New Poverty-Related Neglected Diseases ('The NTDs')

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@PeterHotez
From the MDGs to the SDGs

2000-15 MDGs
The Millennium Development Goals

1. Eradicate extreme poverty and hunger.
2. Achieve universal primary education.
3. Promote gender equality and empower women.
4. Reduce child mortality.
5. Improve maternal health.
7. Ensure environmental sustainability.
8. Develop a global partnership for development.
Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010

The Global Burden of Disease 2013

Expanded use of vaccines
- 83% reduction in measles deaths
- 82% reduction in tetanus deaths
- 57% reduction in diphtheria/pertussis deaths
- 45% reduction in Hib deaths

Development new vaccines
- Pneumococcal disease (36% reduction in deaths)
- Rotavirus (63% reduction in deaths)

2.5 million childhood lives saved through these initiatives
The spread of anti-vax sentiment in California

Share of public school kindergartners with personal belief exemptions to vaccination requirements

2000  2007  2013

Source: California Department of Public Health
• Texas ranks at the bottom of fully immunized children
• 45,000 Personal Belief Exemptions in Texas
Patches of Disorganization in the Neocortex of Children with Autism

Rich Stoner, Ph.D., Maggie L. Chow, Ph.D., Maureen P. Boyle, Ph.D., Susan M. Sunkin, Ph.D., Peter R. Mouton, Ph.D., Subhojit Roy, M.D., Ph.D., Anthony Wynshaw-Boris, M.D., Ph.D., Sophia A. Colamarino, Ph.D., Ed S. Lein, Ph.D., and Eric Courchesne, Ph.D.

ABSTRACT

BACKGROUND
Autism involves early brain overgrowth and dysfunction, which is most strongly evident in the prefrontal cortex. As assessed on pathological analysis, an excess of neurons in the prefrontal cortex among children with autism signals a disturbance in prenatal development and may be concomitant with abnormal cell type and
The Millennium Development Goals

1. Eradicate extreme poverty and hunger.
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4. Reduce child mortality.
5. Improve maternal health.
7. Ensure environmental sustainability.
8. Develop a global partnership for development.
Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013

“Other Diseases”

The Neglected Tropical Diseases

- 13-14 tropical infections:
  - Highly prevalent among the poor
  - Endemic in rural areas of low-income countries
  - Ancient afflictions
  - Chronic
  - Disabling (growth delays, blindness or disfigurement)
  - Stigmatizing
  - Poverty promoting
### NEGLECTED TROPICAL DISEASES:
NTDs infect more than 1 BILLION of the world’s poorest people

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of People Infected</th>
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<tbody>
<tr>
<td>Trachoma</td>
<td>3.6 million</td>
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<tr>
<td>Cysticercosis</td>
<td>1.9 million</td>
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<tr>
<td>Echinococcosis</td>
<td>1.4 million</td>
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<tr>
<td>Hansen’s Disease</td>
<td>514,200</td>
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<tr>
<td>Rabies</td>
<td>17,400</td>
</tr>
<tr>
<td>African Trypanosomiasis</td>
<td>10,700</td>
</tr>
<tr>
<td>Guinea worm</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>Yaws</td>
<td>Not determined</td>
</tr>
<tr>
<td>Buruli ulcer</td>
<td>Not determined</td>
</tr>
<tr>
<td>Mycetoma</td>
<td>Not determined</td>
</tr>
<tr>
<td>Zika</td>
<td>4 million</td>
</tr>
<tr>
<td>Ebola</td>
<td>2,800</td>
</tr>
<tr>
<td>Ascariasis</td>
<td>761.9 million</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>463.7 million</td>
</tr>
<tr>
<td>Hookworm Disease</td>
<td>428.8 million</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>252.2 million</td>
</tr>
<tr>
<td>Dengue and other arboviruses</td>
<td>79.6 million</td>
</tr>
<tr>
<td>Food-borne trematodiases</td>
<td>71.1 million</td>
</tr>
<tr>
<td>Lymphatic Filariasis</td>
<td>38.5 million</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>15.5 million</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>6.7 million</td>
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<tr>
<td>Leishmaniasis</td>
<td>3.9 million</td>
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<tr>
<td>Cysticercosis</td>
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<td>Echinococcosis</td>
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<td>Zika</td>
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<tr>
<td>Ebola</td>
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</tbody>
</table>
“It’s quite a problem for me when I have to stand at work for long periods.”

