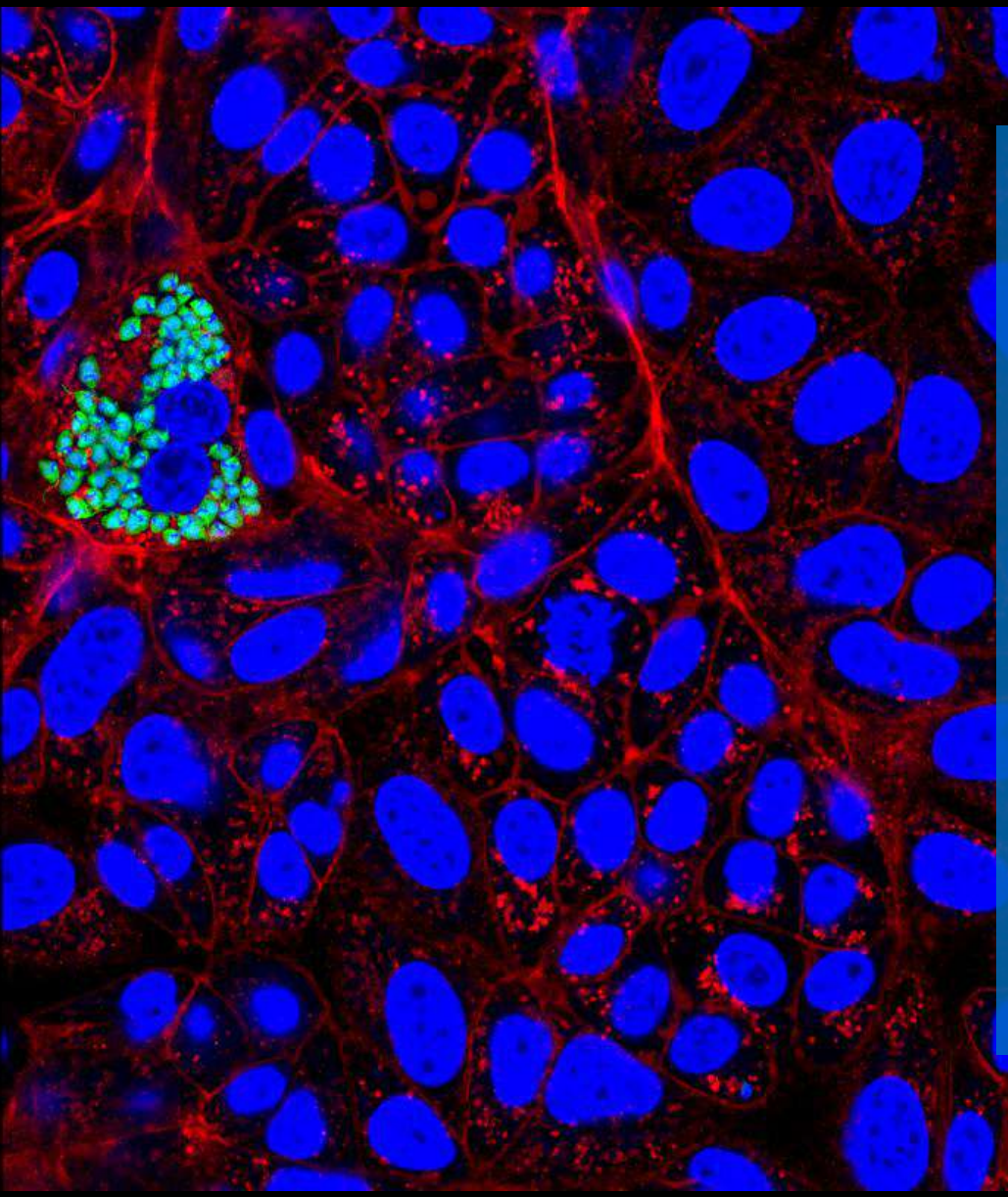


Multi-omic and functional study of the pathogenesis of *Trypanosoma cruzi* infection for the identification of new therapeutic and diagnostic targets

Juan Carlos Gabaldón-Figueira, MD PhD

ISGlobal
Barcelona Institute for Global Health

A partnership of:

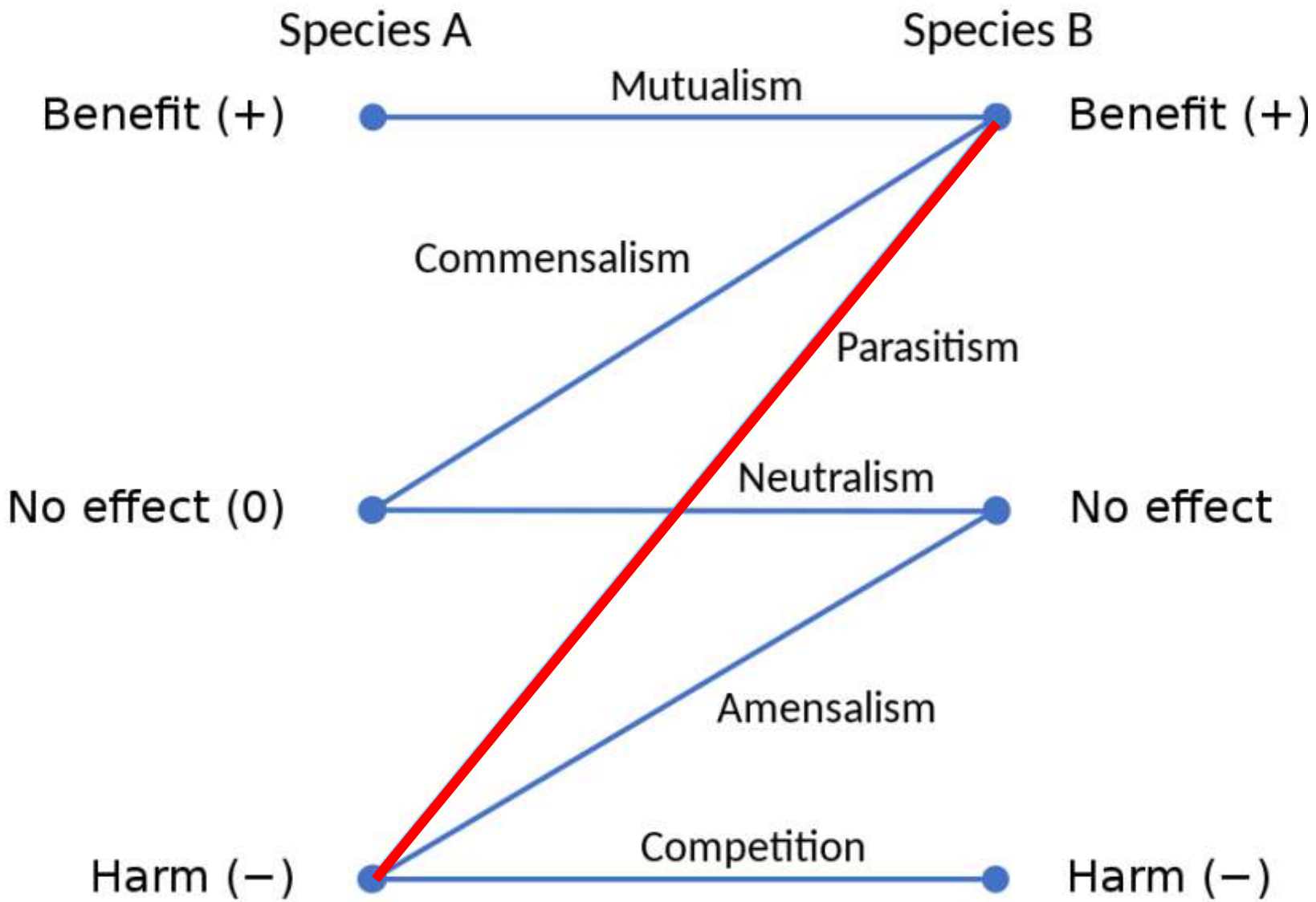
"la Caixa" Foundation

Clínic Barcelona · Parc de Salut MAR · Universitat de Barcelona · Universitat Pompeu Fabra Barcelona · Generalitat de Catalunya · Gobierno de España · Ajuntament de Barcelona

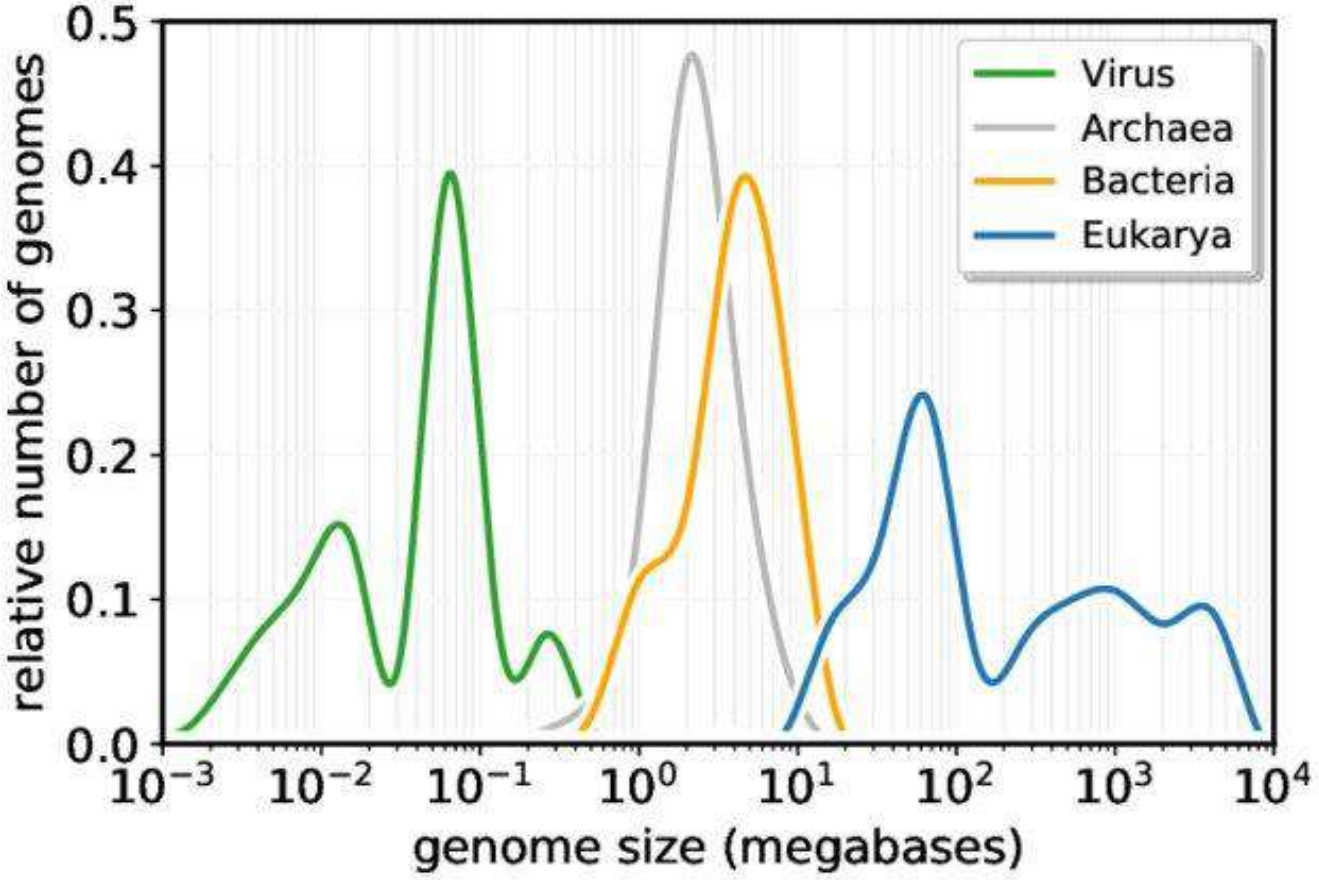
EXCELENCIA SEVERO OCHOA

CERCA Centres de Recerca de Catalunya

What is a parasite?



Parasites are very complex and represent a big problem

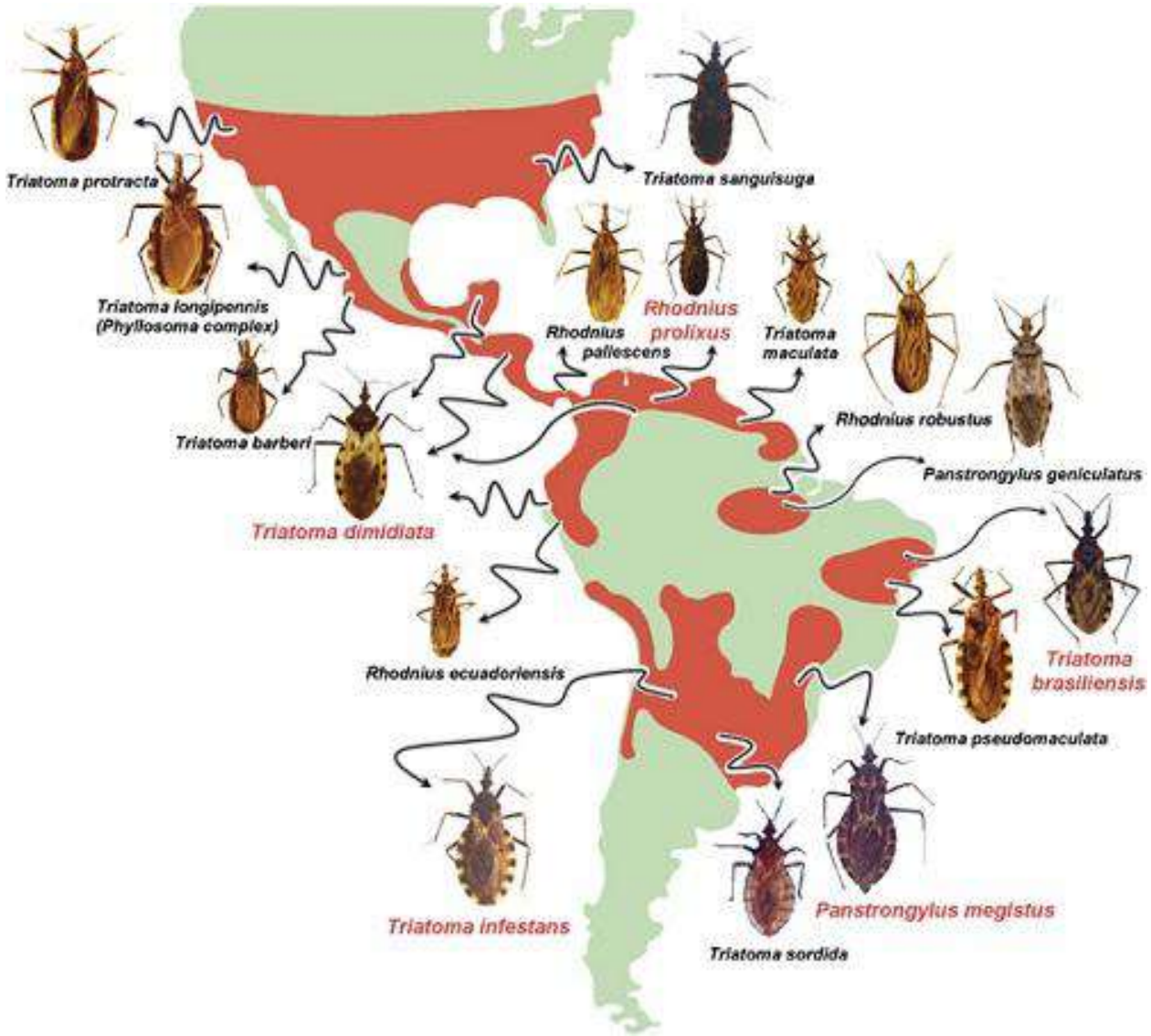


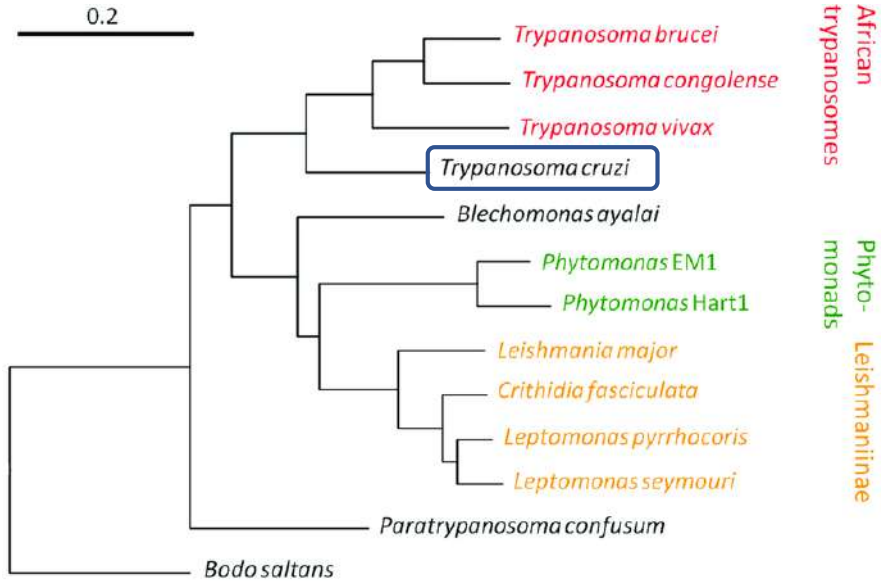
	DALYs (000s)
Parasitic and vector diseases	45,537
a. Malaria	33,398
b. African Trypanosomiasis	102
c. **Chagas disease**	**217**
d. Schistosomiasis	1,628
e. Leishmaniasis	722
f. lymphatic filariasis	1,616
g. Onchocerciasis	1,210
h. Cysticercosis	988
i. Echinococcosis	461
j. Dengue	1,952
k. Trachoma	194
l. Yellow fever	413
m. Rabies	2,635

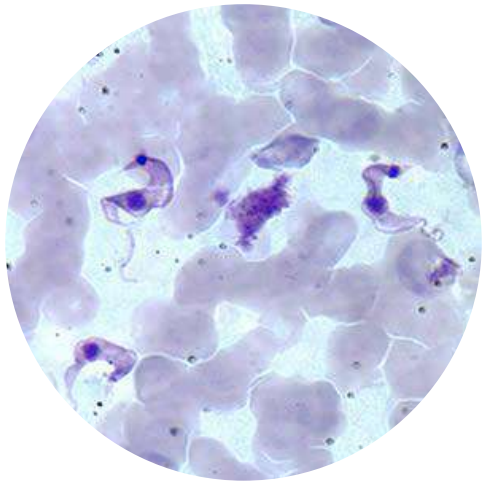
https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys

Bains et al, 2021

What is Chagas disease?



