

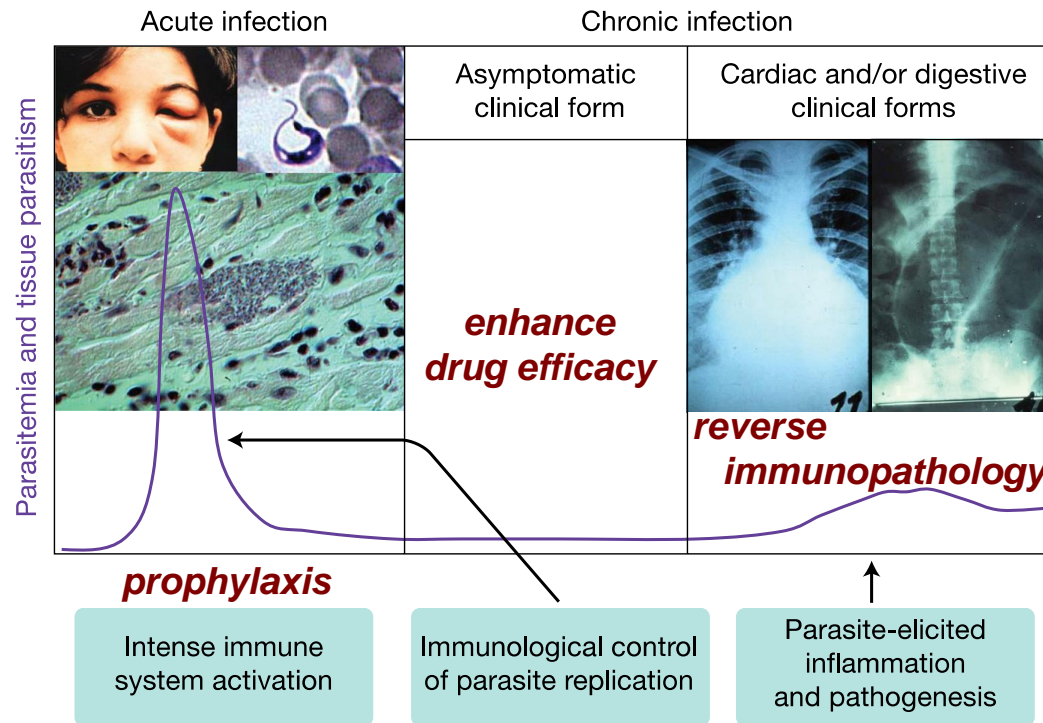


DNDi 2016

Innovation & Access - Partners' Meeting

RIO DE JANEIRO • 6-8 JUNE

Towards a vaccine for Chagas disease

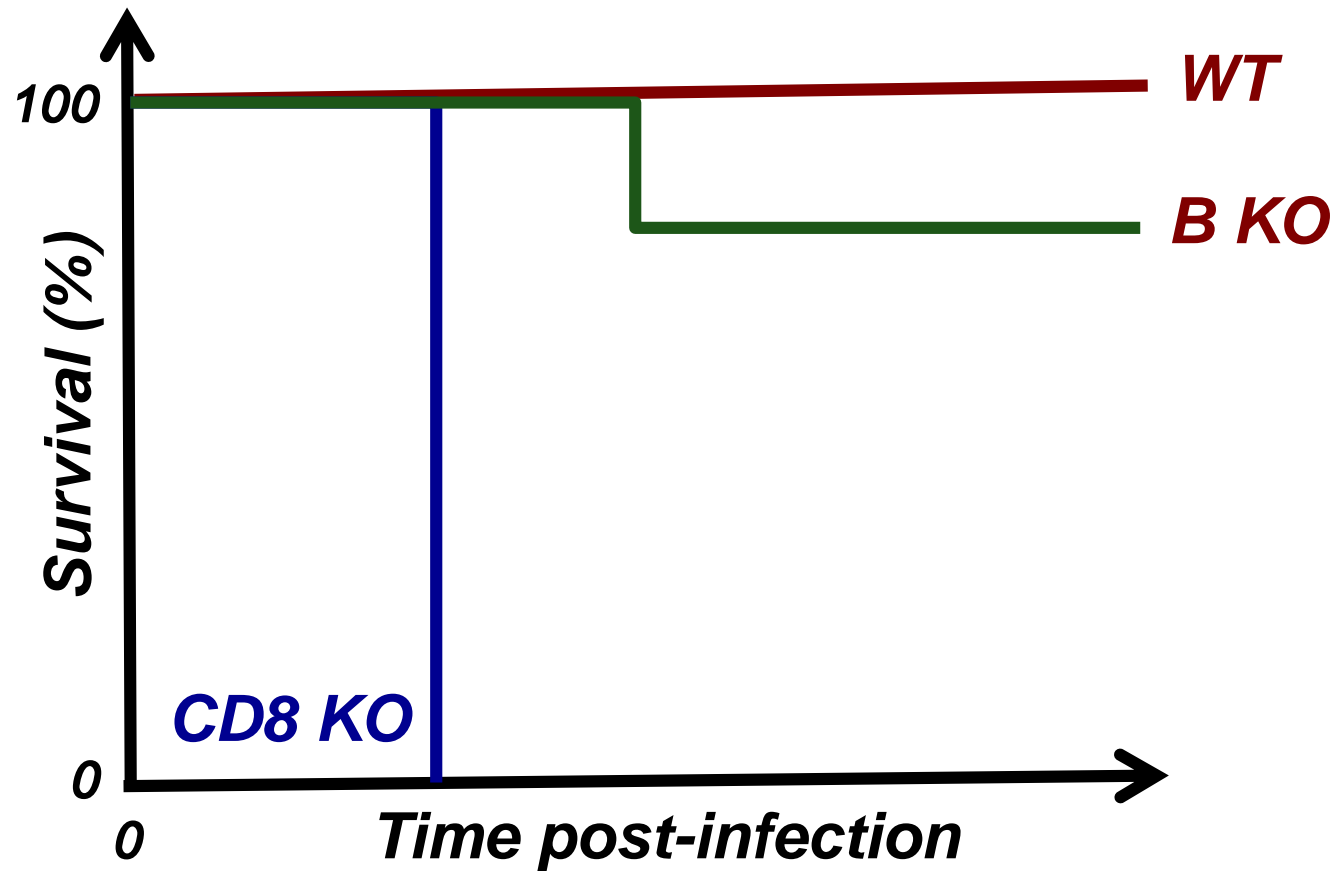


Natural course of *Trypanosoma cruzi* infection and Chagas disease

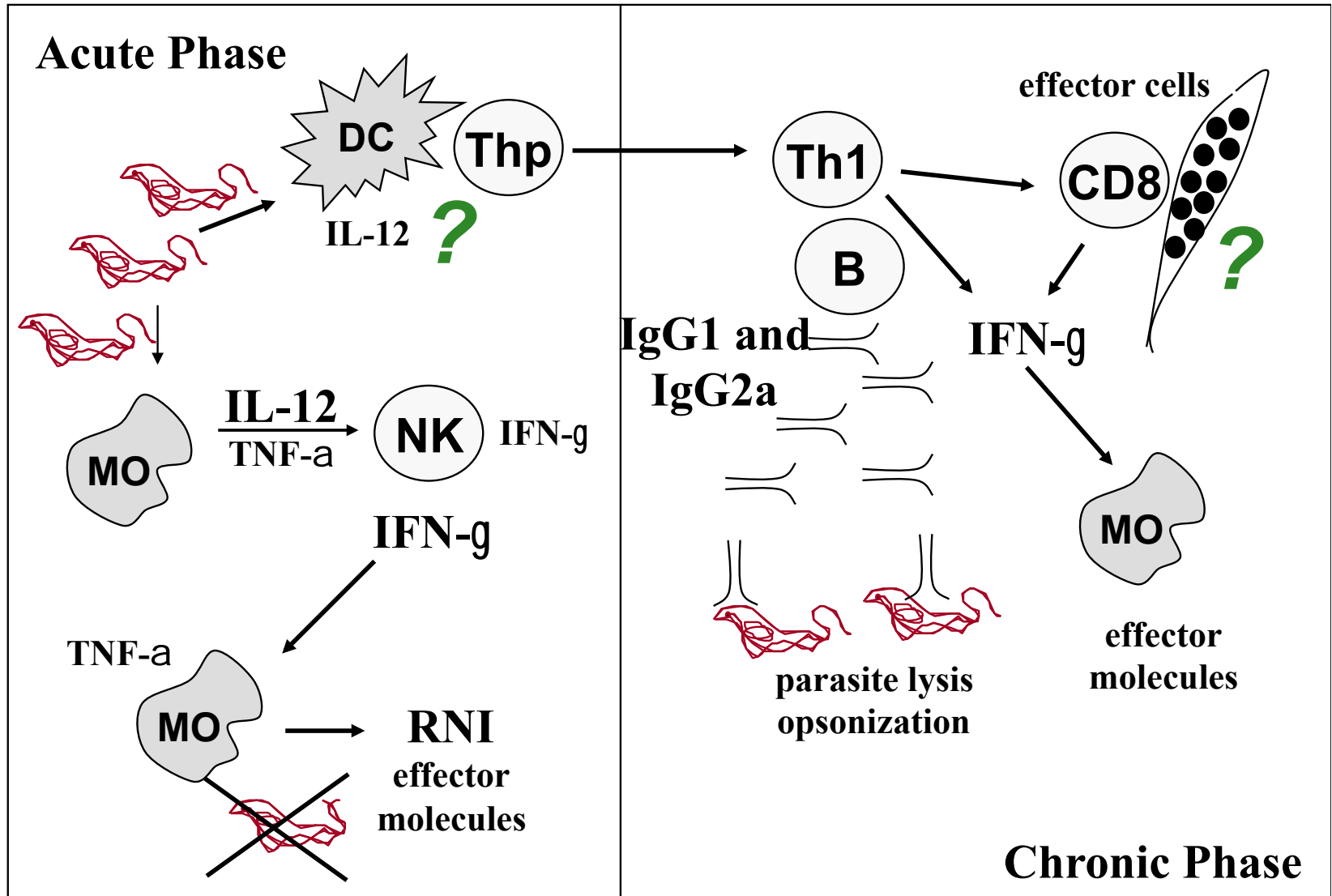
Expert Reviews in Molecular Medicine 2010 Published by Cambridge University Press

Ricardo T. Gazzinelli
Fundação Oswaldo Cruz – Minas
University of Massachusetts Medical School

CD8⁺ T cells mediate resistance to *T. cruzi* infection



Mechanism of immune-mediated resistance to *T. cruzi* infection



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

Parasitol Res (1995) 81:6–12
Negative tissue parasitism in mice injected with a non-infective clone of *Trypanosoma cruzi*