Lymphatic Filariasis ("Elephantiasis")
NTDs and Girls & Women
Female Genital Schistosomiasis

Zimbabwe
OR = 3 increase in HIV/AIDS
Kjetland et al. AIDS 2006

Tanzania
OR = 4 increase in HIV/AIDS
Downs et al. AJTMH 2011

100 million girls & women
Africa’s most common gynecologic condition?

Current Commentary
Helminth Infections
A New Global Women’s Health Agenda
Peter Hotez, MD, MPH, and Megan Whalen

Emerging evidence over the past decade has implicated helminth infections as important yet underrecognized causes of adverse pregnancy outcomes and impaired women’s reproductive health. The two most important helminth infections affecting women living in poverty in Africa and elsewhere in the developing world are hookworm infection and schistosomiasis. In Africa alone, almost 40 million women of childbearing age are infected with hookworms, including about 7 million pregnant women who are at greater risk of severe anemia, higher mortality, and experiencing poor maternal outcomes (reduced birth weight and increased infant mortality). Possibly, tens of millions of women in Africa also suffer from female genital schistosomiasis associated with genital itching and pain, gross incongruence, dyspareunia, and mental to better link global health programs for HIV and AIDS and work with helminth control and to simultaneously launch initiatives for research and development.

Most obstetricians and gynecologists do not routinely think about parasitic worm (helminth) infections nor see them as central or perhaps even relevant to their clinical practice. However, new information published within the last decade has revealed that helminth infections are responsible for a huge but mostly hidden or unreported burden of morbidity among young women living in Africa and other developing regions.
The Bottom Billion Suffers from Multiple NTDs!

Ascariasis, Trichuriasis, Hookworm, Schistosomiasis, LF, Onchocerciasis, Trachoma

Hotez PJ et al. Lancet 2009
NTD Scale up with the U.S. Government + Drug Donations from

43.
George W. Bush 2001-2009
USAID NTD Program

>450 million People Rx: Elimination of some NTDs
## 10 Significant Gains

<table>
<thead>
<tr>
<th>Disease</th>
<th>Improvement</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic filariasis</td>
<td>-52%</td>
<td>2005-2015</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>-52%</td>
<td>1990-2013</td>
</tr>
<tr>
<td>Trachoma</td>
<td>-65%</td>
<td>1990-2013</td>
</tr>
<tr>
<td>Ascariasis</td>
<td>-20%</td>
<td>2005-2015</td>
</tr>
<tr>
<td>Yaws</td>
<td>Not determined</td>
<td></td>
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<tr>
<td>African trypanosomiasis</td>
<td>-78%</td>
<td>2005-2015</td>
</tr>
<tr>
<td>Dracunculiasis</td>
<td>-99%</td>
<td>1990-2013</td>
</tr>
<tr>
<td>Rabies (Canine)</td>
<td>-53%</td>
<td>2005-2015</td>
</tr>
<tr>
<td>Cysticercosis</td>
<td>-21%</td>
<td>2005-2015</td>
</tr>
<tr>
<td>Leprosy</td>
<td></td>
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</tbody>
</table>

