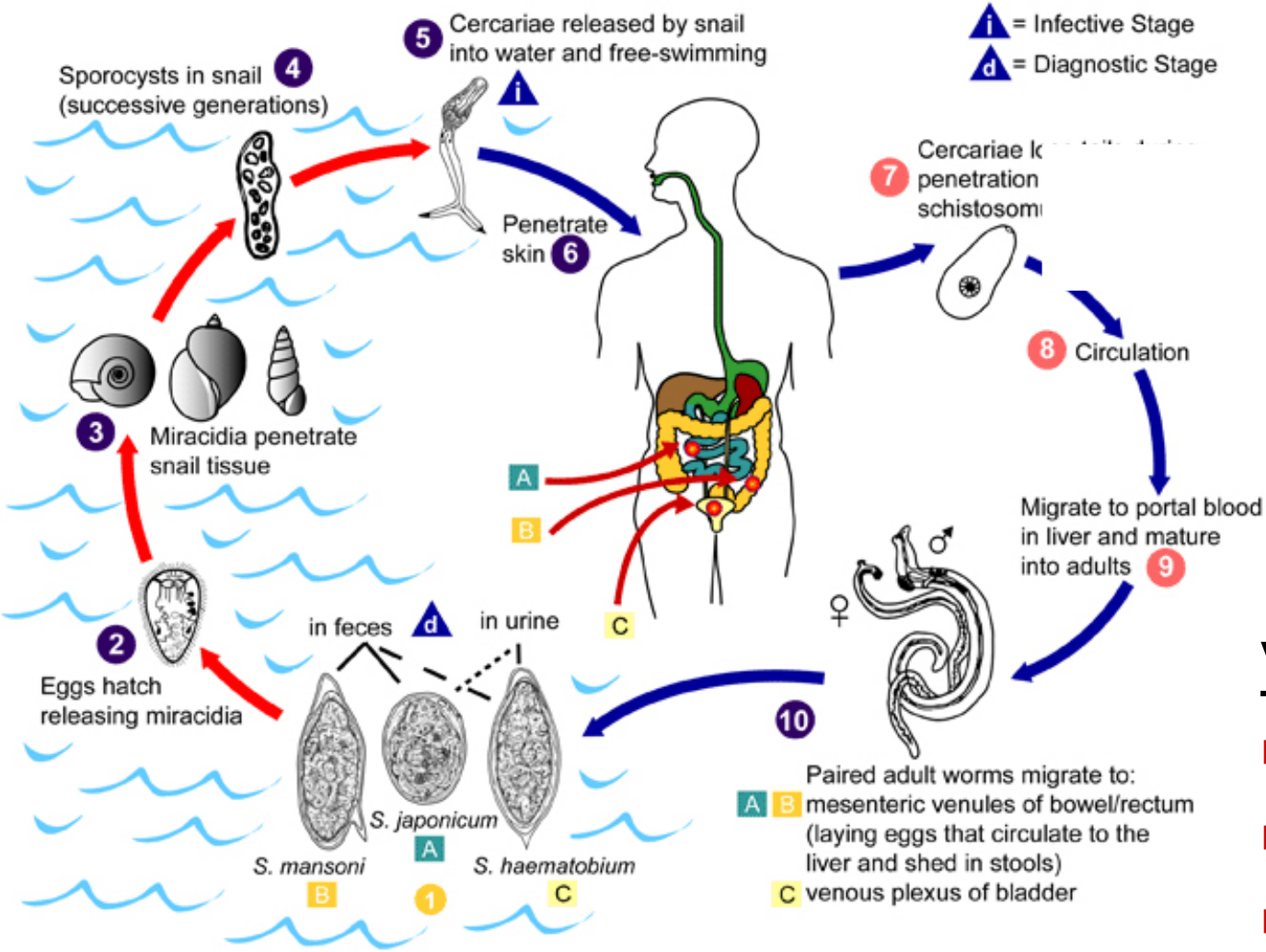


- Global elimination achievable in some focal areas through MDA;
- Integrated approach with other intervention needed;
  - *e.g., vaccine*
- Vaccine strategies complementary to existing control programs;
- Target to different forms of schistosomiasis.