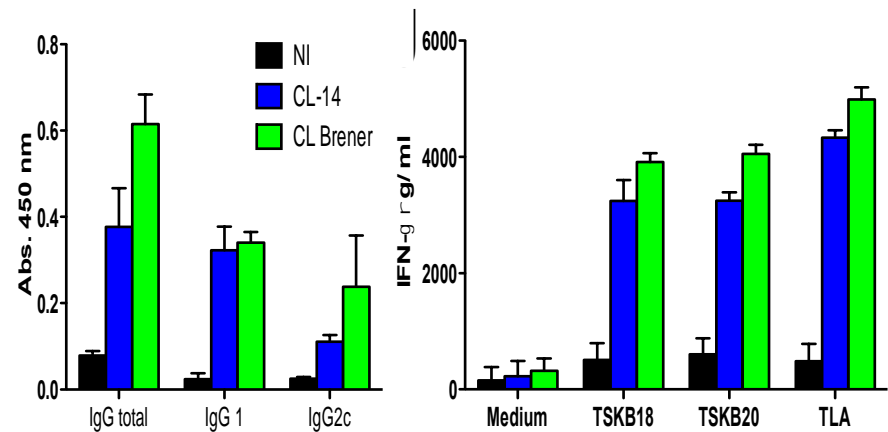
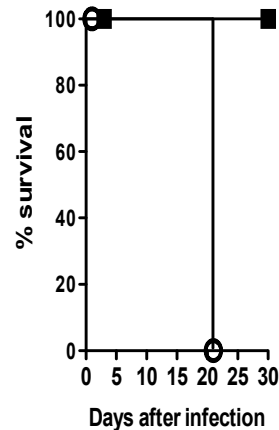
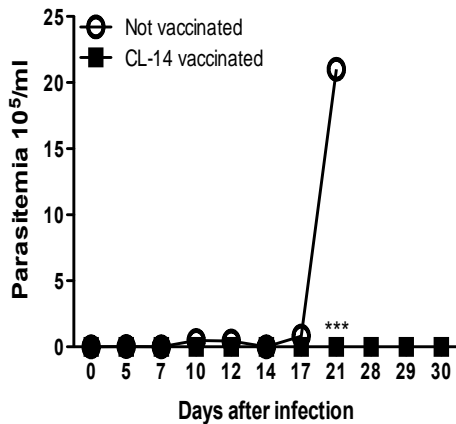
Experimental Parasitology 91, 7–19 (1999)
Protective Response of Vaccinated Mice Is Mediated by CD8+ Cells, Prevents Signs of Polyclonal T Lymphocyte Activation, and Allows Restoration of a Resting Immune State after Challenge



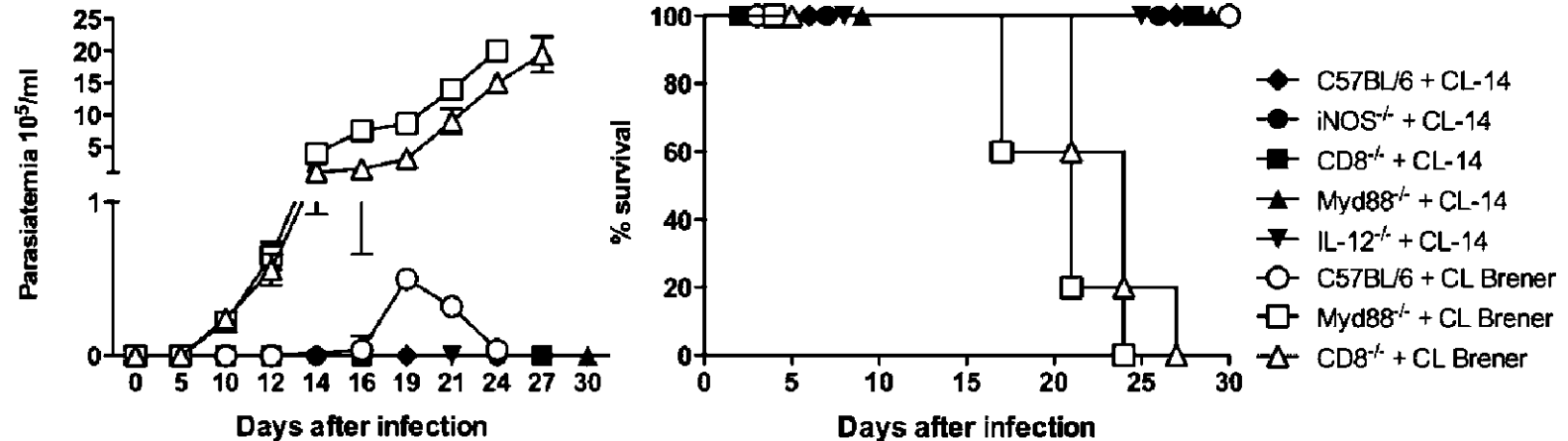


CL-14 induces strong and long-lasting protective immunity against challenge with virulent strains of *T. cruzi*