### Elimination Targets:
- LF
- Trachoma
- Yaws
- African trypanosomiasis
- Dracunculiasis
- Leprosy (Hansen’s Disease)

Source: GBD 2015 and GBD 2013
<table>
<thead>
<tr>
<th>Mass Drug Administration (MDA)</th>
<th>Case detection + Rx + Vector control</th>
<th>WASH</th>
<th>Other approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworm -5% (1990-2013)</td>
<td>Chagas disease +22% (1990-2013)</td>
<td>Coronaviruses</td>
<td></td>
</tr>
<tr>
<td>Trichuriasis -12% (1990-2013)</td>
<td>Dengue &amp; Other Arbovirus Infections +610% (1990-2013)</td>
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</tr>
</tbody>
</table>

**Losing the Battle:**
Vector-borne Neglected Diseases
Arthropods
Snails
Zoonotic Neglected Diseases
Viral Diseases

Source: GBD 2015 and GBD 2013
Are we playing “global health whack-a-mole”?

MDGs
- AIDS
- Malaria
- Some NTDs
- Childhood dz

SDGs
- NTDs V.2.0
- Vector-borne NTDs
- Zoonotic NTDs
Explosive Outbreaks in the Americas

Emergence of Dengue in the New World in 1980s, 1990s

Emergence of Chikungunya in New World in 2013 (Saint Martin)
Emerging Vector-borne Disease in Southern Europe

Emerging Vector-borne Disease in Southern Europe

Dengue
Malaria
Chikungunya
Schistosomiasis
WNV
Opisthorchiasis

EMERGING VECTOR BORNE NEGLECTED DISEASE IN SOUTHERN EUROPE
The Anthropocene is a proposed epoch that begins when human activities started to have a significant global impact on Earth's geology and ecosystems.
Anthropocene forces promoting NTDs

Poverty

- Deforestation
- Climate Change
- Conflict and Political Destabilization
- Urbanization and Human Migrations
POVERTY: “Blue Marble Health”

- Neglected diseases of the poor living amidst wealth

- A new framework for global science policy and the poverty-related diseases
Blue Marble Health: The poor living among the wealthy (G20 + Nigeria)

WHO + GBD 2013
- 73-78% Leprosy
- 61-78% Chagas
- 60-61% Dengue
- 57-60% TB
- 45-67% VL
- 50-52% Helminths

G20 + Nigeria = 54% Population and 86% Global Economy

http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0002570
Chagas disease in Argentina, Brazil, Mexico

- Ranking By GDP
  1. Brazil
  2. Mexico
  3. Argentina

- Ranking By Chagas
  1. Argentina 1.5 million
  2. Brazil 1.2 million
  3. Mexico 0.9 million
Brazil and Blue Marble Health

Introduction to Brazil

LARGEST Economy in Latin America

5th Largest country by land mass + population

7th Largest economy by nominal GDP

Member MERCOSUL Member BRICS

Poverty & Disease NE Brazil:
Schistosomiasis, Leishmaniasis, Chagas, Dengue
Zika Microcephaly cases in NE Brazil

-Microcephaly rates by state in Brazil, 2015 (cases per 100,000 live births)
  - 1
  - 10
  - 100

-Microcephaly rates by state in Brazil, 2010-2014 (cases per 100,000 live births)
  - 1
  - 5
  - 10

-Countries with Zika confirmed cases
  - in 2015
  - in 2014
  - Country limits
  - Brazil state boundaries

One case of autochthonous transmission of Zika virus infection in Easter Island, Chile, 2014. The presence of the virus was reported until June of the same year and was not detected later.

Data Source:
- Reported from the IHR National Focal Points and through the Ministry of Health websites.

Map Production:
- PAHO-WHO-IDCHA IR ABD
Poverty in Northeastern Brazil

Recife  Salvador de Bahia
Spread of Zika in the Americas

- Countries where the virus is normally found
- Countries where the virus has spread
POVERTY IN TEXAS


Fifth Ward, Houston Texas
Anna Grove

South Texas “Colonias” Shaghayegh Tajvidi.
The Most Vulnerable
Predicted locations of the yellow fever mosquito, which transmits the Zika virus and other diseases.

