Towards a vaccine for Chagas disease

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Natural course of *Trypanosoma cruzi* infection and Chagas disease

Expert Reviews in Molecular Medicine 2010 Published by Cambridge University Press
**CD8^+ T cells mediate resistance to T. cruzi infection**

![Graph showing survival over time post-infection for WT, B KO, and CD8 KO mice.](image)
Mechanism of immune-mediated resistance to T. cruzi infection

Acute Phase

- DC
- Thp
- IL-12
- NK
- IFN-
- IL-12
- TNF-
- MO
- RNI
- TNF-
- MO (effector molecules)

Chronic Phase

- Th1
- CD8
- B
- IgG1 and IgG2a
- IFN-
- parasite lysis
- opsonization
- effector molecules

Effector cells
A live attenuated vaccine for Chagas’ disease

- Potent stimulator of Toll-Like Receptors immunological adjuvant (stimulation of CD4+ Th1 lymphocytes)
- Antigen delivery to host cell cytoplasm antigen presentation via the endogenous pathway (stimulation of CD8+ T lymphocytes)
- Impaired replication but persistence in the host immunological memory (persistent T cell response)
Trypanosoma cruzi CL-14 clone

Egler CHIARI - Diferenciação do Trypanosoma cruzi em cultura. PhD thesis- Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais

Claudia Paiva, Cerli R. Gattass, Henrique Lenzi, Joseli Lanes

Parasitol Res (1990) 77:77–81
Trypanosoma cruzi: properties of a clone isolated from CL strain

Negative tissue parasitism in mice injected with a non-infective clone of Trypanosoma cruzi

Experimental Parasitology 91, 7–19 (1999)
Protective Response of Vaccinated Mice Is Mediated by CD8+ Cells, Prevents Signs of Polyclonal T Lymphocyte Activation, and Allows Restoration of a Resting Immune State after Challenge
CL-14 induces strong and long-lasting protective immunity against challenge with virulent strains of T. cruzi.
Infection with CL-14 do not reactivate in immunodeficient mice

Junqueira et al, PNAS, 2011
Comparative Genome/Transcriptome
CL-14 (avirulent) x CL Brener (virulent)

Shotgun Sequencing
Genomic Analysis
Maxcircle Mitocondrial
Multigenic Families

RNAseq
Western Bloting
Imunofluorescence

Southern Bloting/ PCR
**CL Brener and CL-14 strains have very similar genomes**

<table>
<thead>
<tr>
<th>Família</th>
<th>CL-14</th>
<th>CL Brener</th>
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**Identity %**

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Trans-sialidase genes from CL-14 strain lack the SAPA repeats
Active Trans-Sialidase (TcS I) Sub-Family

Previatos et al.
Schenkman et al.
Frash et al.
Trypanosoma cruzi - Life Cycle (Vertebrate Host)

Extracellular Trypomastigotes

Intracellular Amastigotes

Intracellular Trypomastigotes

Amastigote Surface Protein-2 of \( T. \) cruzi (Group II of TS)

Trans-sialidase of trypomastigotes of \( T. \) cruzi

Maurício M. Rodrigues – UNIFESP
Long-Term Protective Immunity Induced Against *Trypanosoma cruzi* Infection After Vaccination with Recombinant Adenoviruses Encoding Amastigote Surface Protein-2 and *Trans*-Sialidase

ALEXANDRE V. MACHADO,1,2 JARBAS E. CARDOSO,3 CARLA CLASER,4,5 MAURICIO M. RODRIGUES,4,5 RICARDO T. GAZZINELLI,1,2 and OSCAR BRUNA-ROMERO1,2,6
Sterile immunity induced by genetic vaccination in mice challenge with Y strain of *T. cruzi*
Pereira et al, Plos Pathogens, 2015
**Mechanism of action of granulysin-induced microptosis**

![Diagram showing the mechanism of action of granulysin-induced microptosis](image)

- **Step 1:** PFN-dependent entry into the host cell
- **Step 1:** GNLY-dependent entry into parasites

**Cleavage of mitochondrial electron transport chain complex I**
- Molecules involved in host cell death
- Cleavage of bacterial electron transport chain complex I
  - ROS induction
    - DNA damage
    - Destruction of ROS defense
    - Impact on Fe-S containing enzymes
    - Impact on RNA and protein synthesis
- Molecules involved in bacterial death

**Dotiwala et al, Nature Medicine, 2016**
Conclusions:

1) Adenovirus encoding the Transialidase (AdTS) and Amastigote Surface Protein (AdASP-2) induces strong and long-lasting protection against challenge with different strains of *T. cruzi*.

2) Therapeutic vaccination with AdASP-2 reverses cardiac pathology in mice chronically infected with myotropic strain Colombiana strains of *T. cruzi*.

3) The highly attenuated CL-14 lacks genes expressing the SAPA containing domain, and induces a long lasting protective immunity in single immunization dose.

4) Both recombinant vaccine and attenuated parasites induce protective immunity that is mediated by CD8\(^+\) T cytotoxic lymphocytes and IFN\(\gamma\)
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