Schistosomiasis Vaccine: Scientific Rationale

- **Age-dependent concomitant immunity;**
- **Putative resistant individuals (endemic normals);**
- **Irradiated cercariae conferring up to 80% protection in animals;**
- **Significant efficacy with recombinant veterinary vaccines against other multicellular parasites**
  - ***cysticercosis (Taenia solium)***
  - ***cystic echinococcosis (Echinococcus granulosus)***

Schistosoma Life Cycle &Vaccine Antigens



Candidates:

Sh28 GST
Sm14
Sm-TSP2
Sm-p80

Vaccine Targets:

- **Anti-infection**
- **Anti-morbidity**
- **Transmission blocking**

Sh28GST(Glutathione-S-Transferase)/Alum Vaccine for Urinary Schistsomiasis Recurrences

Phase I (Vaccine)

Phase Ia
Healthy Adult (Europe)
N=24
Safety&Imm.

↓

Phase Ib
Healthy Children (Senegal)
N=24
Safety&Imm.

Phase II (Vaccine+PZQ Treatment)

Phase IIa/b
Infected Adult (Senegal)
N=40
Safety&Imm.

↓

Phase IId
Infected Children (Niger)
N=24
Safety &Imm.

Phase III (Vaccine+PZQ Treatment)

Phase III
Infected Children (Senegal)
N=250
Efficacy (delay in pathological relapses), Safety&Imm
3 year follow-up after 1st immunization

Safety and Immunogenicity of rSh28GST Antigen in Humans: Phase 1 Randomized Clinical Study of a Vaccine Candidate against Urinary Schistosomiasis

PlosNTD, 2012

Gilles Riveau[1]*, Dominique Deplanque[2,3], Franck Remoué[1], Anne-Marie Schacht[1], Hubert Vodougnon[2], Monique Capron[1], Michel Thiry[4], Joseph Martial[4], Christian Libersa[2,3], André Capron[1]

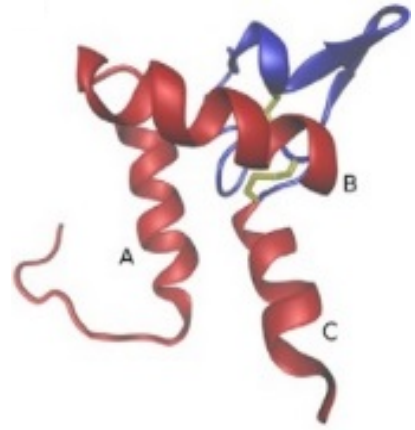
1 Inserm – Université Lille 2, Institut Pasteur de Lille, Lille, France, 2 Inserm CIC-CRB 9301, CHRU, Lille, France, 3 Université Lille – Nord de France, Département de Pharmacologie Médicale, Faculté de Médecine, Lille, France, 4 Eurogentec, Parc Scientifique, Seraing, Belgium

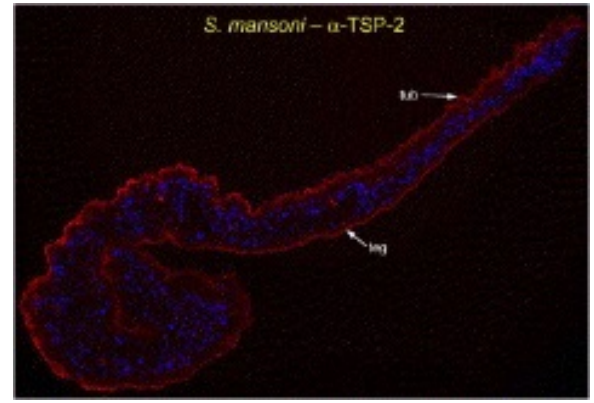
Sm-14/GLA-SE Vaccine Candidate

- **Fatty acid binding protein, supports fatty acid transportation;**
- **65-90% protection against *S.m.* challenges;**
- **Complete protection against *Fasiola hepatica* challenges;**
- **Development path:**
  - **Veterinary use again liver fluke**
  - **Human vaccine against *Schistosoma***
- **Phase I trial in Brazil completed: safe&immunogenic (Vaccine, 2016);**