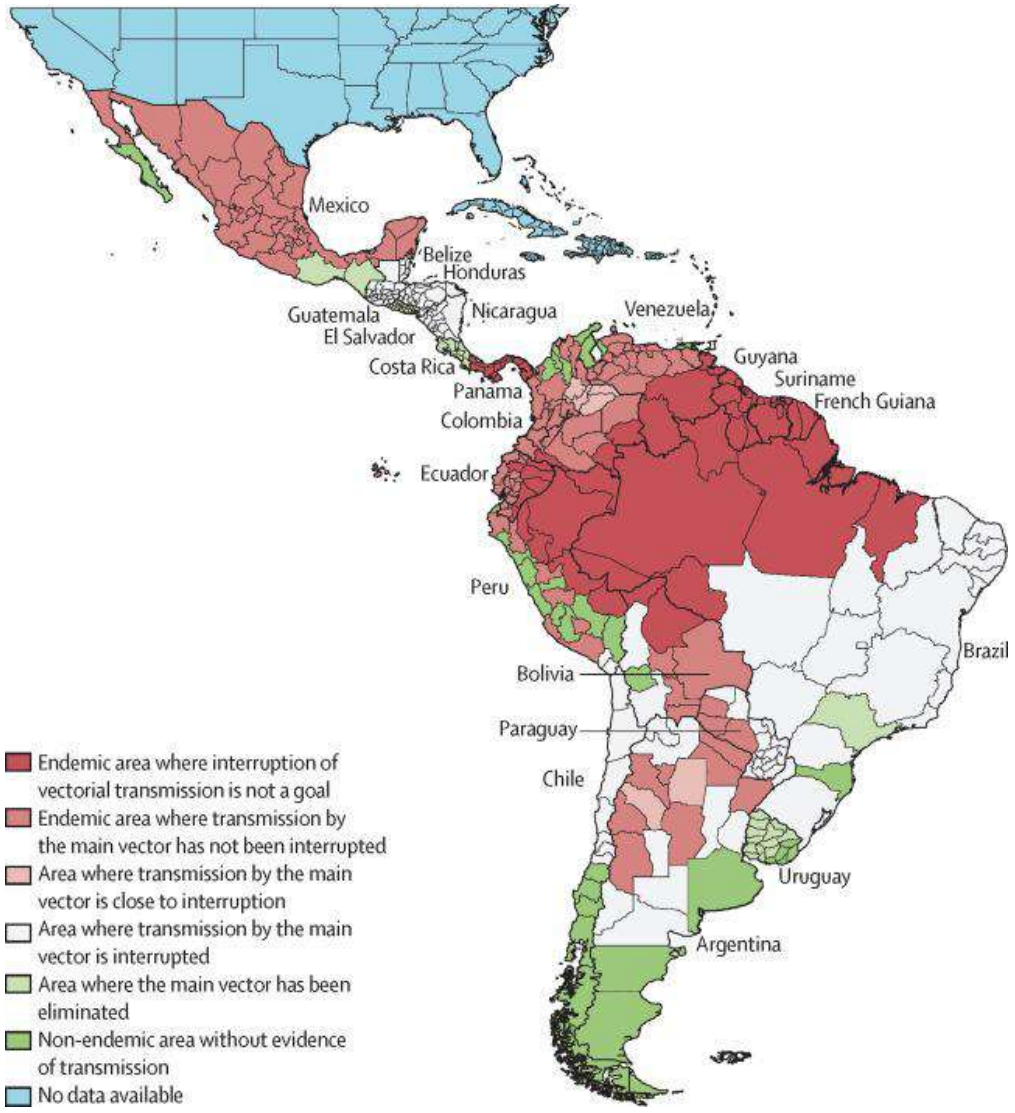




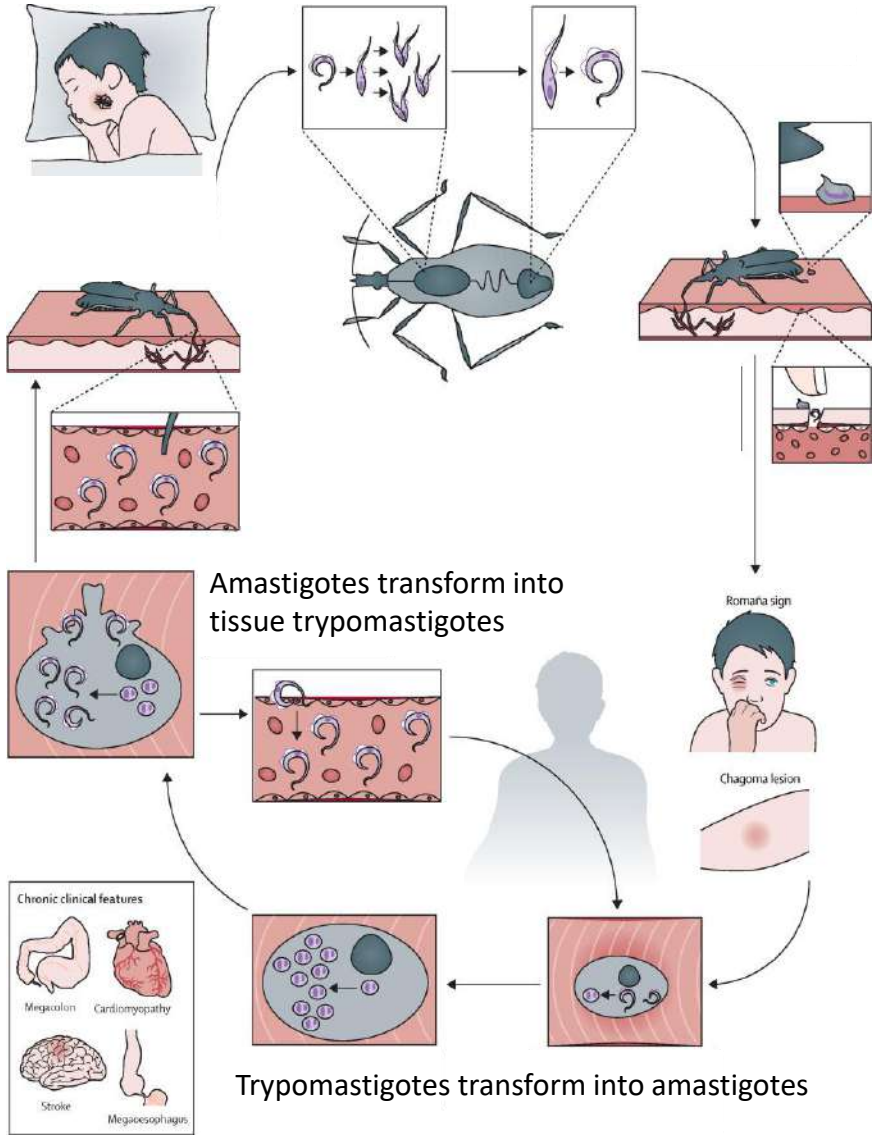
- Over 7 million people infected.
- 9,000 deaths per year
- Over 200k DALYs/year-

Gourbiere et al, 2011

Epidemiology and transmission of Chagas disease



Epimastigotes transform into metacyclic trypomastigotes



Pérez-Molina and Molina et al 2018

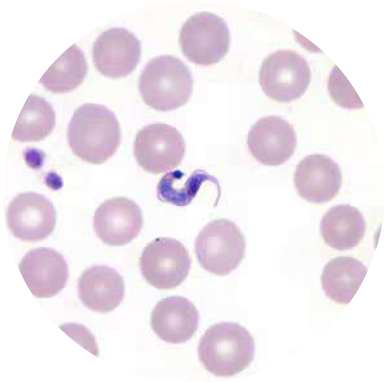
Epidemiology and transmission of Chagas disease