Caroline Junqueira



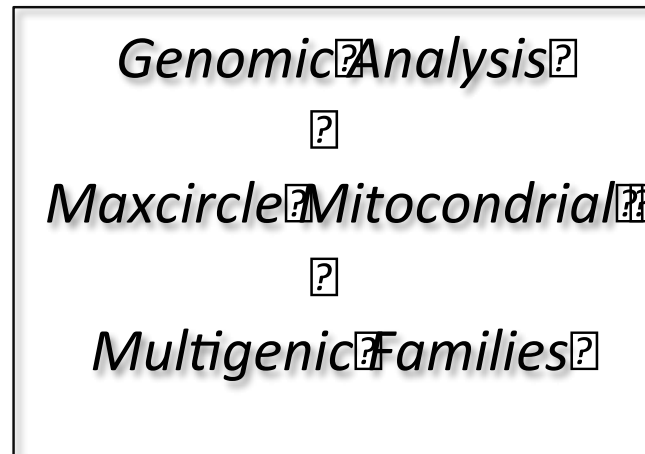
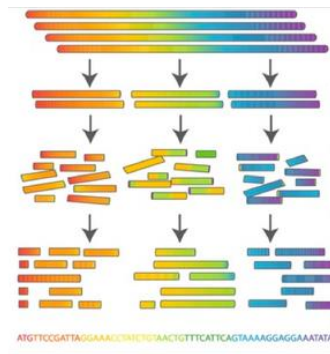
Infection with CL-14 do not reactivate in immunodeficient mice



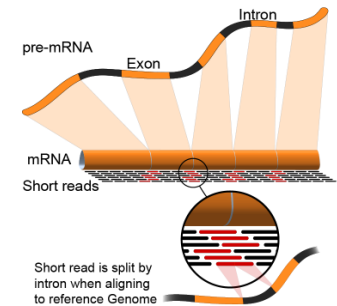
Comparative Genome/Transcriptome

CL-14 (avirulent) x CL Brener (virulent)

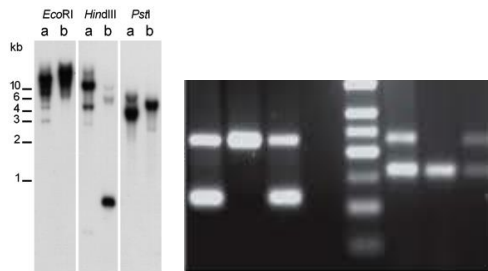
Shotgun Sequencing



RNAseq

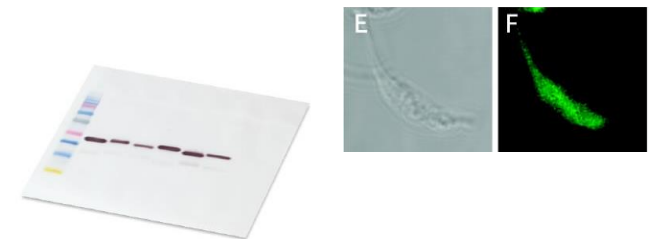


Southern Blotting/PCR



Western Blotting

Immunofluorescence

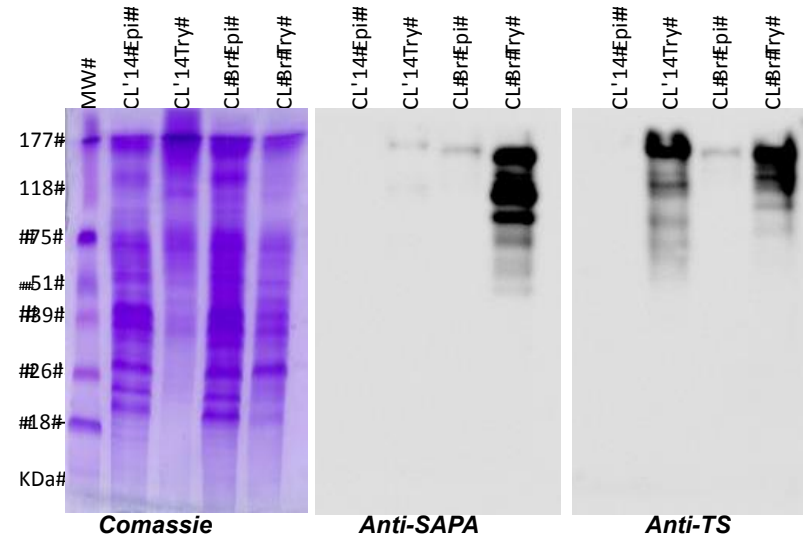
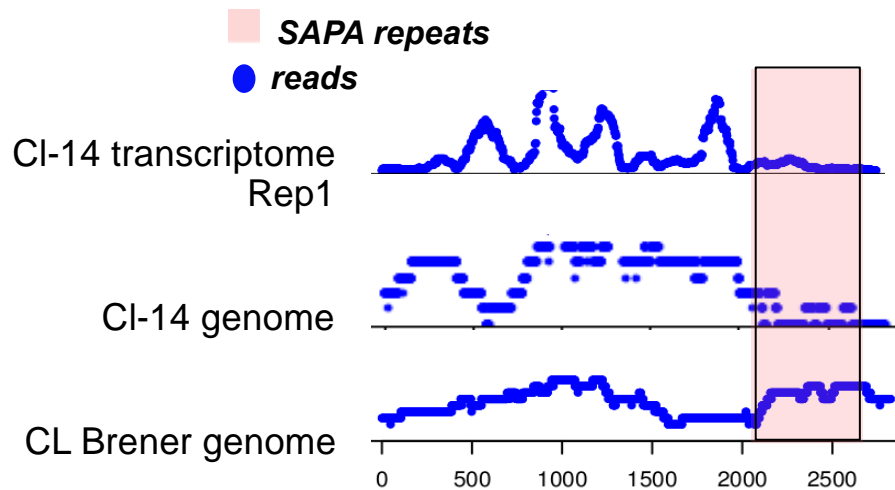