Sm Tetraspanin Vaccine: Sm-TSP2/Adjuvant

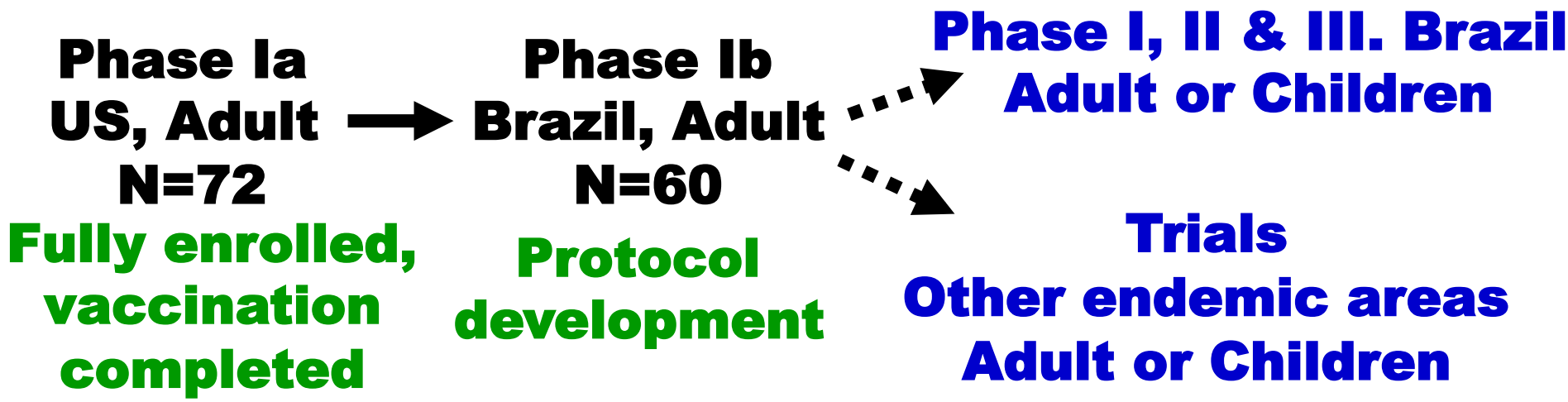
- **Large extracellular domain of the Sm-TSP2, 9 kDa, expressed in *Pichia;***
- **On the surface of the parasite tegument, important for parasite development and maturation;**
- **Response to IgG of putatively resistant individuals;**
- **Reducing adult worm (50-60%) and eggs (60-75%) in *S.m.* infected mouse model.**



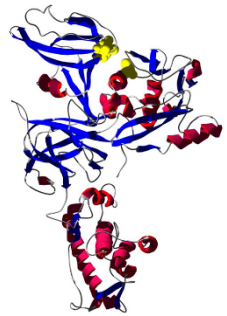


Tran et al Nat Med, 2006
Loukas et al, International J Path., 2006
Curti, et al, Hum Vac Immu 2013
Jia et al, JBC, 2014