Chagas disease is an increasingly **global** public health concern

Courtesy of Berta Barnadas, 2025

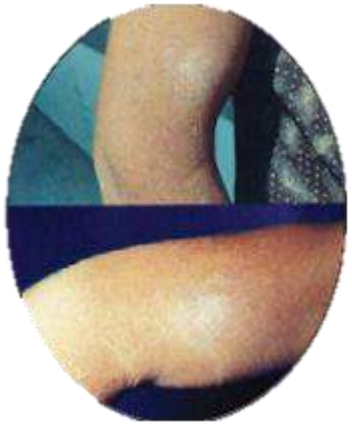
Clinical manifestations and evolution

Peripheral parasitaemia

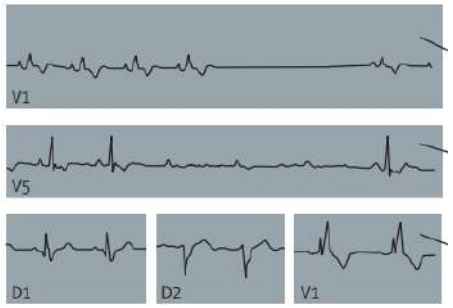


Romaña's sign

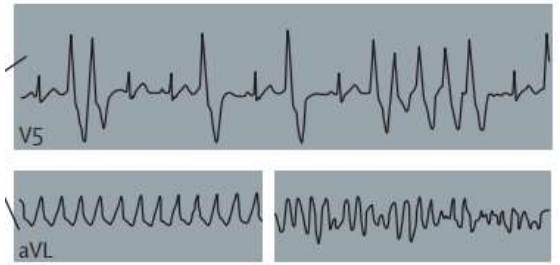
Chagoma



Supraventricular arrhytmias

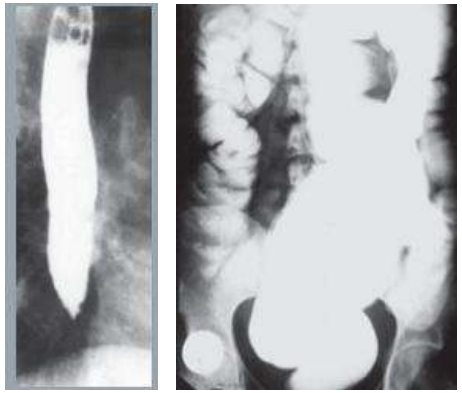


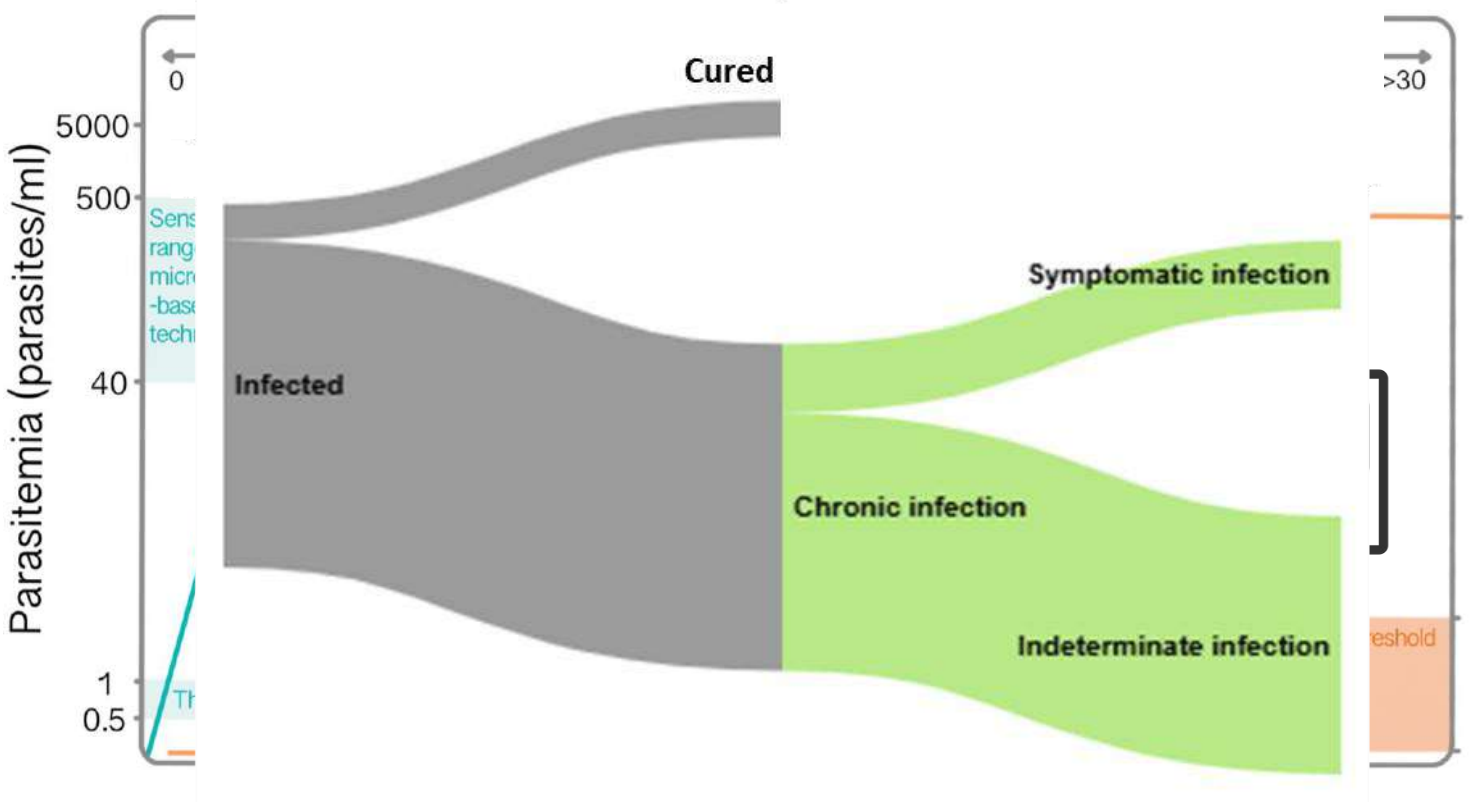
Ventricular arrhytmias



Apical aneurysm/ dilated cardiomyopathy

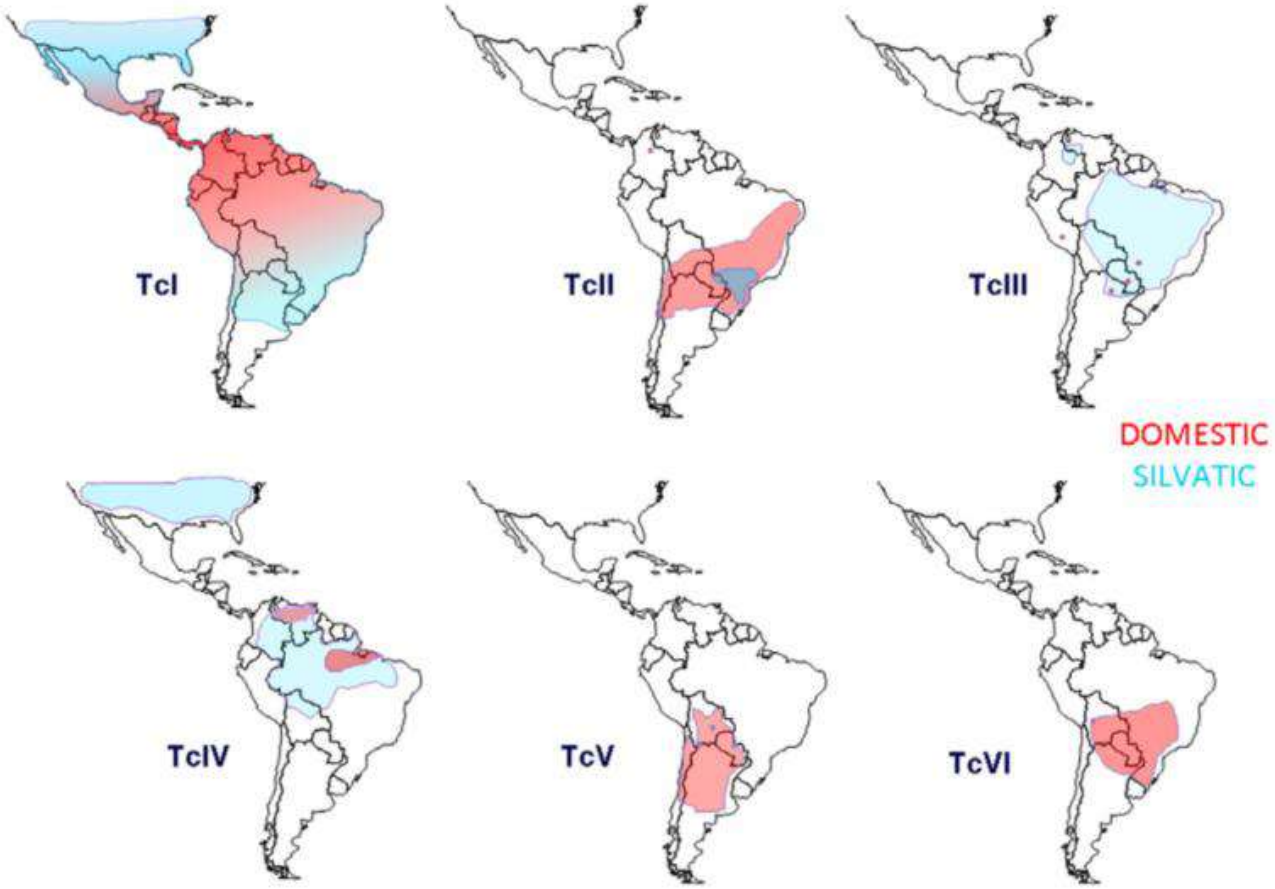
Digestive mega-syndromes



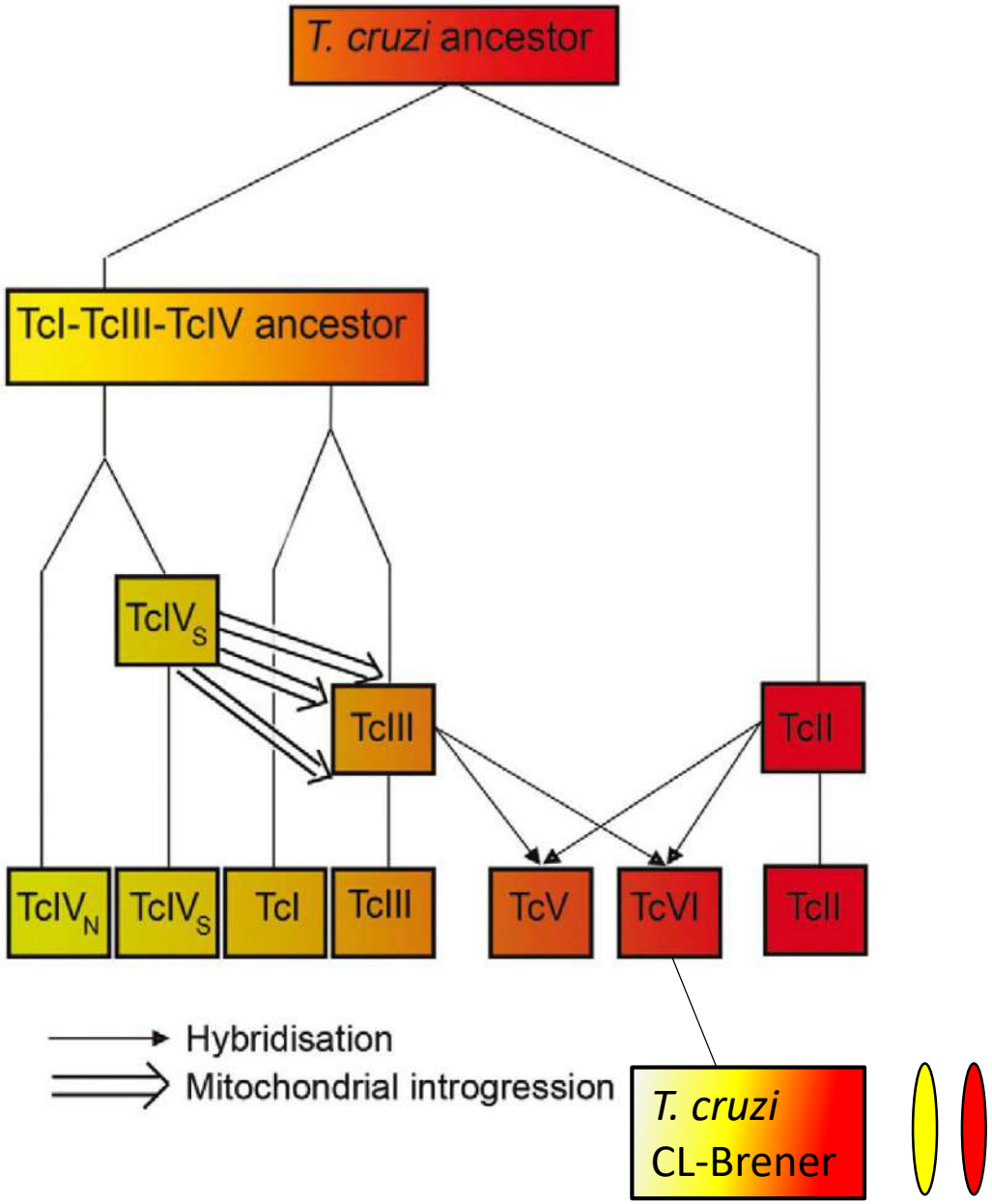


Adapted from Schijman et al 2024, and Rassi et al 2010.

Epidemiology and transmission of Chagas disease

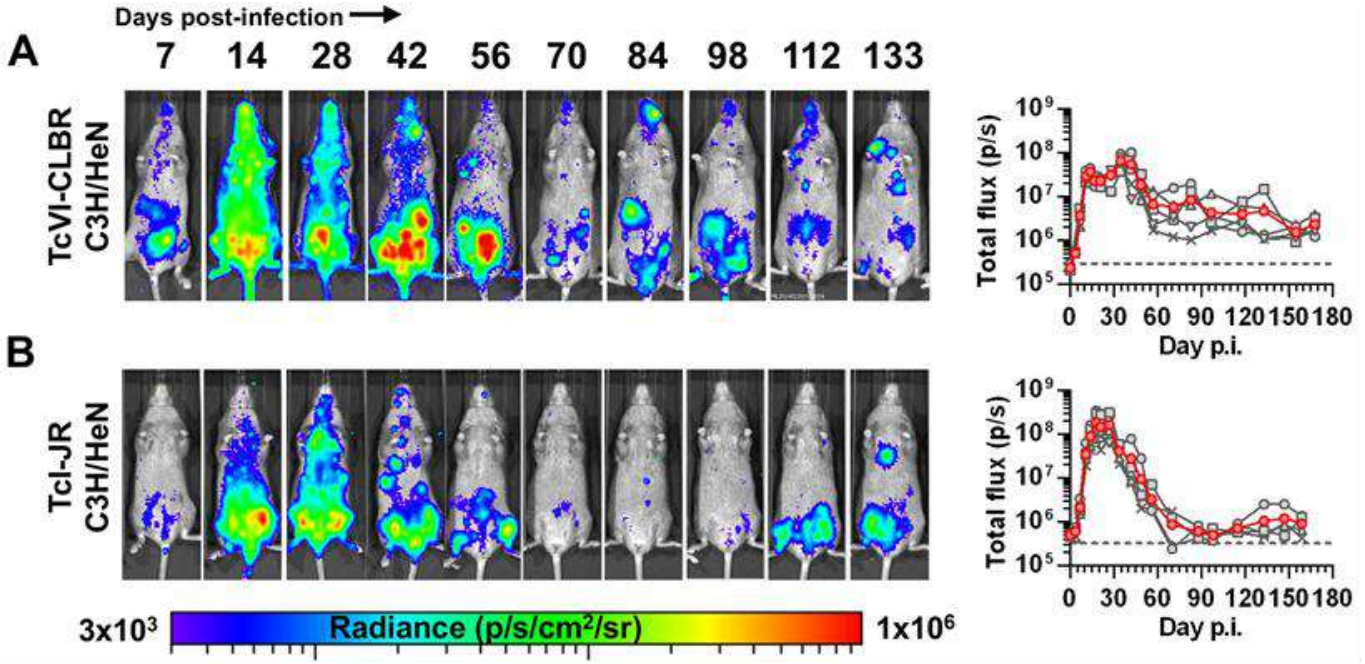


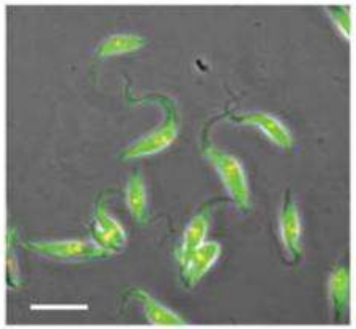
Zingales et al, 2012



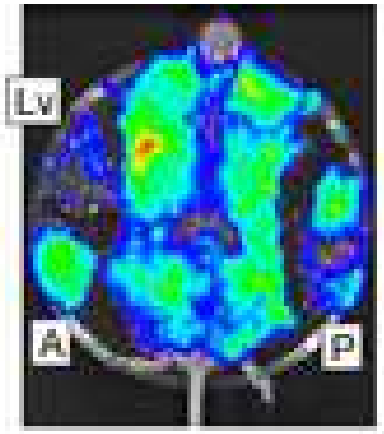
Tomasini et al, 2015

What determines the clinical evolution of Chagas disease?