CL Brener and CL-14 strains have very similar genomes

Família	CL-14	CL Brener
Trans-sialidasas	1463	1481
Mucin	999	992
RHS	773	777
DGF	565	569
GP63	491	449
RNA helicase	156	157
Kinesin	102	102
RNA-Binding	102	104
Tuzinas	83	83
Cruzaínas (calpain)	67	66
Dynei heavy chain	45	45
Amastinas	27	27
GAPDH	21	20
Cyclin dependent kinase	19	19
HSP70	11	9
L7a	4	4
HSP100	3	3
Argonaute****	2	2
GPI8****	2	2
MAPK2 (inclusa nas kinases)	2	2
MSH2	2	2

	Identity %
Coding sequences	99.79
MASP	99.87
Trans-sialidase	99.80
RHS	99.74
DGF	99.84
GP63	99.73
RNA-binding	99.83
Amastin	99.69

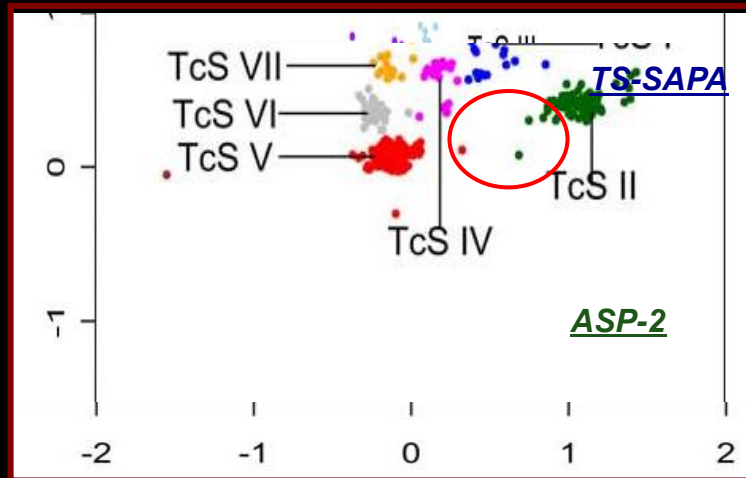
Trans-sialidase genes from CL-14 strain lack the SAPA repeats



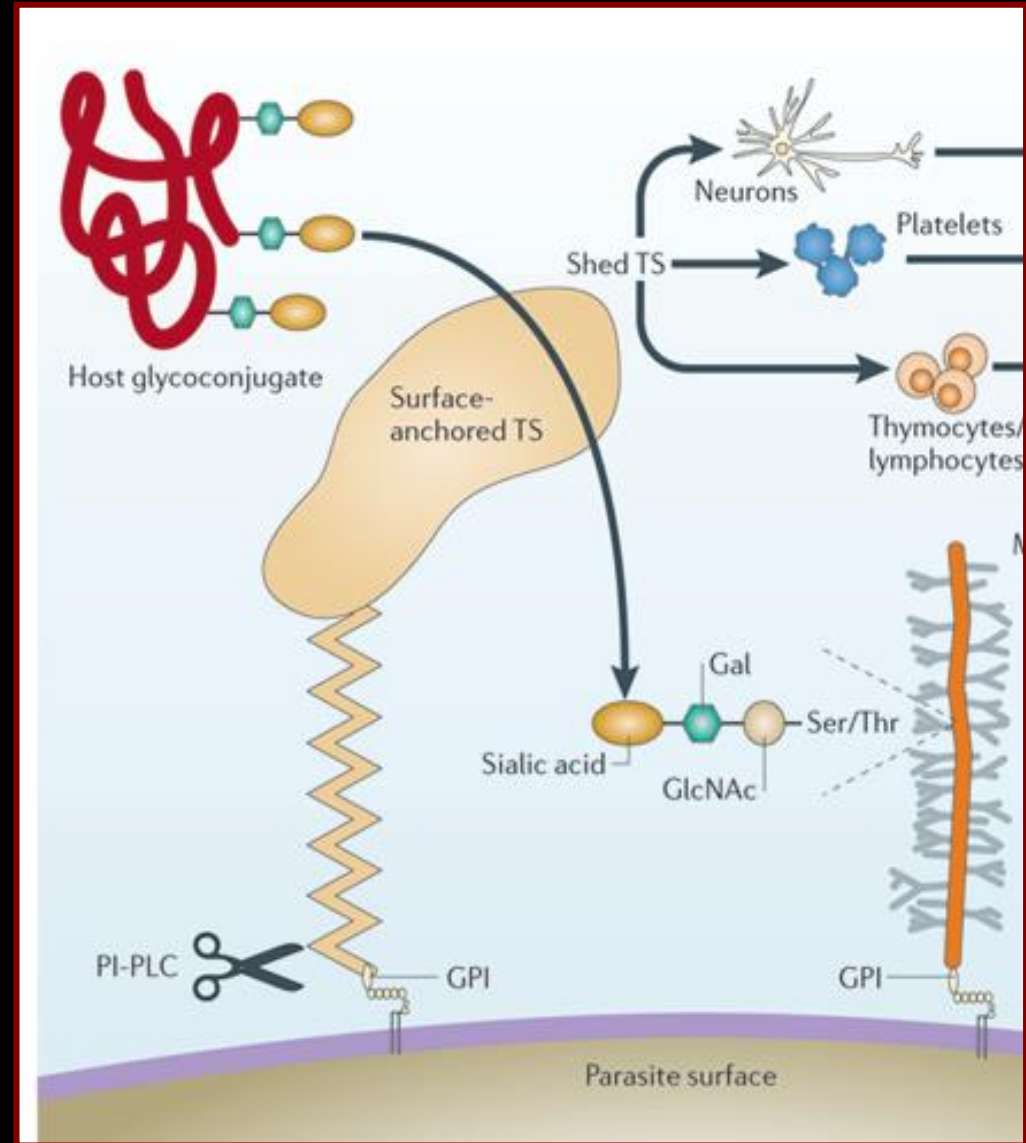
DSSAH[GHSA][KT]PS[TI][TP][AV]



Active Trans-Sialidase (TcS I) Sub-Family



Previatos et al.
Schenkman et al.
Frash et al.