Source: Moritz U. G. Kraemer et al., eLife Sciences; Simon Hay, University of Oxford
By The New York Times
WAR & POLITICAL DESTABILIZATION: Ebola

Data are based on reported cases up to the end of 13 September 2014 for Guinea and Sierra Leone. Data for Liberia are based on reported cases up to the end of 9 September 2014. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
ISIS-Occupied Syria, Iraq, Libya
Yemen

- Measles/Polio
- Leishmaniasis
- Schistosomiasis
- Brucellosis
- MERS CoV
- Dengue
- Malaria/TB
- Rift Valley Fever
Vaccinating Against The Anthropocene’s NTDs
Pepsi has a new Doritos-flavored Mountain Dew. No, we don't have an Ebola vaccine, but we do have the Doritos-flavored Mountain Dew.

— David Letterman —
Coalition for Epidemic Preparedness Innovations (CEPI)

Presentation to the WHO
21 July, 2017
Professor John-Arne Røttingen, Interim CEO, CEPI

• Building on the WHO R&D blueprint
• Need for improved R&D preparedness for diseases of epidemic potential
• Prioritization of pathogens
• Identification of R&D priorities
• Exploration of funding models for R&D preparedness and response
  Nipah
  Lassa
  MERS CoV

Vaccines
Putting shots in the locker

How to anticipate epidemics
Sep 3rd 2016 | From the print edition

FOREWARNED, the proverb has it, is forearmed. But what happens when there is no warning? That was the case in December 2013, when an outbreak of Ebola haemorrhagic fever began in Guinea. It spread rapidly to Liberia and Sierra Leone and raged on for over a year. Around 20,000 people were infected. More than 11,000 of them died.

The world responded to this crisis, shipping in doctors, nurses and medical equipment. But what it could not ship in, for none existed, was the thing that would most quickly have stopped the epidemic: a vaccine. Such a vaccine was created eventually, but by the time it was ready, the outbreak was all but over. Had it been available from the beginning, things could have been different.

Next time, though, they might be, for on August 31st a new organisation came into being. CEPI, the Coalition for Epidemic Preparedness Innovations, was founded this week in London, at the headquarters of the Wellcome Trust, a medical charity. It is the joint brainchild of the Wellcome, the Bill and Melinda Gates Foundation, the World Economic Forum and the government of Norway, and its purpose is precisely to forewarn the world against future outbreaks of disease, without foreknowledge of what those outbreaks will be.

Paradoxically, part of the inspiration for CEPI’s creation was not the failure to deliver an Ebola vaccine in time for it to be useful, but how close that project came to success. Creating a new vaccine from scratch is a long-winded undertaking, but in the case of Ebola several candidate vaccines were already on the shelf thanks to earlier, but stalled, work by America’s army and that country’s National Institutes of Health. There were also three pharma companies, GlaxoSmithKline, Johnson & Johnson and Merck, willing, pro bono publico, to take these candidates and try to turn them into the real thing as quickly as possible. That they succeeded in doing so by the summer of 2015 was, by most standards, extraordinary
Sabin PDP Pipeline and Disease Portfolio

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
Rino Rappuoli: Reverse Vaccinology

**In silico prediction of vaccine candidate antigens**

- Genome sequence of *Neisseria meningitidis* serogroup B

**600 potential vaccine candidates identified**

- 350 proteins successfully expressed in *E. coli*
- 91 novel surface-exposed proteins identified

**28 novel proteins have bactericidal activity**

**Vaccine candidates selected for development**

- Protein purification
- Testing mouse sera
- Mouse immunization

*Nature Reviews | Immunology*
Reverse vaccinology as a ‘holy grail’ for complex eukaryotic organisms

- Large genomes of similar complexity to human genome
- Inadequacy of bacterial expression systems for eukaryotic antigens
- Low throughput not high throughput
- Deficiencies in animal models
Vaccine Targeting
Hookworm and Schistosomiasis Co-Infections