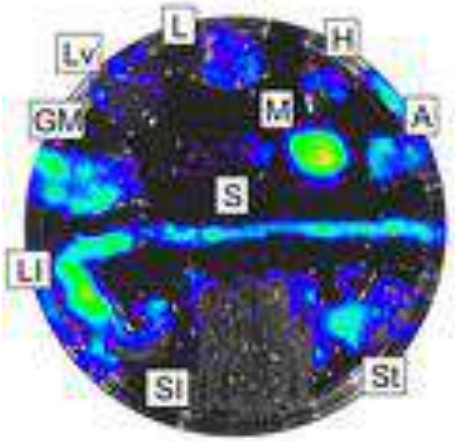


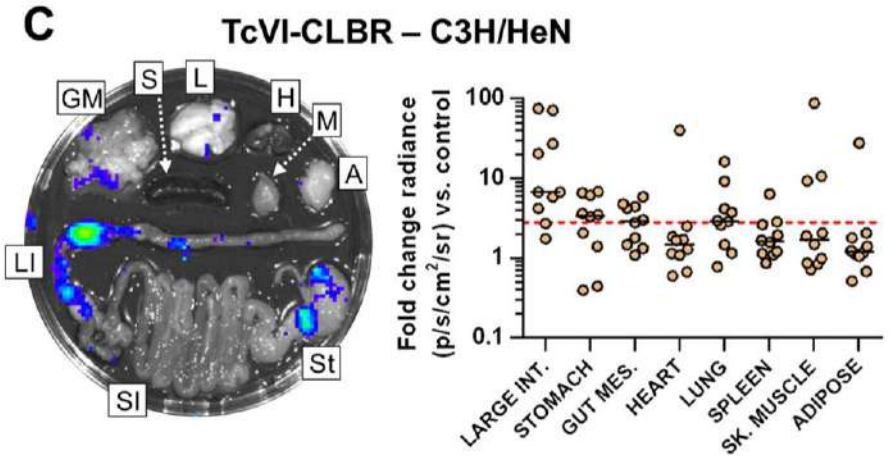


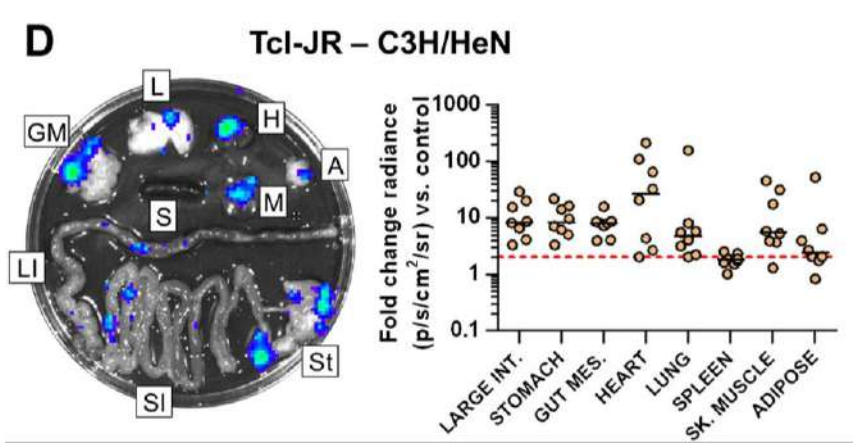
Immunosuppression



14 days immunosuppression



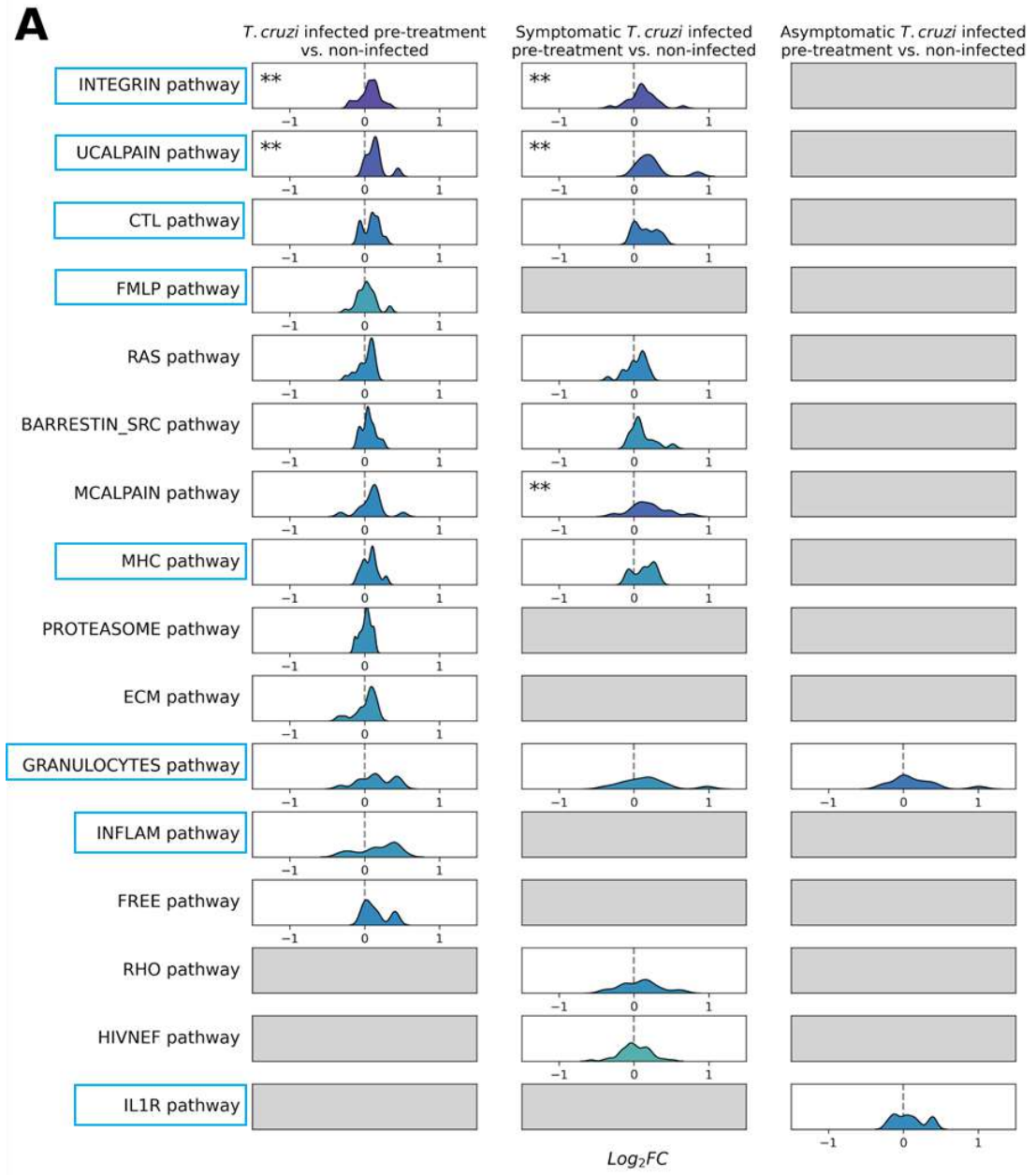




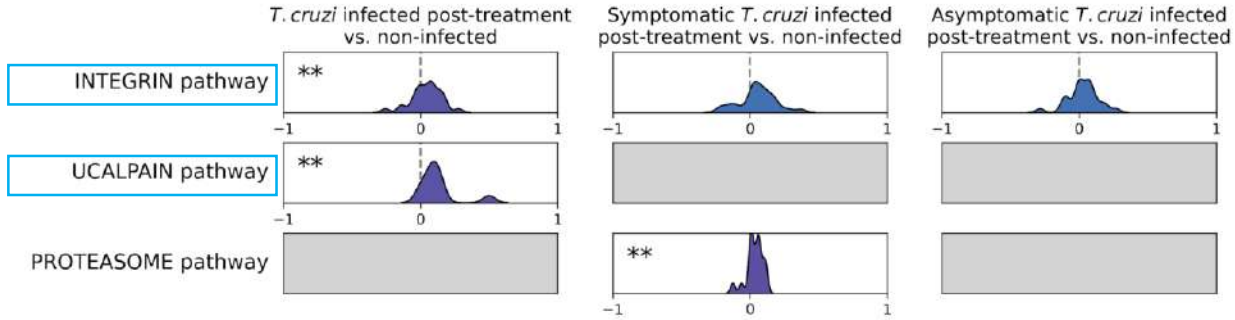
Lewis et al, 2016

Transcriptomic evidence of immune modulation during infection and treatment

Pre-treatment compared with controls



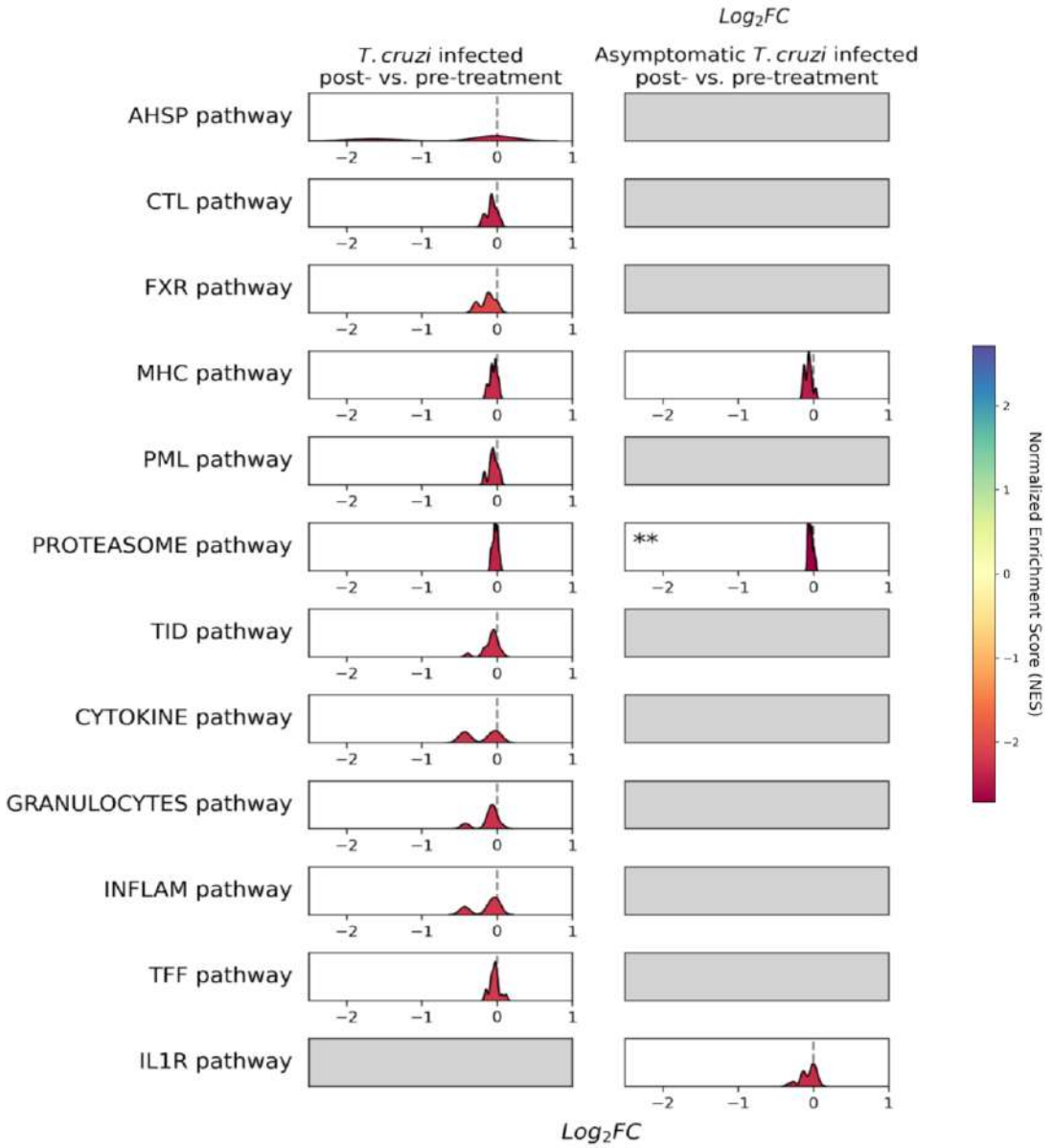
Post-treatment compared with controls

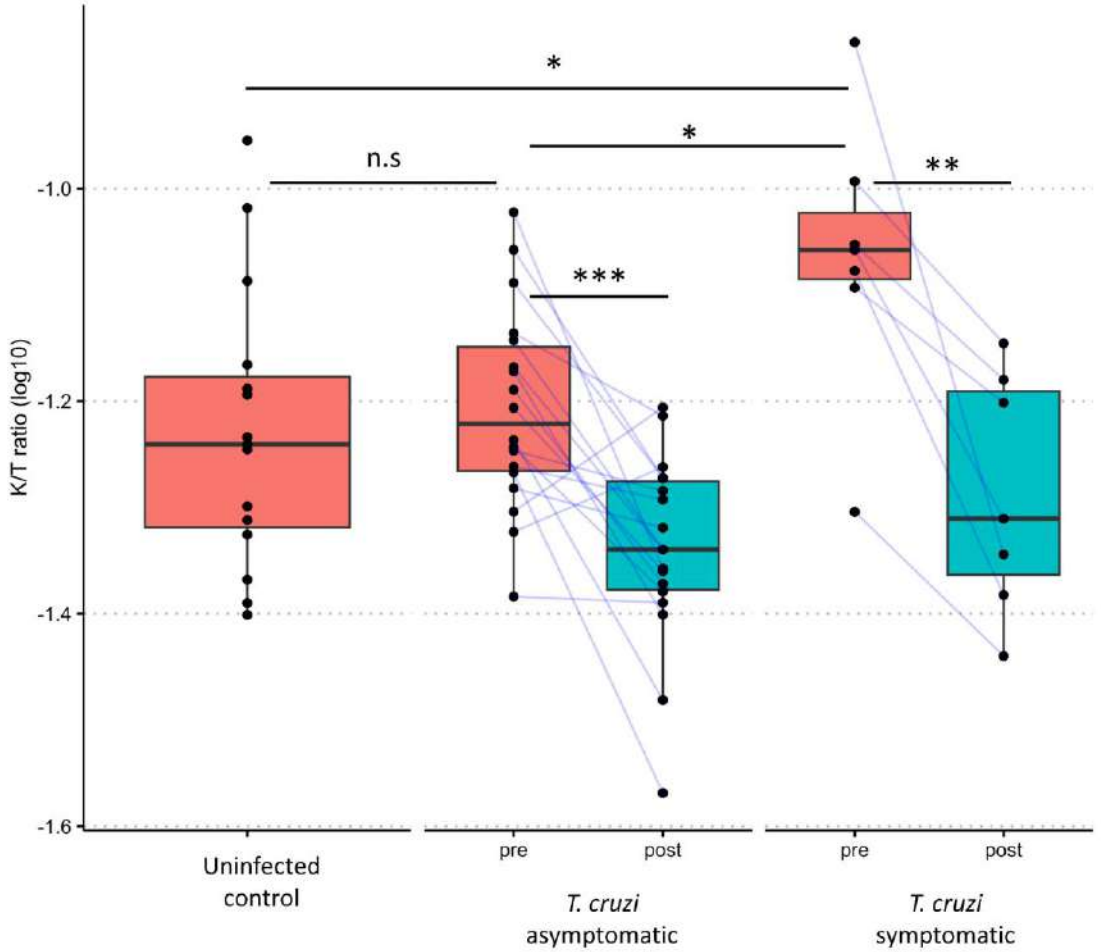


Comparison	Downregulated	Upregulated
***T. cruzi* infected pre-treatment vs. non-infected**	206	12
Symptomatic *T. cruzi* infected pre-treatment vs. non-infected	215	47
Asymptomatic *T. cruzi* infected pre-treatment vs. non-infected	1	0
Symptomatic vs. Asymptomatic *T. cruzi* infected pre-treatment	1	1
***T. cruzi* infected post-treatment vs. non-infected**	4	0
Symptomatic *T. cruzi* infected post-treatment vs. non-infected	3	0
Asymptomatic *T. cruzi* infected post-treatment vs. non-infected	0	0
Symptomatic vs. Asymptomatic *T. cruzi* infected post-treatment	0	0
T. cruzi infected post- vs. pre-treatment	0	0
Symptomatic *T. cruzi* infected post- vs. pre-treatment	0	0
Asymptomatic *T. cruzi* infected post- vs. pre-treatment	0	0

Ros-Lucas et al, 2024.

Chronic immune stimulation and exhasution are associated with symptomatic disease

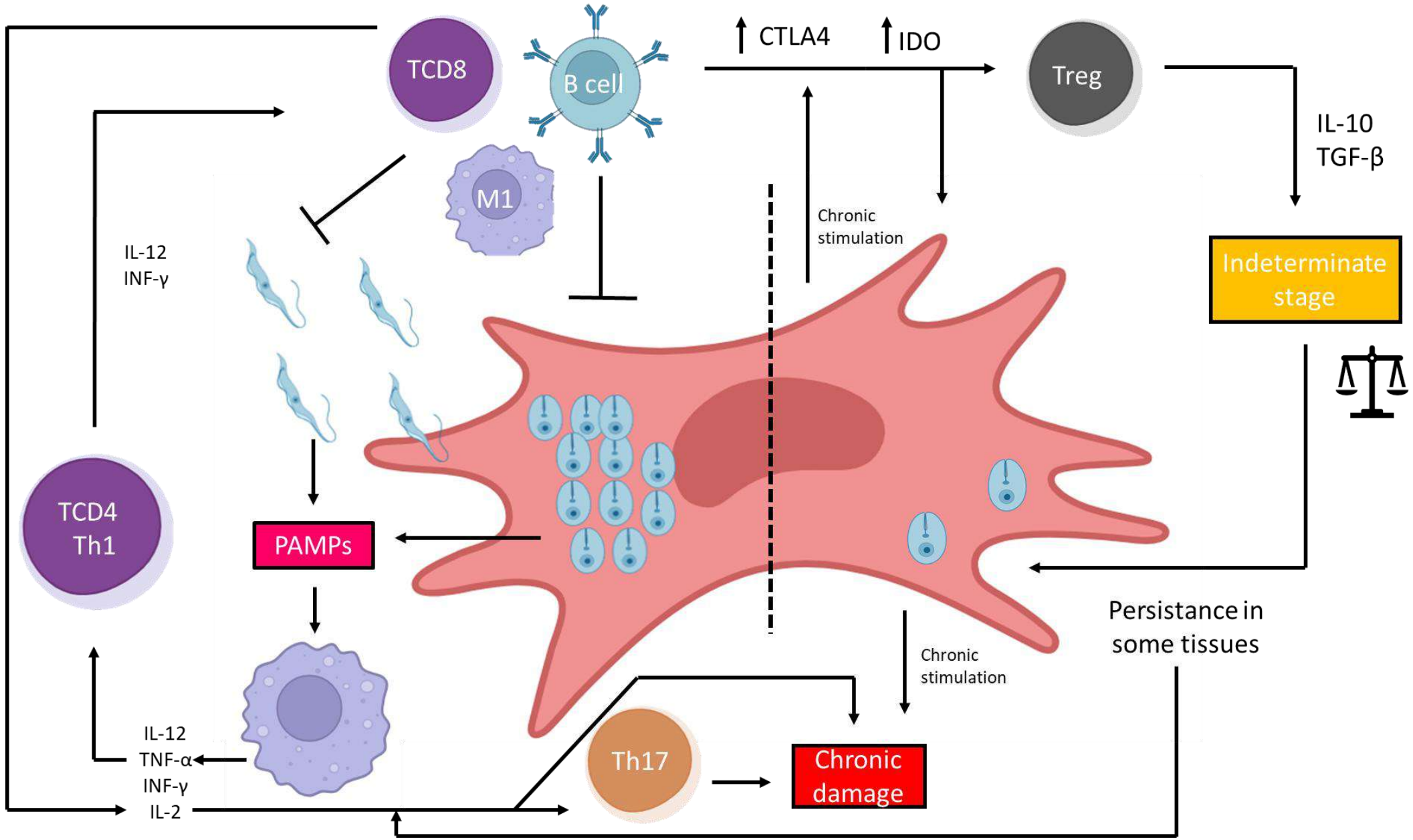




Treatment is associated with down-regulation of pro-inflammatory pathways and reductions in the K/T ratio.

Ros-Lucas et al, 2024.