PUBMED
Rodrigues MM cruzi



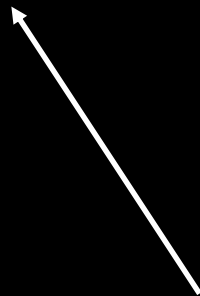
Mauricio M. Rodrigues

Trypanosoma cruzi - Life Cycle (Vertebrate Host)

*Extracellular
Trypomastigotes*



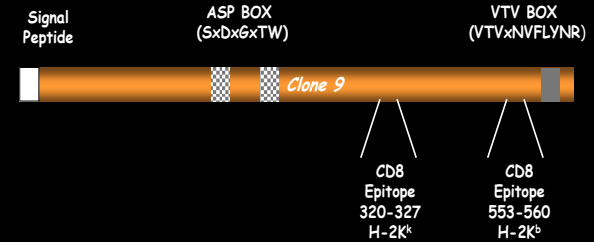
*Intracellular
Amastigotes*



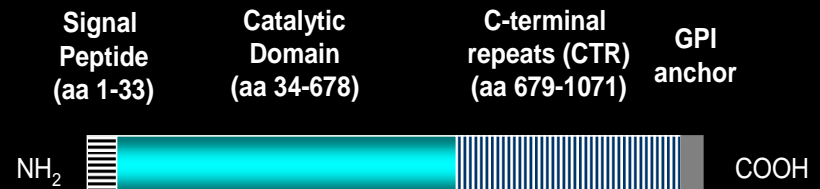
*Intracellular
Trypomastigotes*



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



Trans-sialidase of trypomastigotes of *T. cruzi*



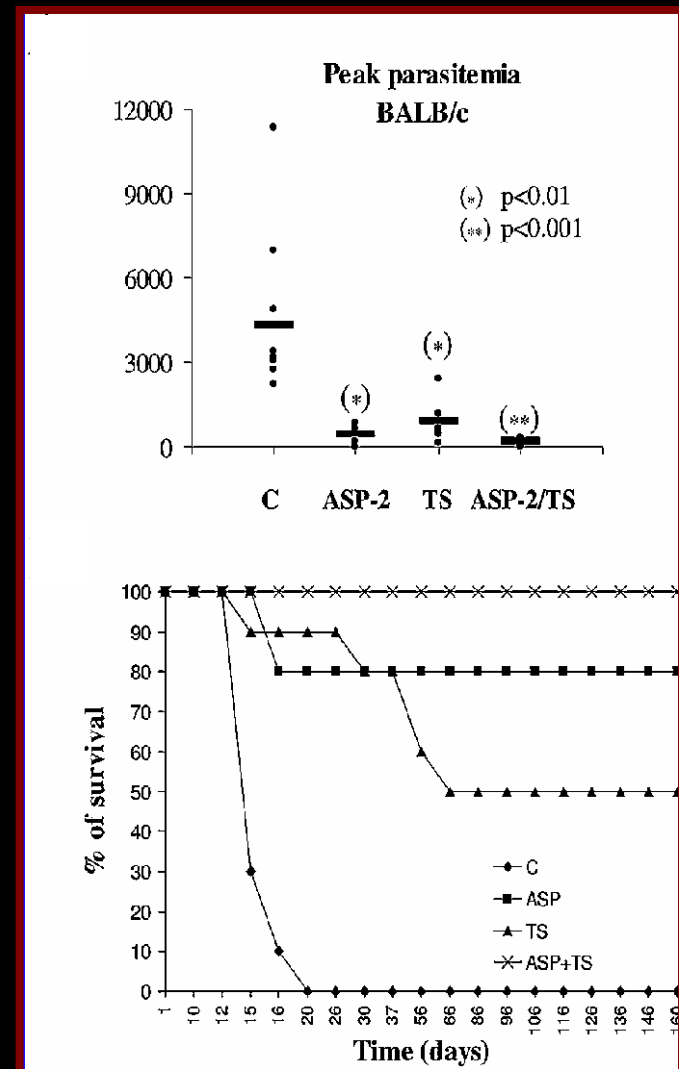
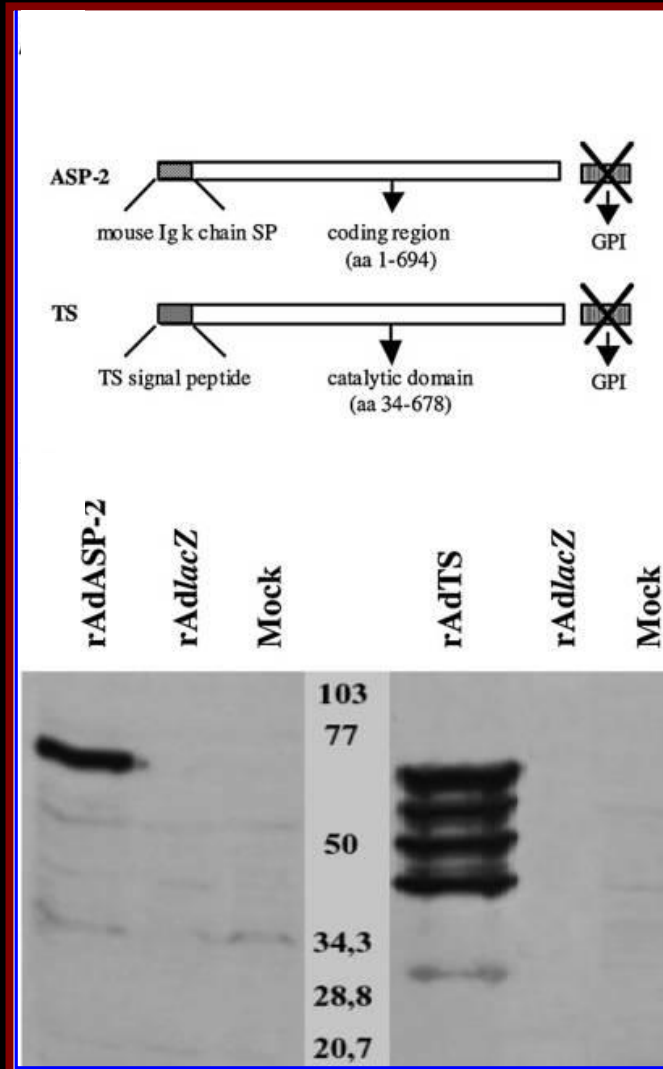
HUMAN GENE THERAPY 17:898–908 (September 2006)