Sm-TSP/Adjuvant Clinical Evaluation in the Field

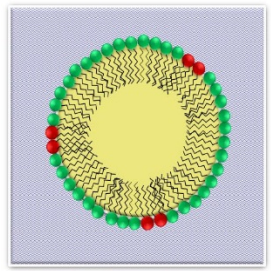


The Sm-p80 Vaccine Reduced Worm Burden, Egg Shedding, and Pathology in Baboons

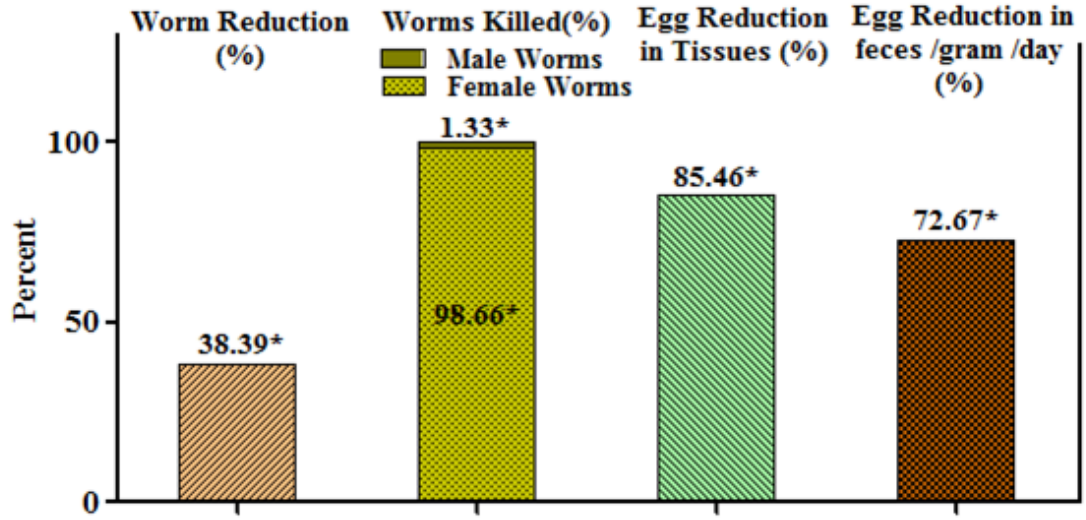


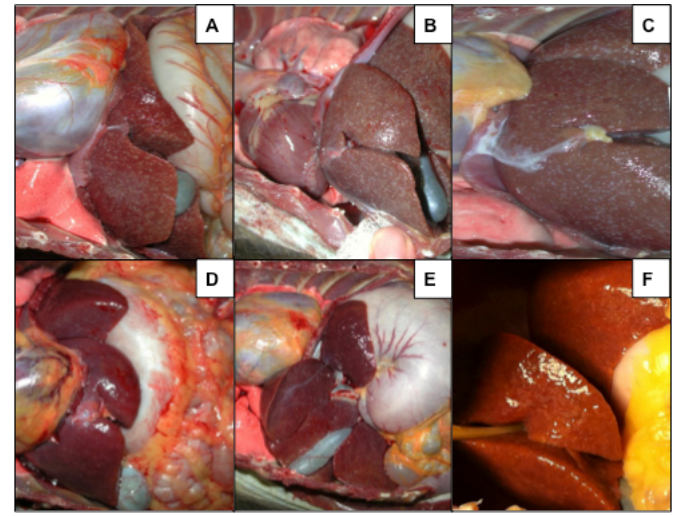
Calpain subunit Sm-p80

+



GLA-SE



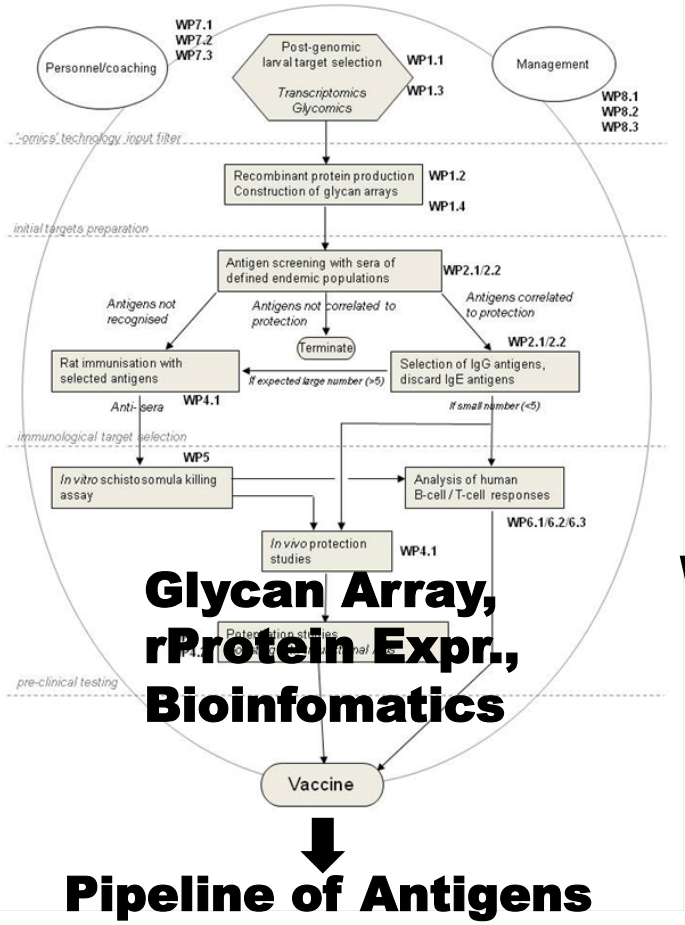


Control

Vaccinated

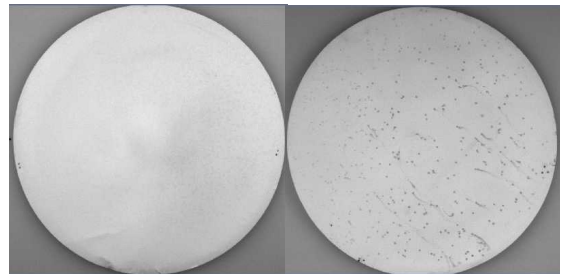
>> cGMP production 4Q2017

Antigen Discovery via Differential Screening Using Samples from Endemic Areas

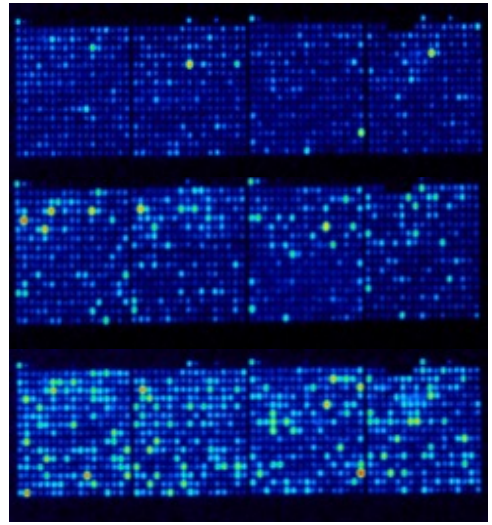


Glycan Array, rProtein Expr., Bioinfomatics

Pipeline of Antigens



Whole Proteom Library Phase Display (~10^6 clones)



Protein Array (992 Proteins, 1600 Arrays)

Paravac, SchistoVac Projects (funded by EU)

NIH R01AI101274

NIH P50 AI098507

Challenges and Opportunities: Preferred Product Characteristics &Clinical Development

Schistosomiasis Vaccine Clinical Development and Product Characteristics
Mo et al., 2015

- **Modeling is valuable in defining TPP**
- **Provide >75% protection against infection for 2-3 yrs**
  - ***Parasite(s): all three parasites preferred;***
  - ***Target population: High risk adults or school age children;***
- **Clinical evaluation is feasible**
  - ***Efficacy readout: egg output (or worm burden);***
  - ***Sensitive assays for efficacy trials need to be established;***
  - ***Human challenge model for testing deemed not feasible at the time.***
- **Collaborative research & synergized effort are encouraged**

Summary

- A vaccine is needed to achieve and sustain the ultimate control and elimination;
- Clinical evaluation in the field is possible;
- New vaccine candidates are on the horizon;
- Vaccine R&D pipeline are weak;
- Collaboration and partnership are needed.

Thank You!