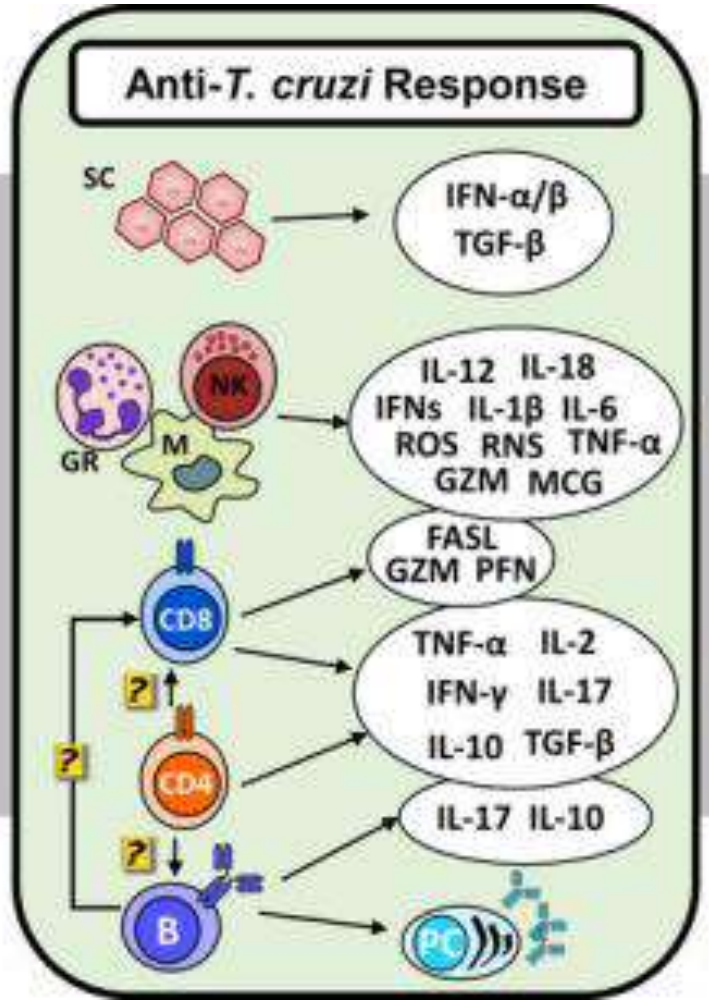
Again, balance…



A very complex balancing act…

Parasite Factors

- Complement Inhibition
- Phagosome escape → cytosolic residence
- Anti-oxidant network
- B cell mitogens → Polyclonal B activation
- DC phenotype modulation
- Thymocyte & B cell apoptosis
- Cruzipain (+ others?) → TGFβ activation
- Trans-sialidase (+ others?) → IL-10 ↑
- Extracellular vesicles, decoy antigens
- Antigenic diversity (population, individual)
- Metabolic quiescence, dormancy?
- Low MHC expression environments
- 'Trojan horse' intracellular dissemination

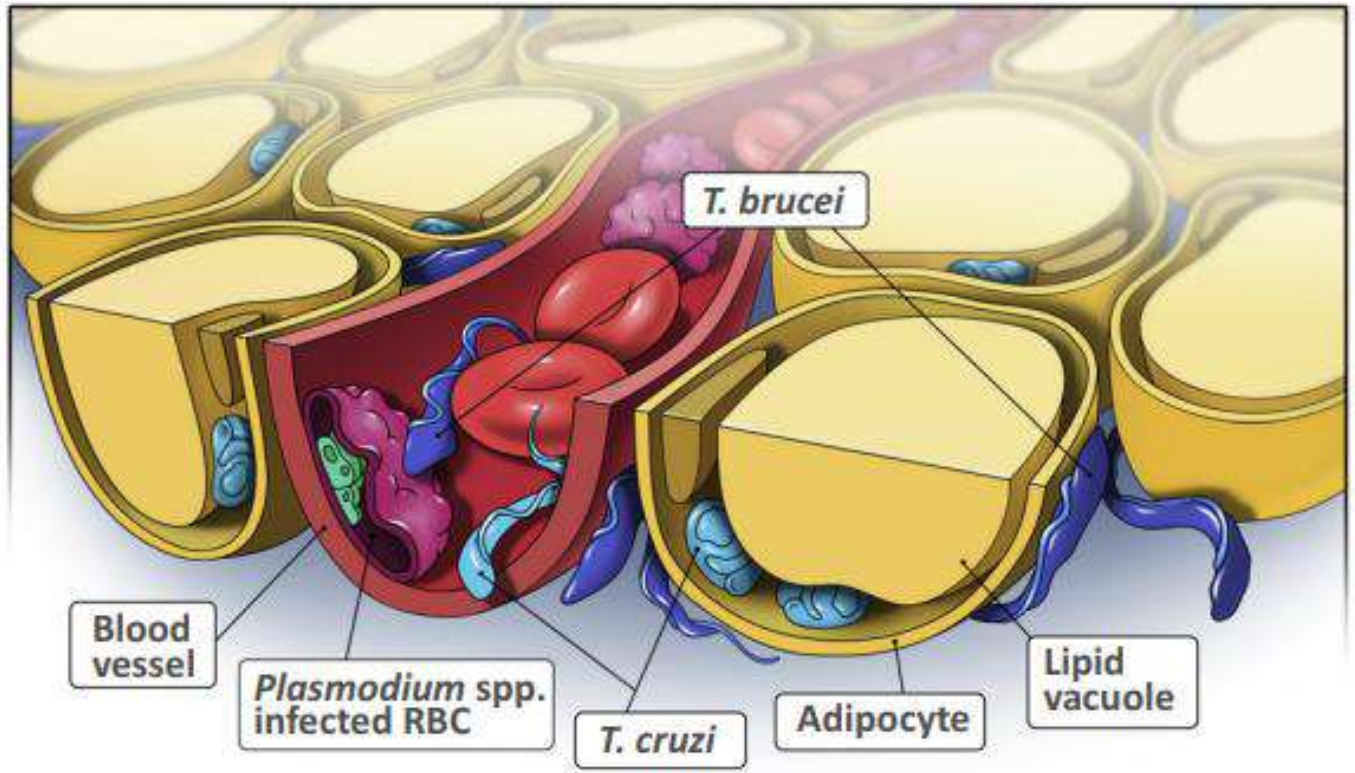


Host Factors

- Cytokine-mediated deactivation (IL-10, TGF-β, SOCS)
- Myeloid-derived suppressor cells
- Alternatively activated macrophages
- Regulatory T and B cells
- T cell inhibitory receptors (PD-1, CTLA4, TIM-3 etc.)
- Immunodominance hierarchies
- Compartmentalisation
- Privileged sites
- Microbiota
- Other infections
- Co-morbidities

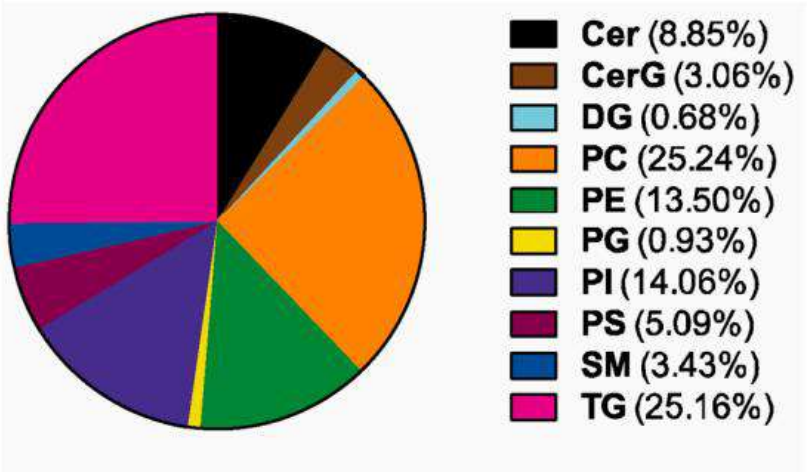
Pérez-Mazliah et al, 2020

Parasite and host metabolism play a key role too…

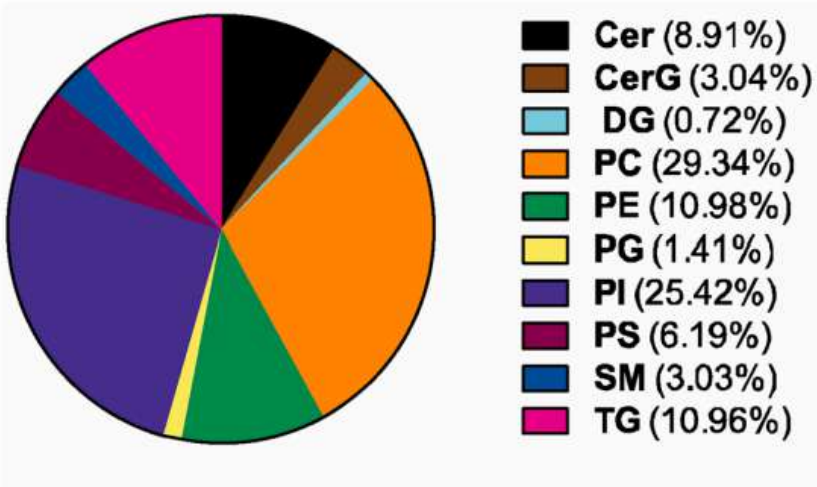


Tanowitz et al, 2017

Amastigote



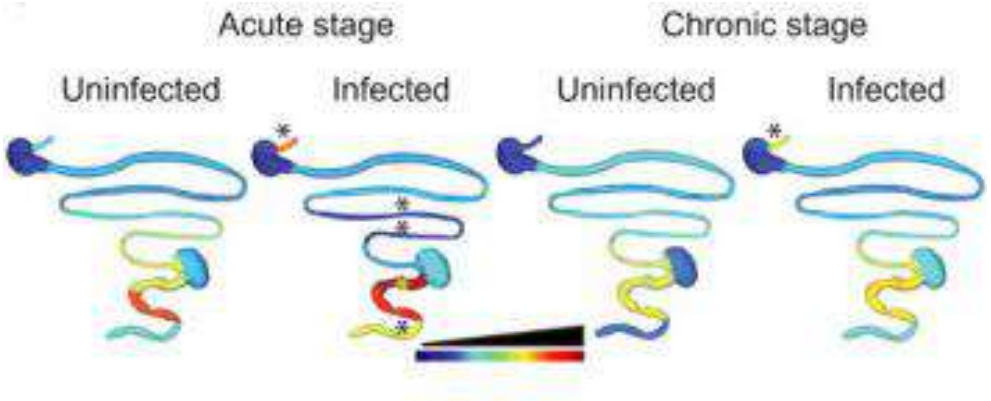
Trypomastigote



Parreira de Aquino et al, 2021

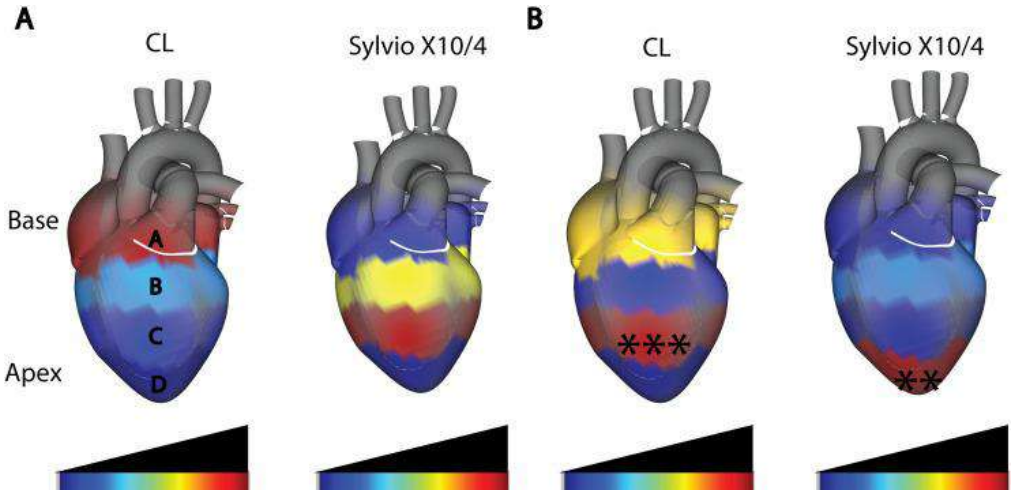
Infection with *T. cruzi* leads to detectable metabolic changes

Abundance of PC(20:4)