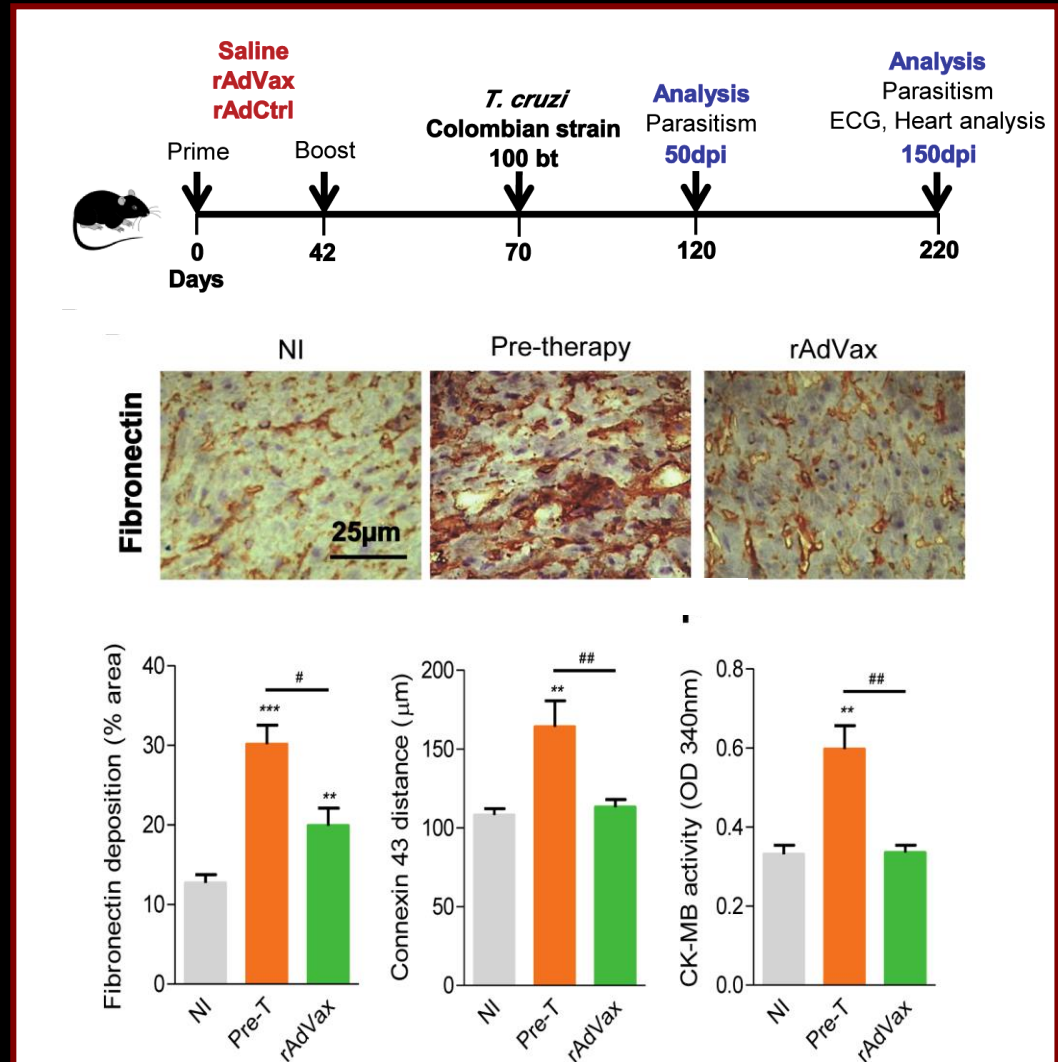
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Long-Term Protective Immunity Induced Against
Trypanosoma cruzi Infection After Vaccination with
Recombinant Adenoviruses Encoding Amastigote
Surface Protein-2 and *Trans*-Sialidase