A MULTIVALENT VACCINE TARGETING HOOKWORM + SCHISTO
Goals of Anti-schistosome Vaccine

- Worm burden reduction
- Egg reduction
- Reduced end-organ pathology
- Reduction in inflammation
- Reduction in anemia and malnutrition
**Immunomics Approach:**

**Schistosome protein microarrays**

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<tr>
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<th>ASC</th>
<th>MTC Uninfected</th>
<th>MTC Infected</th>
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<tbody>
<tr>
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<td>Ctrl</td>
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<tr>
<td>No DNA</td>
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</tbody>
</table>

**Legend:**
- **Red** indicates high expression.
- **Green** indicates low expression.
- **Yellow** indicates intermediate expression.

**Colors:**
- **Red** indicates high expression.
- **Green** indicates low expression.
- **Yellow** indicates intermediate expression.

**Key Proteins:**
- SjDiag, hypothetical protein
- Sj23, 23 kDa integral membrane protein
- Sj22.6, tegumental antigen
- Filamin
- Acetylcholinesterase precursor
- Calponin homolog
- XP 217452 proteol
- Myosin heavy chain
- Hypothetical protein
- SJCutA
- SNaK1
- Tetraspanin TE736
- Sm29
- Putative uncharacterised protein
- Hypothetical protein
- Hyp. prot. /DNA-binding SAP domain
- Phosphoglycerate mutase
- Sm ACTIN 2
- Alkaline phosphatase
- Facilitated glucose transporter 8
Immune localization of *Sm*-TSP-2
Suppression of tsp-2 mRNA expression results in impaired tegument turnover \textit{in vitro}
Intestinal Schistosomiasis Vaccine

Expression at a 20L scale and purification of the extracellular domain of the Schistosoma mansoni TSP-2 recombinant protein

A vaccine candidate for human intestinal schistosomiasis

Elena Curtis1, Clifford Kwiter1,2,3, Bin Duan1, Portia Gillespie1, Jill Kakunda1, Yahia Deumou1, Jordan Plasker1, Wendorf Connell1, Eric Tsung2, Bao Kalempasany3, Peter H Horst1,2, and Maria Berta Bettazzi1,2,4

Departments of Pediatrics and Medicine and Microbiology/Immunology, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX 77030; Department of Microbiology/Immunology and Tropical Medicine, the George Washington University, Washington, DC, USA; Henry Ford Health System; James A. Baker III Institute for Public Policy, Rice University, Houston, TX 77030

Current affiliations: Redwood Cytokine, Inc., Chula Vista, CA

Keywords: Schistosomiasis, Schistosomes, vaccine, S. mansoni, TSP-2, schistosome and parasitic vaccine

A novel recombinant protein vaccine for human schistosomiasis caused by Schistosoma mansoni is under development. The S. mansoni TSP-2 recombinant protein is comprised of a S. mansonii tetraspanin protein corresponding to the extracellular domain of Schistosoma mansoni TSP-2. We describe for the first time the expression and purification of the extracellular domain of S. mansoni TSP-2 recombinant protein secreted by Pichia pastoris. The protein is highly purified and is a candidate for Phase 1 clinical trials.