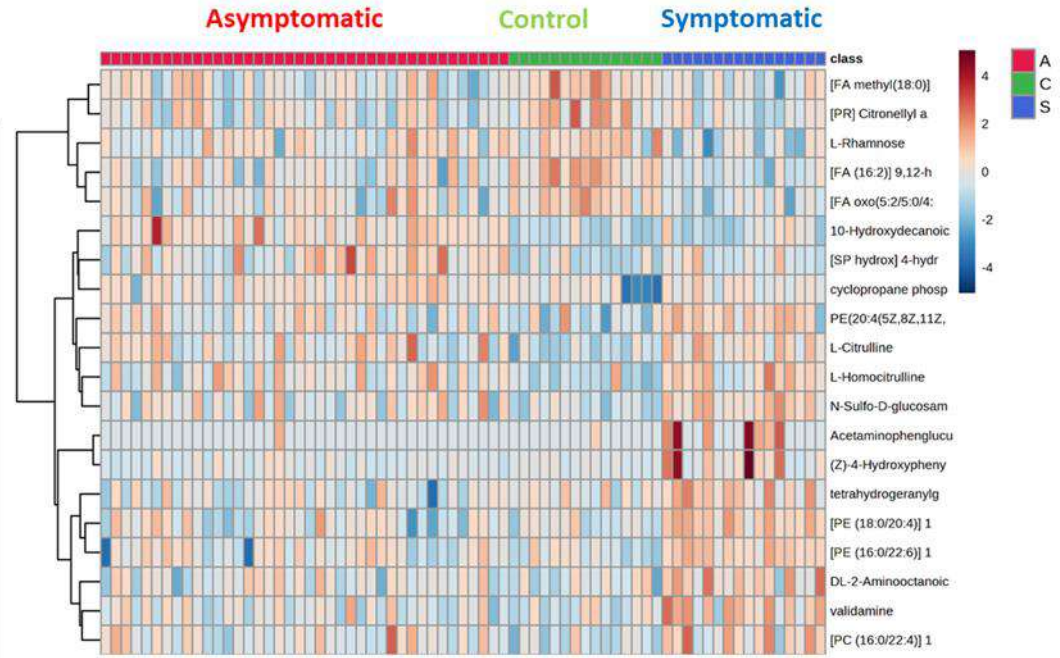


Overall metabolic disturbance

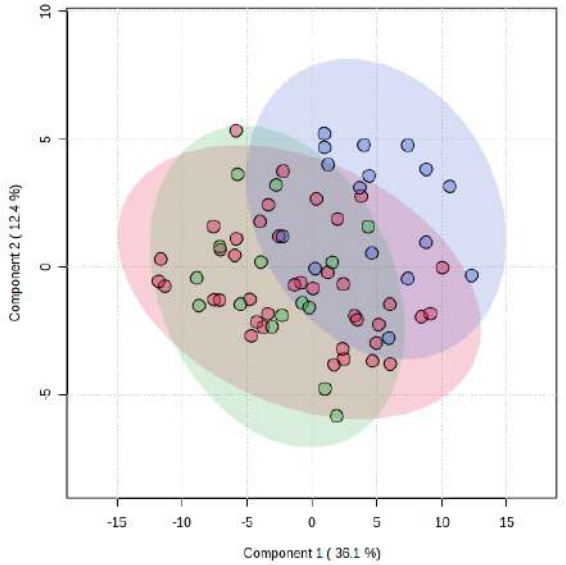
Hossain et al, 2020



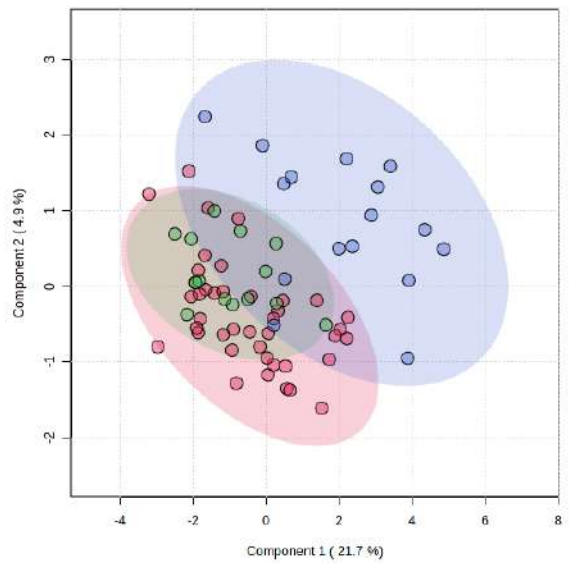
Dean et al, 2021



Negative lipids

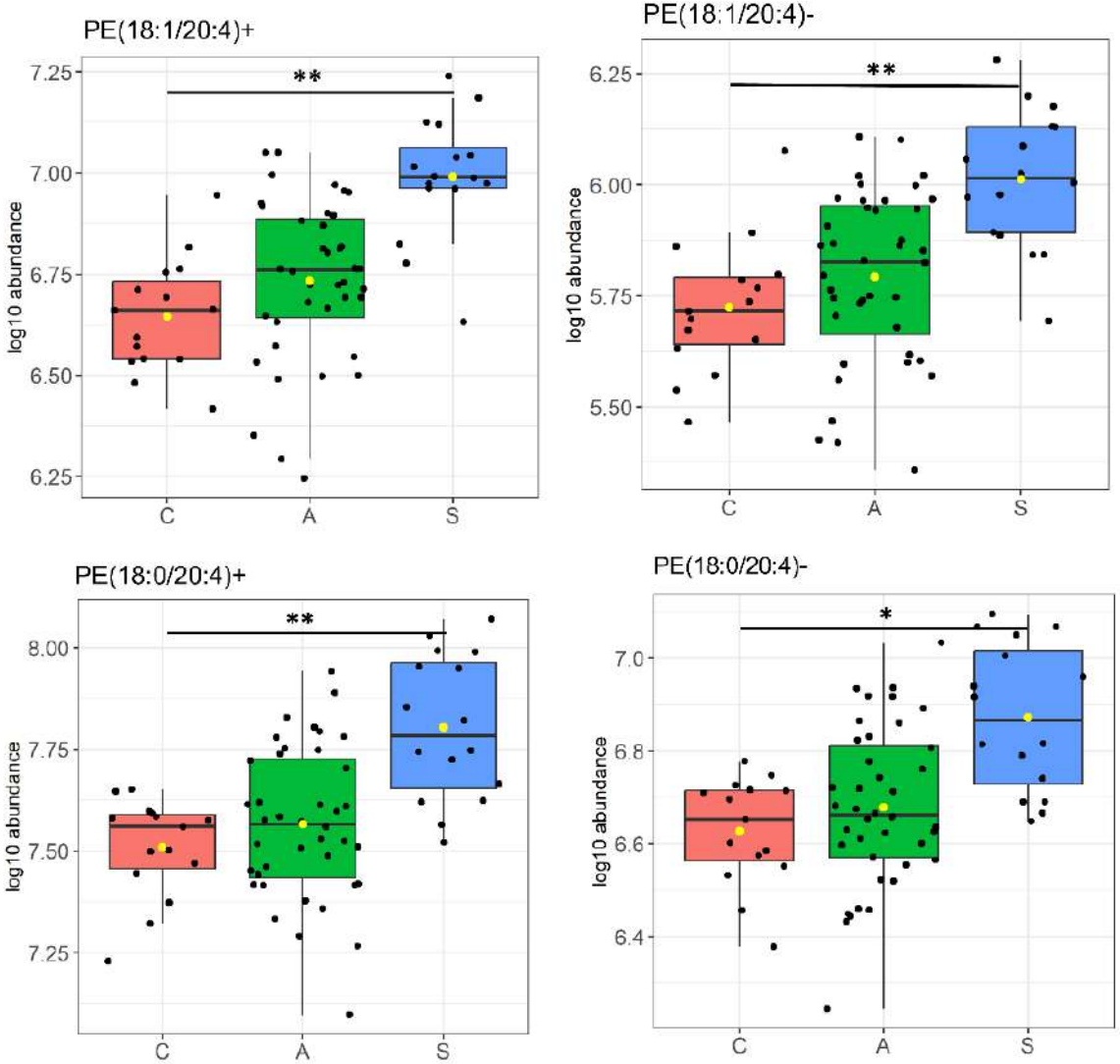


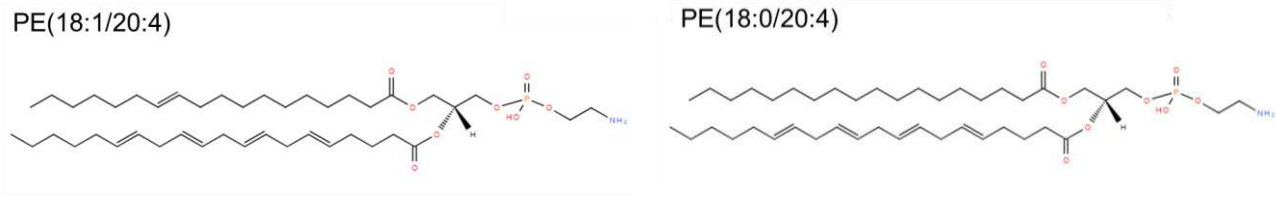
Positive lipids

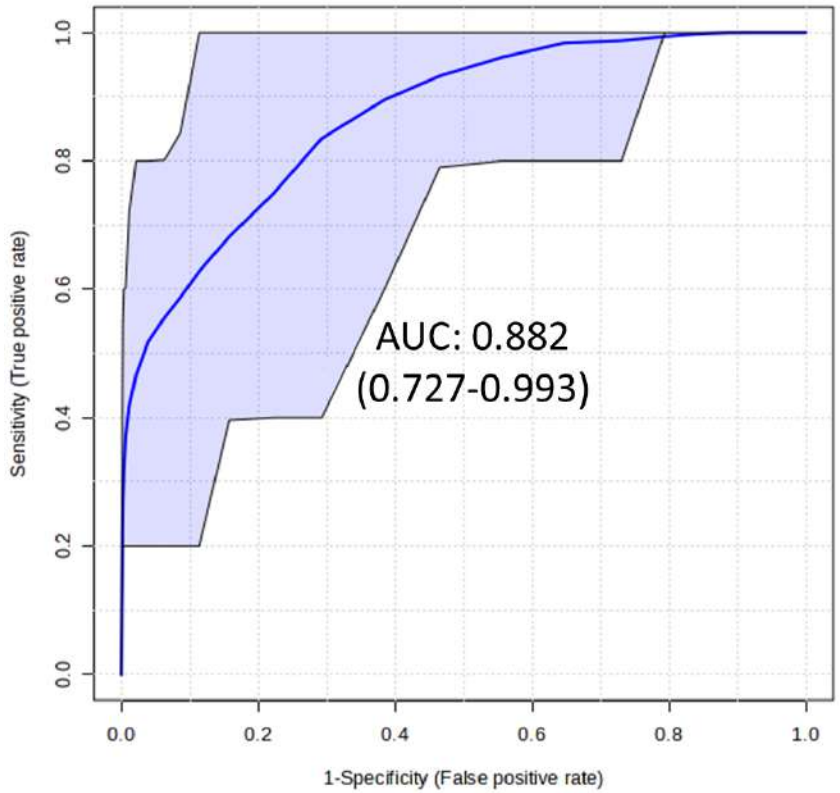


Gabaldón-Figueira et al, 2024

Some lipids are differentially abundant in symptomatic participants







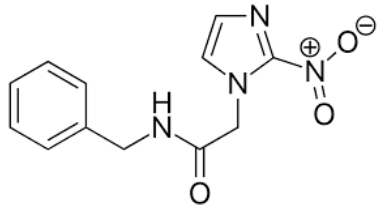
Phosphoethanolamines have a good capacity to discriminate symptomatic and asymptomatic participants

More likely a consequence rather than a cause…

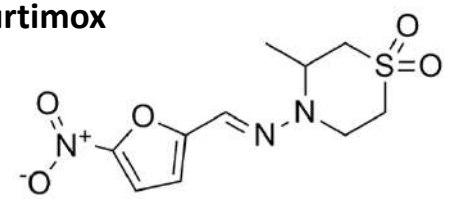
Gabaldón-Figueira et al, 2024

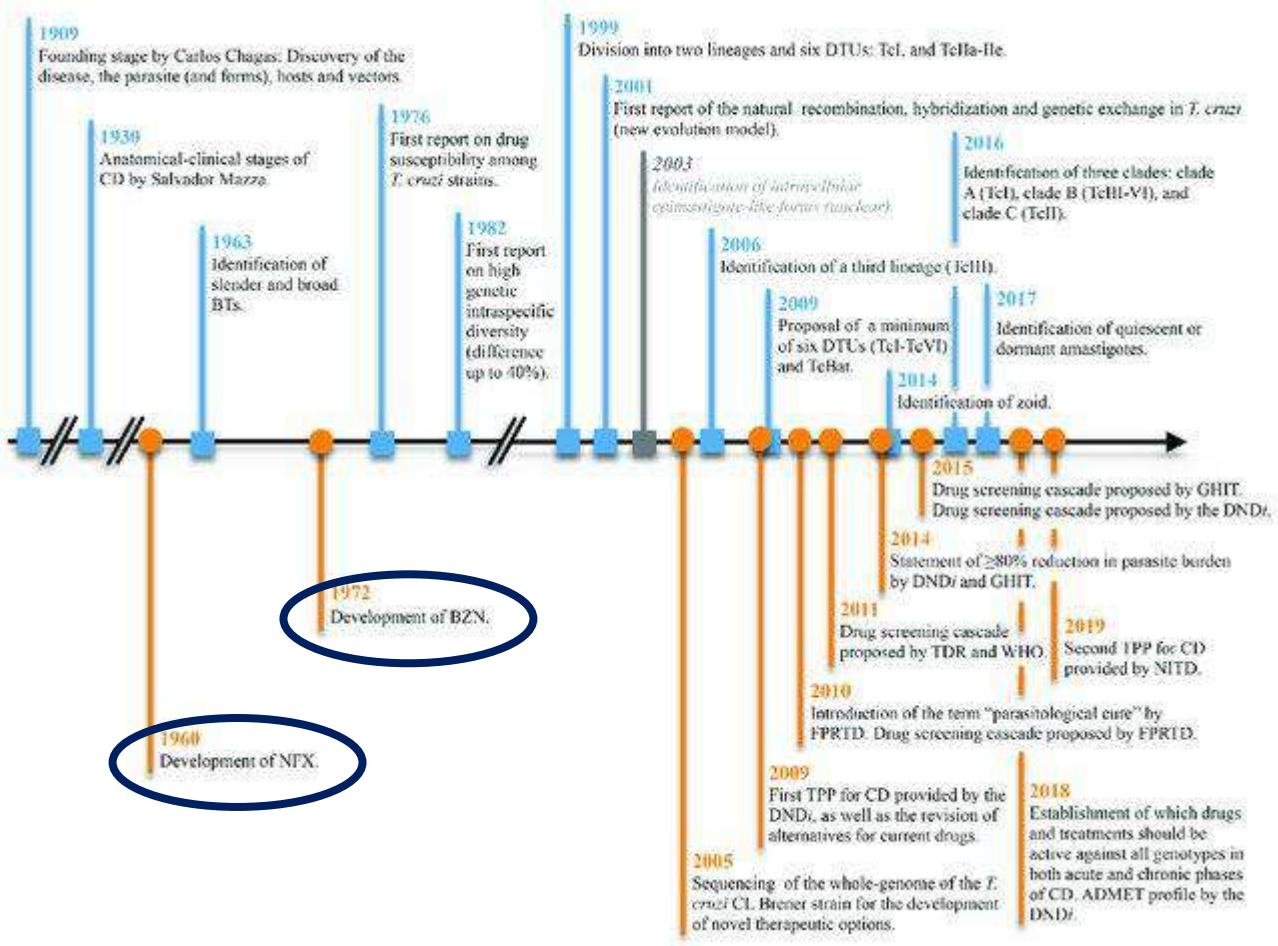
Modulating host-pathogen interactions can help us improve treatment alternatives