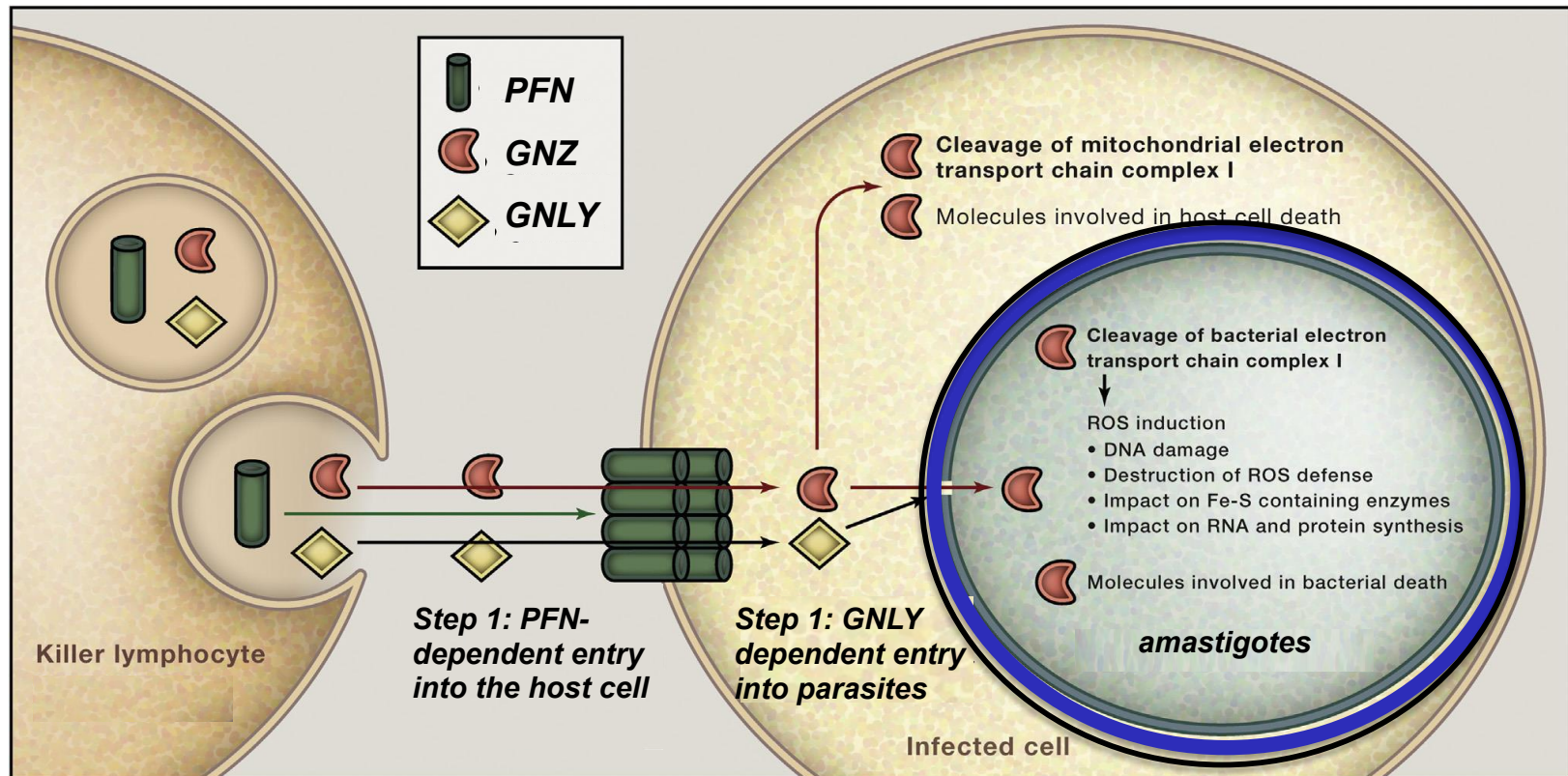
ALEXANDRE V. MACHADO,^{1,2} JARBAS E. CARDOSO,³ CARLA CLASER,^{4,5}
MAURICIO M. RODRIGUES,^{4,5} RICARDO T. GAZZINELLI,^{1,2} and OSCAR BRUNA-ROMERO^{1,2,6}

Sterile immunity induced by genetic vaccination in mice challenge with Y strain of T. cruzi





Mechanism of action of granulysin-induced microptosis



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 straind 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 γ***

Acknowledgements:

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Joseli Lannes-Vieira et al.

Harvard Medical School

Farokh Dotiwala

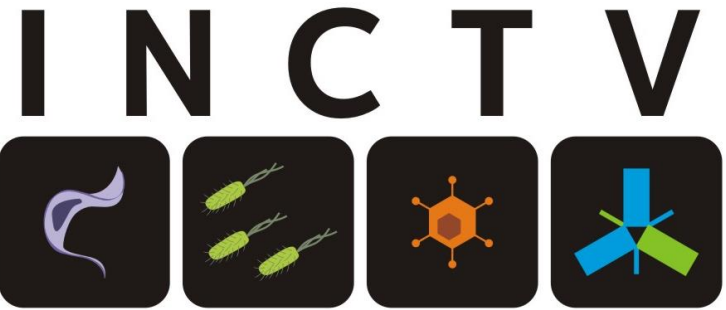
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Maurício Rodrigues et al.

Sergio Schenkman



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