Introduction

Schistosomiasis is a parasitic infection caused by blood flukes of the genus Schistosoma. Today, human schistosomiasis is considered one of the most important human helminth infections in terms of prevalence and morbidity, especially in Africa, where more than 200 million people are infected worldwide, with 800 million people at risk. However, additional studies indicate that this number may be underestimated and as many as 600-600 million people may be infected with schistosomes. Although schistosomiasis is a treatable infection, the current treatment of choice does not provide an optimal strategy for controlling the disease. Since 1990, praziquantel (PZQ)-based mass chemotherapy has been the main approach to controlling schistosomiasis, primarily targeting school-aged children with annual mass treatment. However, the non-availability of PZQ treatment for the long-term control and elimination of schistosomiasis remains a concern and has limitations. For instance, PZQ does not resolve schistosomiasis in the absence of PZQ. Although there is no clear evidence for the existence of PZQ-resistant schistosomiasis strains, increased susceptibility to the drug has been observed in several countries. To overcome these challenges, a prophylactic vaccine or a vaccine-based chemotherapy would be ideal to complement the existing treatment strategies. Evidences for the feasibility of developing a schistosome vaccine include studies showing that immunization with irradiated schistosome cercariae induces high levels of protection in experimental animal models, with further increasing the level of protection. In addition, a subset of human populations living in endemic areas has been shown to develop various degrees of natural resistance, while seroepidemiologic vaccine trials in the past with live and inactivated parasites have been developed successfully and applied in practice.

Expanded information on the mechanisms of immunity to schistosomiasis and the recent availability of the schistosome genome for both E. multilocularis and E. granulosus in the discovery of several schistosome antigen, while additional candidates are now being found through proteomic approaches. Within the last year results of a Phase 1 trial for a plasmid-based Schistosoma mansoni vaccine in the form of a targeted approach.
The Rise of Emerging + Neglected Diseases in the “New Texas”

- **Leading TX NTDs**
  - Toxocariasis 700,000
  - Trichomoniasis 450,000
  - Chagas disease 37,000
  - WNV 183-1,900
  - Intestinal protozoan 1,000
  - Cysticercosis 195-754
  - Murine Typhus >100
  - Dengue, Zika, Chik
The role of trypanocidal therapy in patients with established Chagas’ cardiomyopathy is unproven.

Trypanocidal therapy with benznidazole in patients with established Chagas’ cardiomyopathy significantly reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration through 5 years of follow-up.
Tc24 protein combined with E6020 in a Stable Squalene Emulsion as a lead candidate vaccine

**Candidate Antigen**

Tc24- 24kDa *Trypanosoma Cruzi* Flagellar Calcium Binding Protein

**Candidate Adjuvant**

TLR4 agonist:

Additional antigens also under evaluation and development
ADVANCES IN A THERAPEUTIC CHAGAS VACCINE INITIATIVE

• Preclinical Efficacy:
  - Pilot studies were performed to evaluate efficacy of recombinant Tc24 combined with imiquimod or MPLA when used as a preventative vaccine

• Preliminary Results
  • Reduce parasitemia
  • Increase survival during acute phase
  • Antigen specific IgG2a
  • Antigen specific IFNγ
  • Reduced cardiac parasite burden
Western Blot comparison of Tc24-WT (A), Tc24-C2 (B), and Tc24-C4 (C) purified proteins. Lanes 1-3: Non-Reduced. Lane 4: SeeBlue Plus Molecular Weight Marker. Lanes 5-7 Reduced. Lanes 1,5: Sample before size-exclusion chromatography (SEC) 8 µg load. Lanes 2,6: Post SEC low load (3 µg). Lanes 3,7: Post SEC high load (8 µg). Detection was performed using mouse polyclonal antibody against Tc24 expressed in *Pichia pastoris* as primary antibody diluted 1:2,500 in PBST and an alkaline phosphatase conjugated goat anti-mouse secondary antibody diluted 1:7,500 in PBST.
Structural comparison of Tc24 constructs. a) Circular Dichroism (CD). Far UV CD spectrum of different constructs of Tc24 were taken on a Jasco J-1500. All tested Tc24 protein have a virtual identical CD profile with overlapping spectra. Negative peaks at 222 nm and 208 nm and a positive peak at 193 nm indicate that Tc24 is an α-helical protein. b) Thermal melting profile of Tc24-WT and Tc24-C4 measured using Protein Thermal Shift™ kit (Life Technologies).
Therapeutic Chagas Disease Vaccine

Experimental Chagas disease vaccine improves
Cardiac Echocardiography function