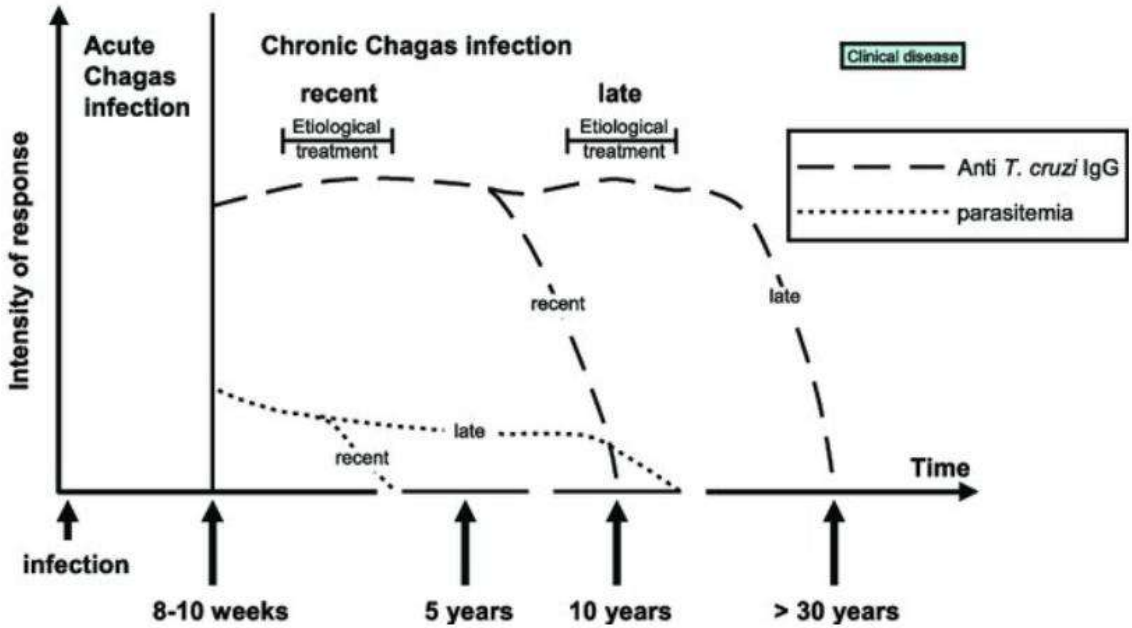
Benznidazole



Nifurtimox



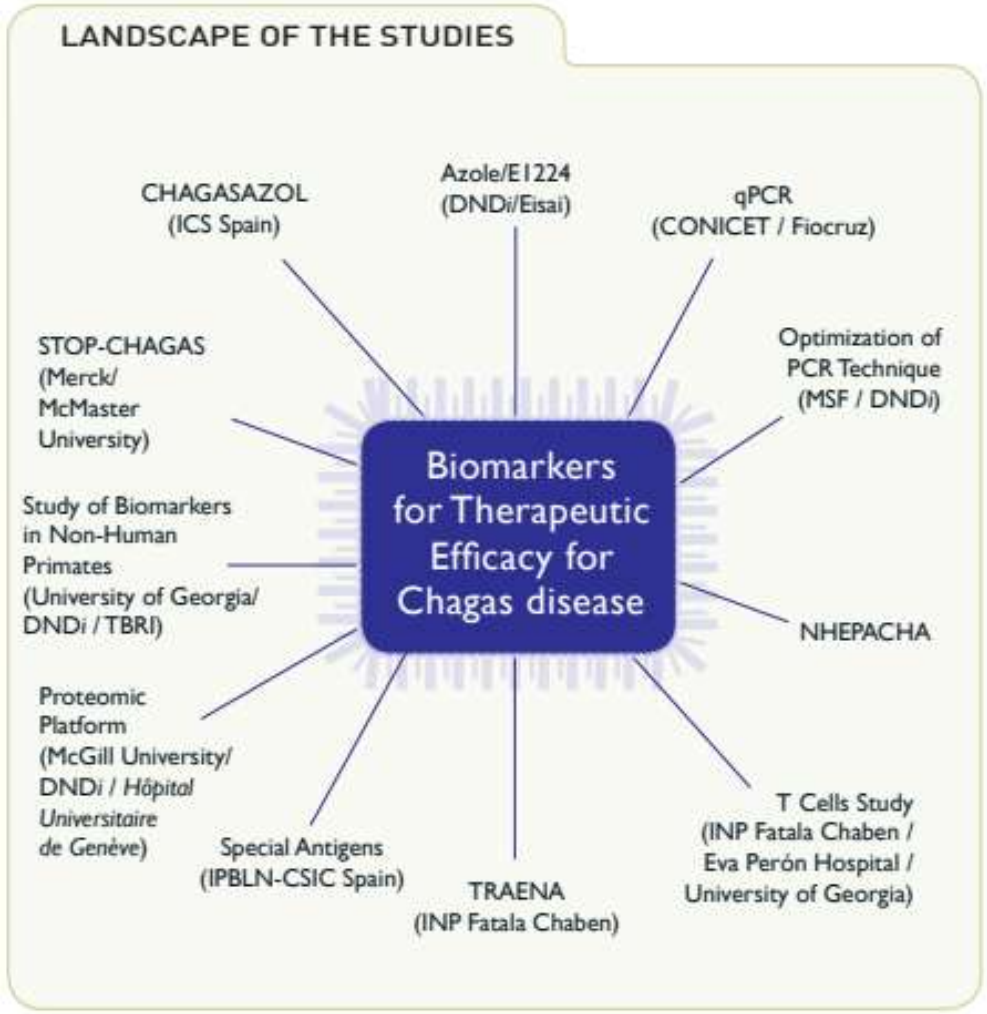


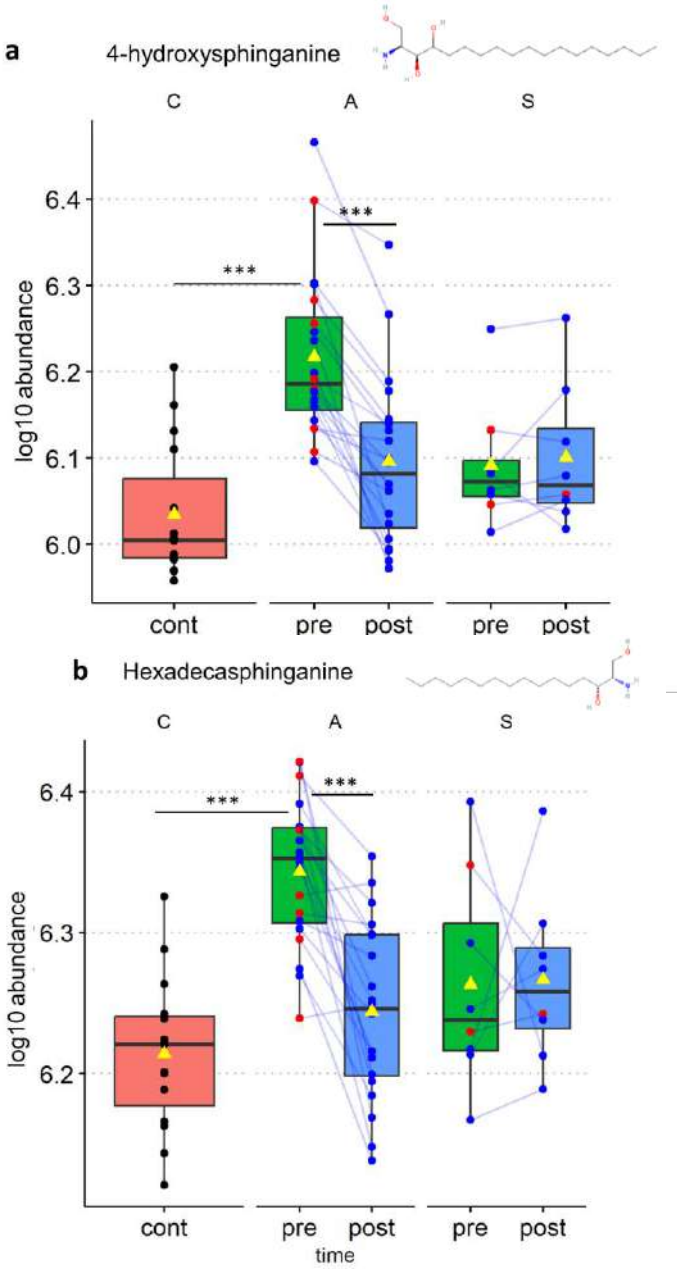


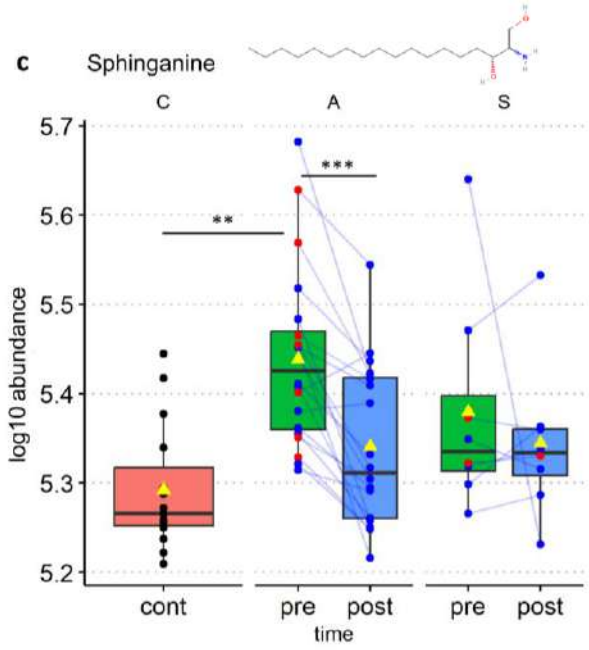
Knowing if an infected patient has been cured **is incredibly difficult!**

Escolano et al, 2024

Changes during the course of infection can be useful for monitoring early treatment efficacy



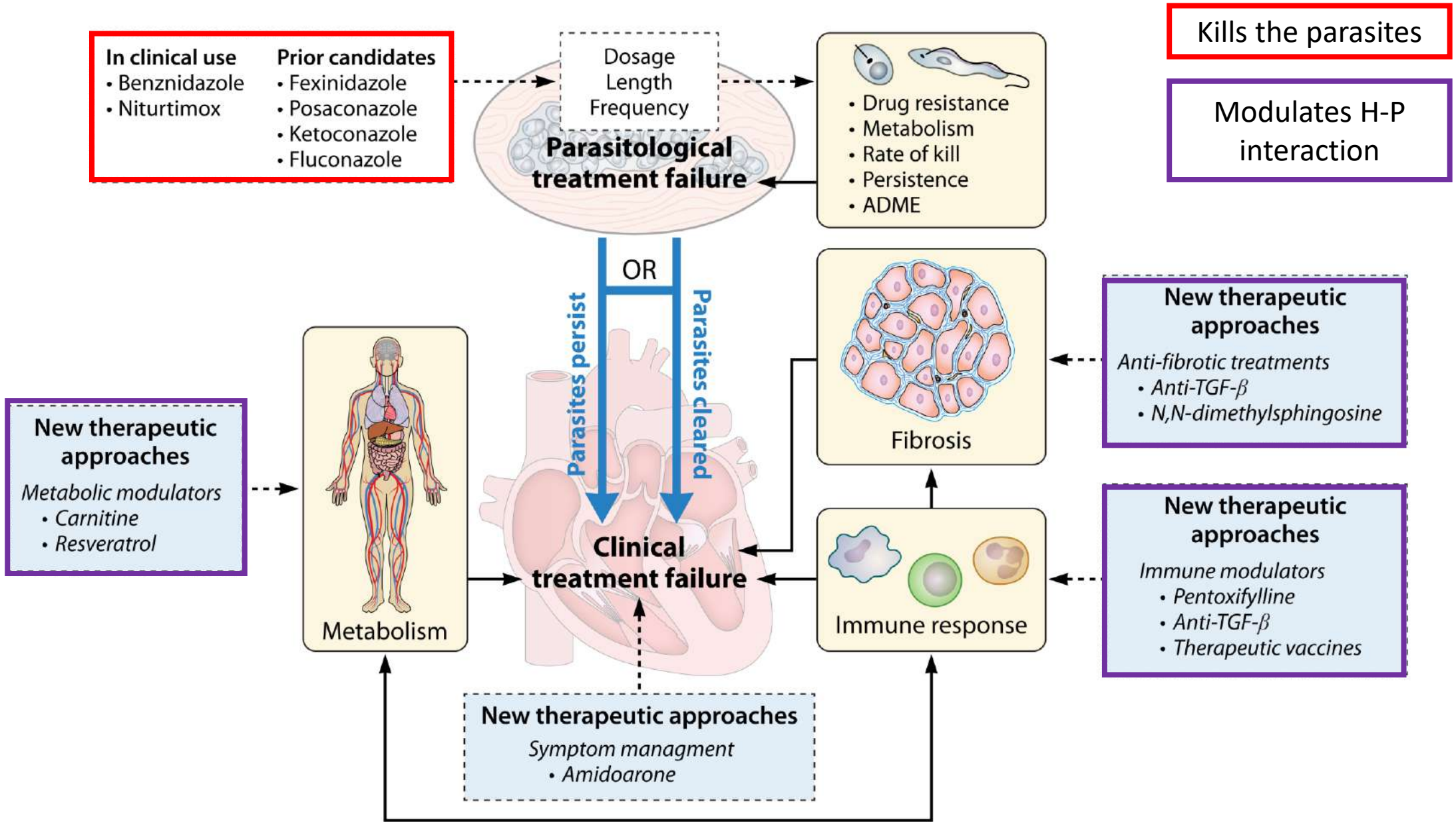




The abundance of sphingoid bases decreases less than a year after completion of anti-parasitic therapy in asymptomatic patients with a negative qPCR.

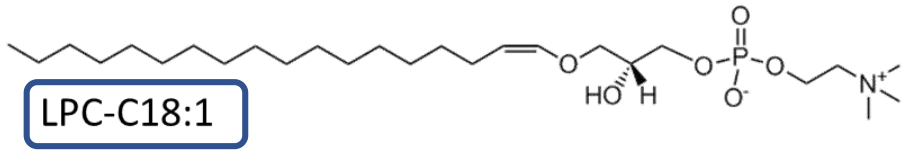
Gabaldón-Figueira et al, 2024

New medications should not exclusively focus on killing the parasites



Ernst et al, 2025

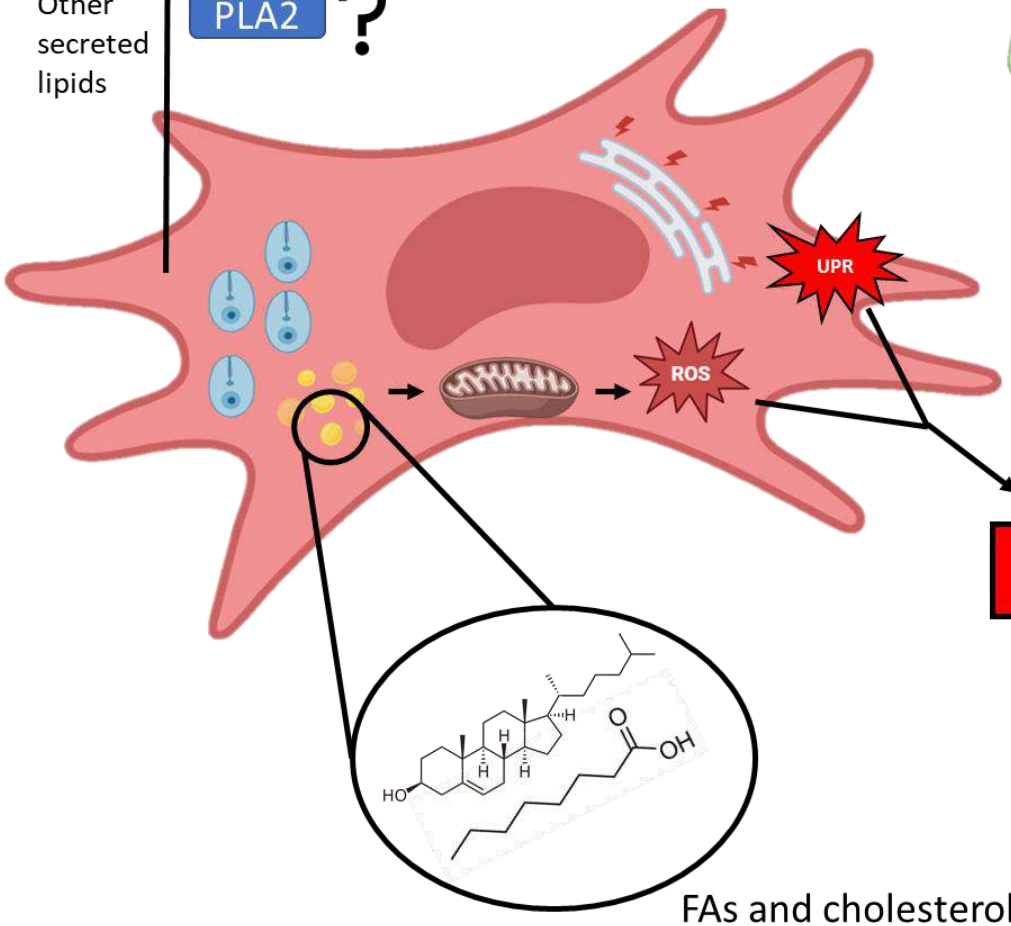
Disruption of lipid metabolism also conditions organ damage



LPC-C18:1

Other secreted lipids

PLA2 ?



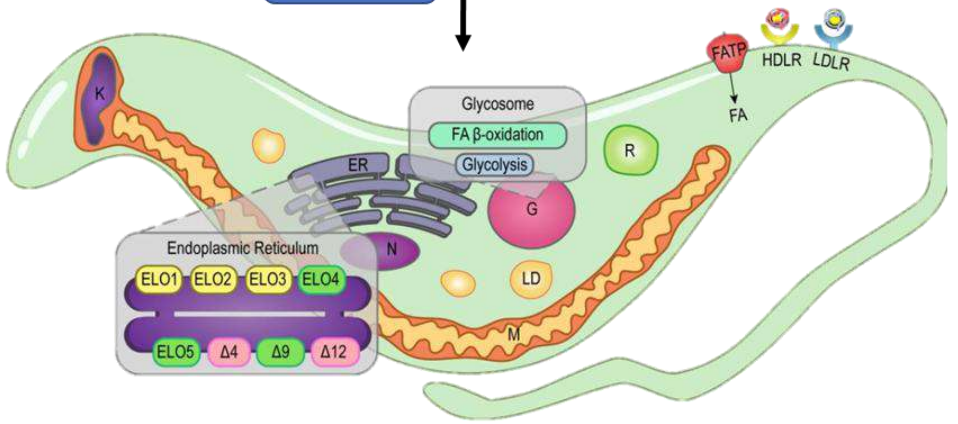
FAs and cholesterol

Chronic damage

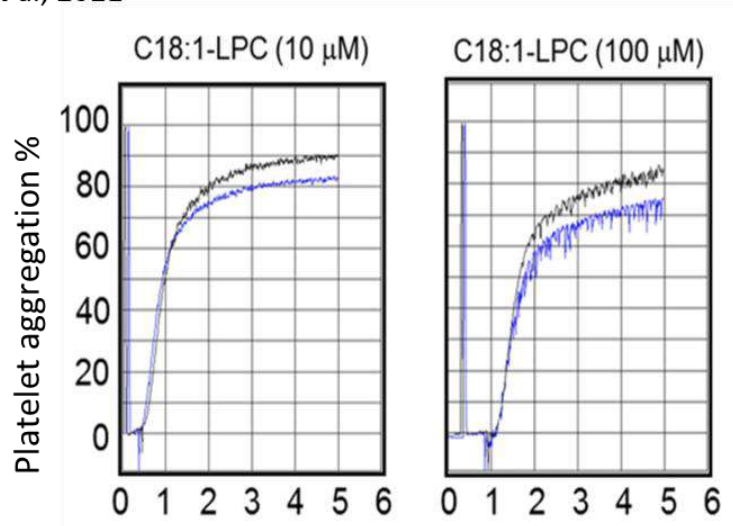
TcPAQR

Virulence

Thrombosis



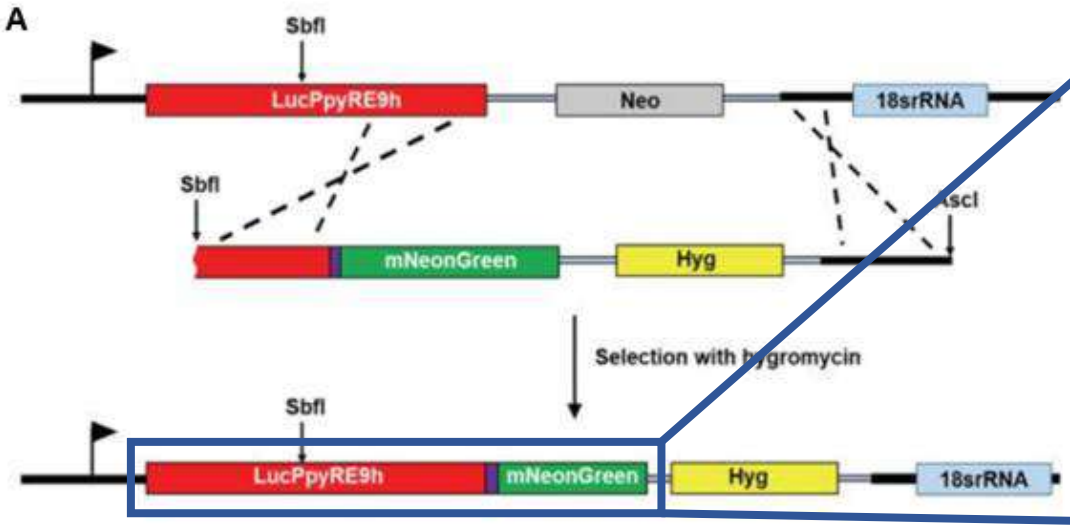
Parreira de Aquino et al, 2021

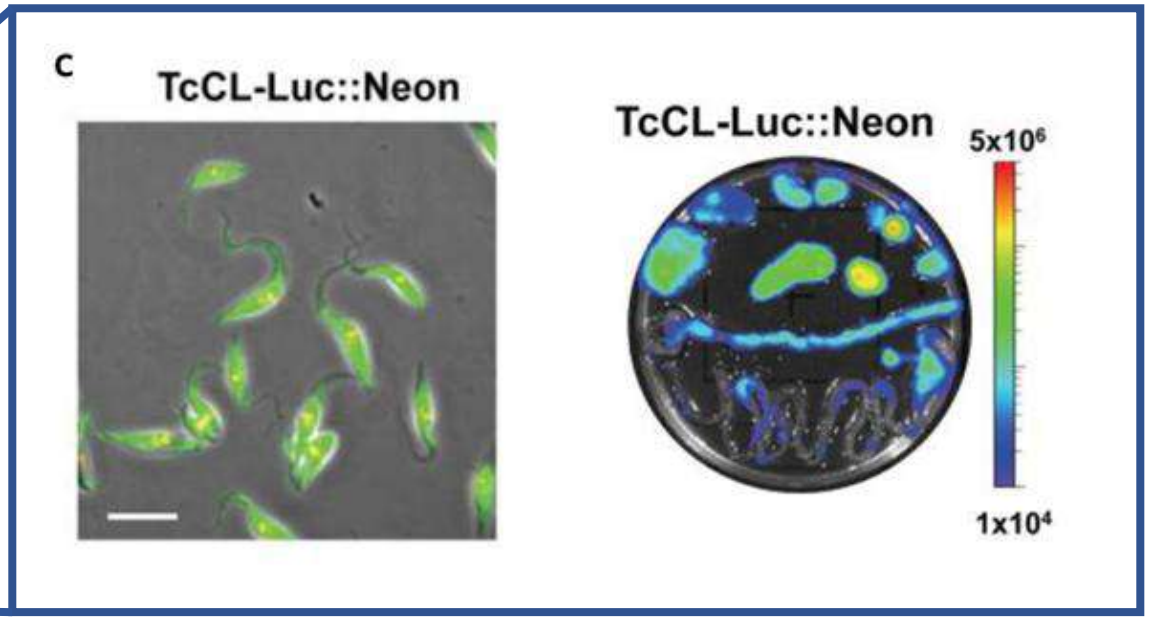


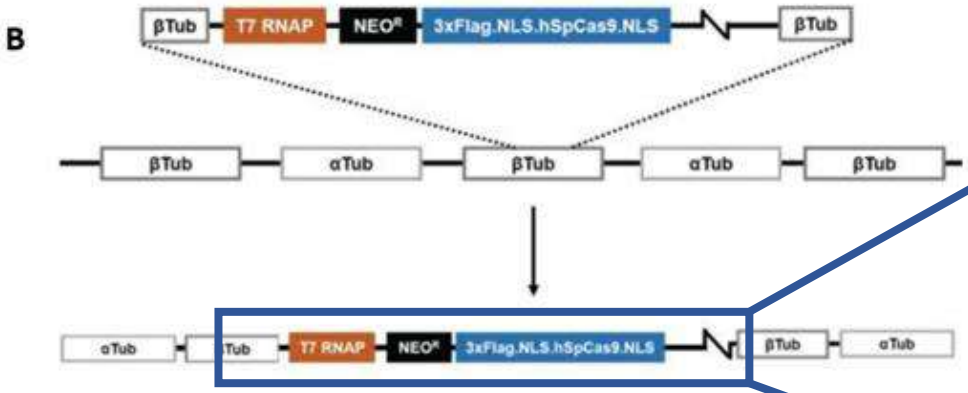
Gazos-Lopes et al, 2014

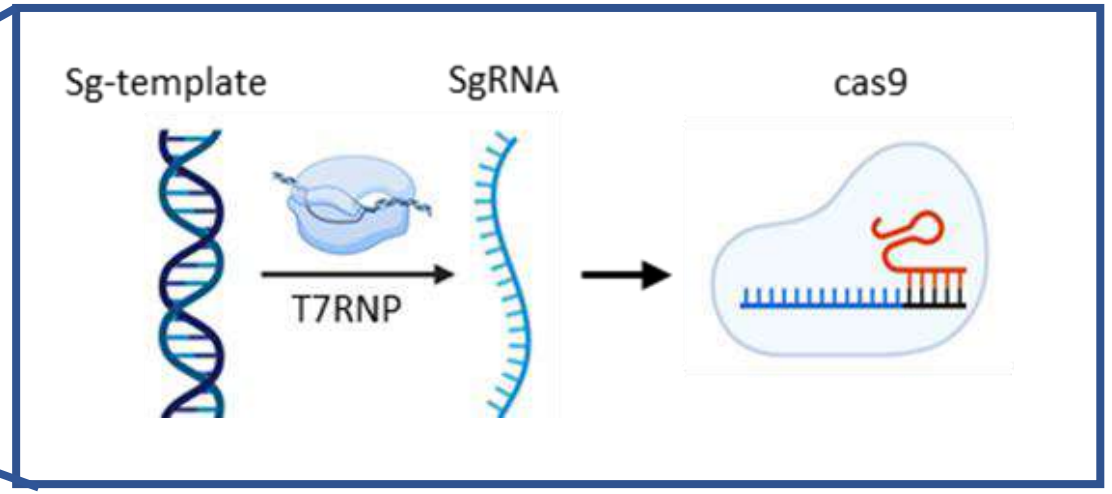
PAF

Recent tools to understand host-pathogen interactions during *T. cruzi* infection



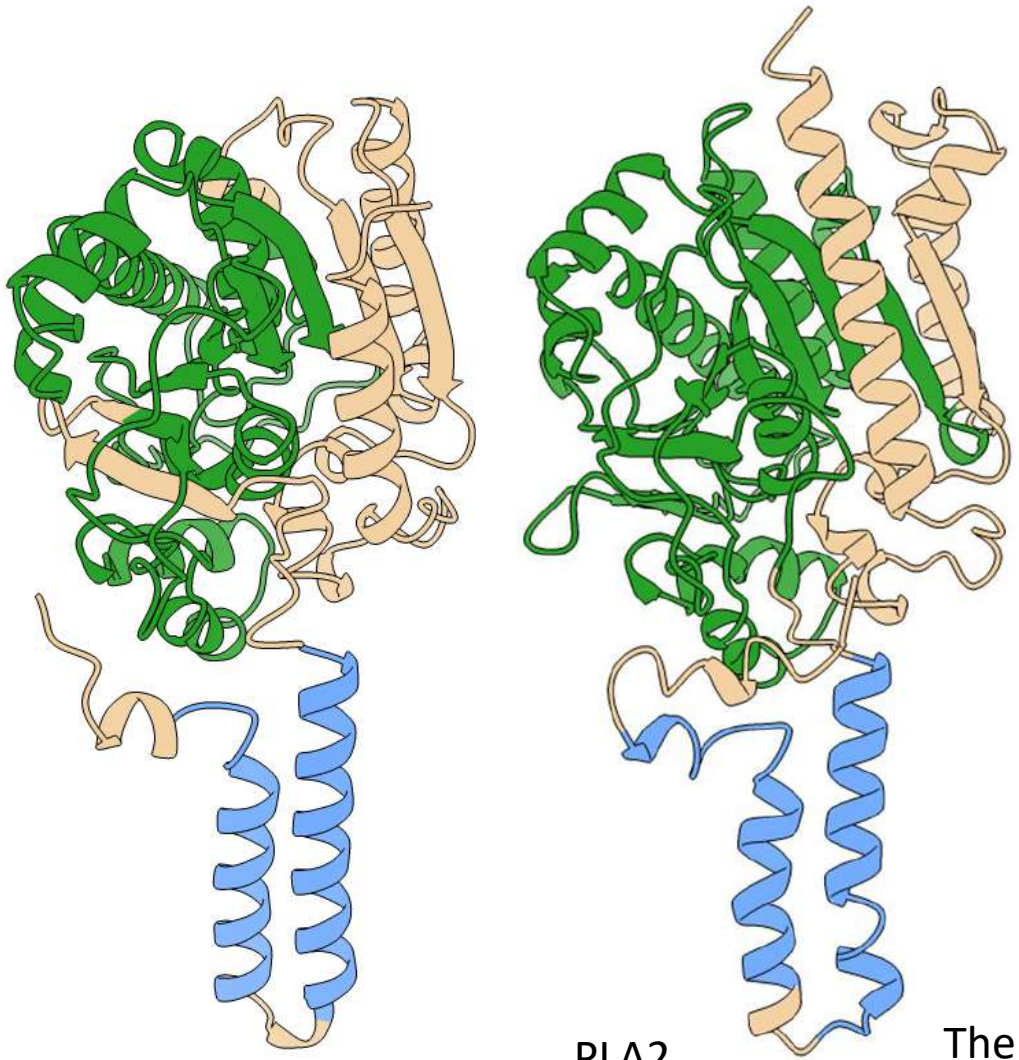




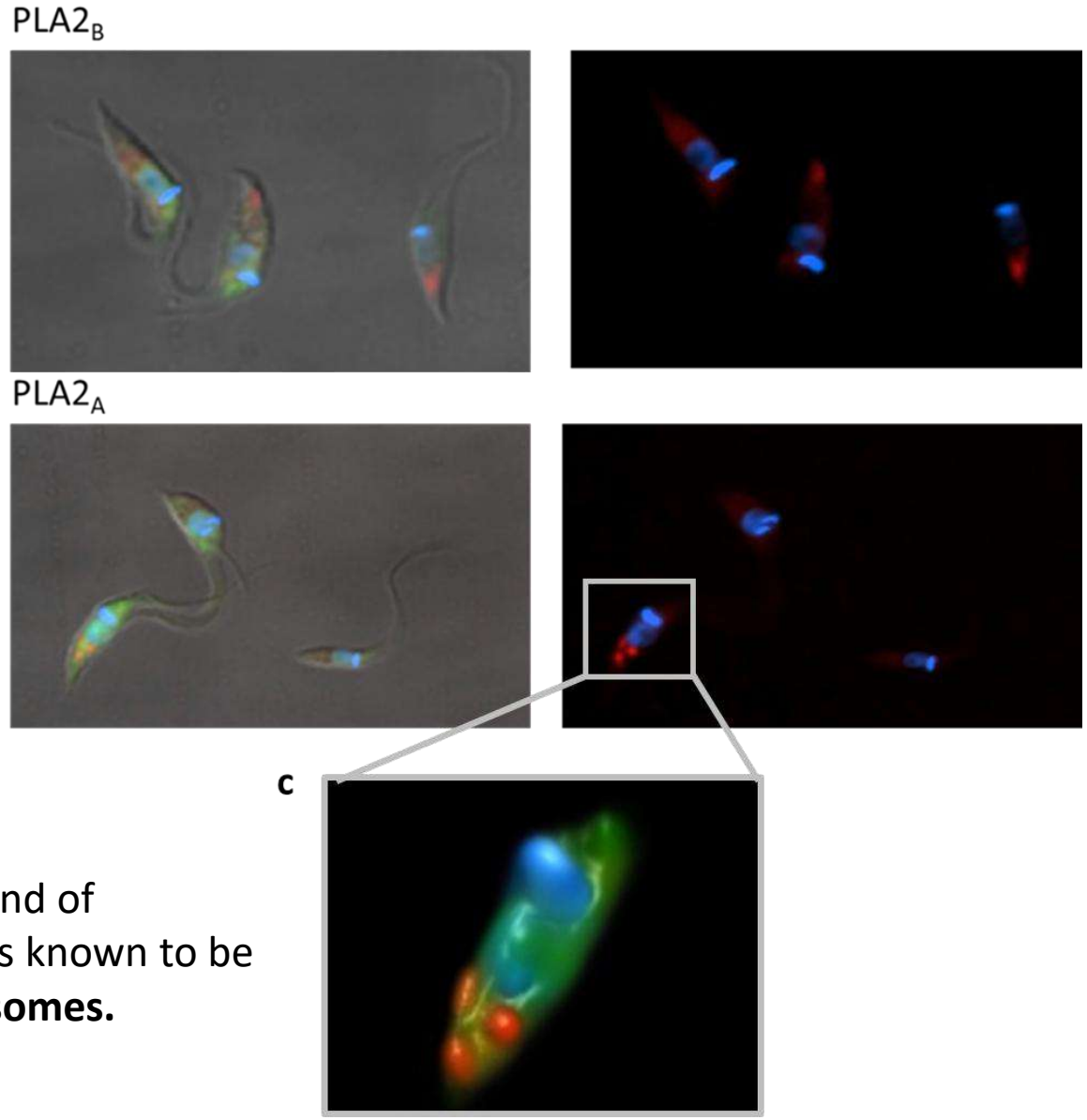


Adapted from Costa et al 2018.

Structure and localization of $PLA2_A$ and $PLA2_B$



$PLA2_A$ $PLA2_B$

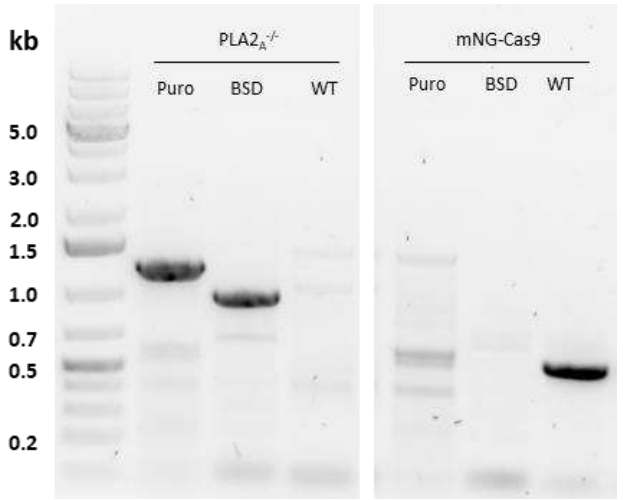


The posterior end of epimastigotes is known to be rich in **reservosomes.**

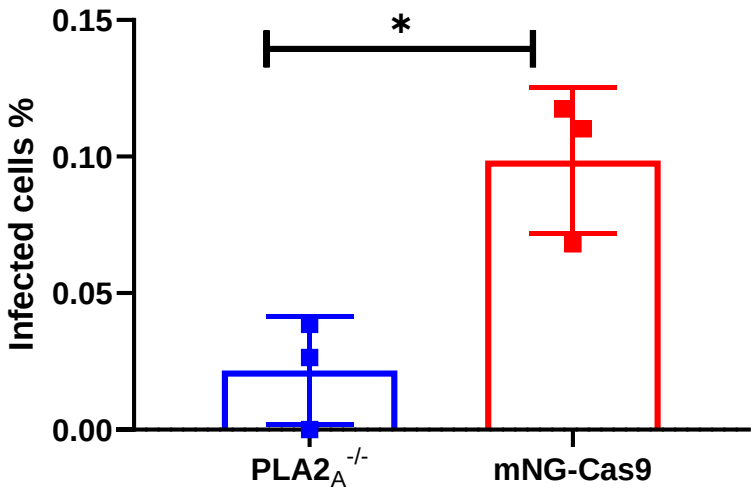
Gabaldón-Figueira et al, unpublished data

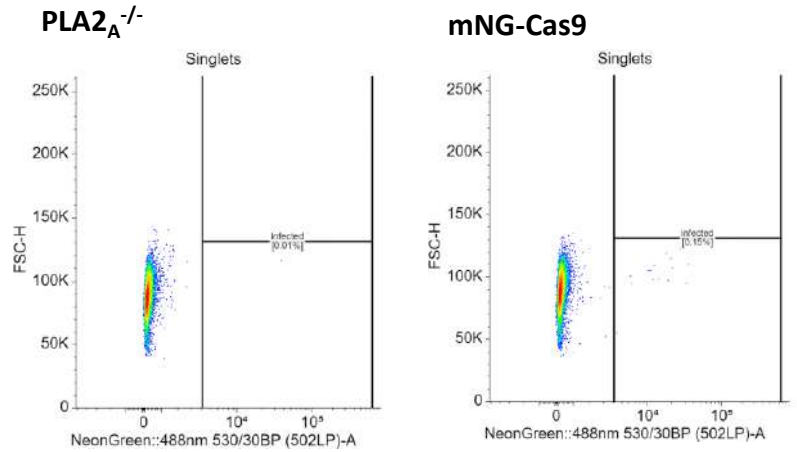
Phenotypic characterization of the PLA2$_A^{-/-}$ line

PLA2$_A$

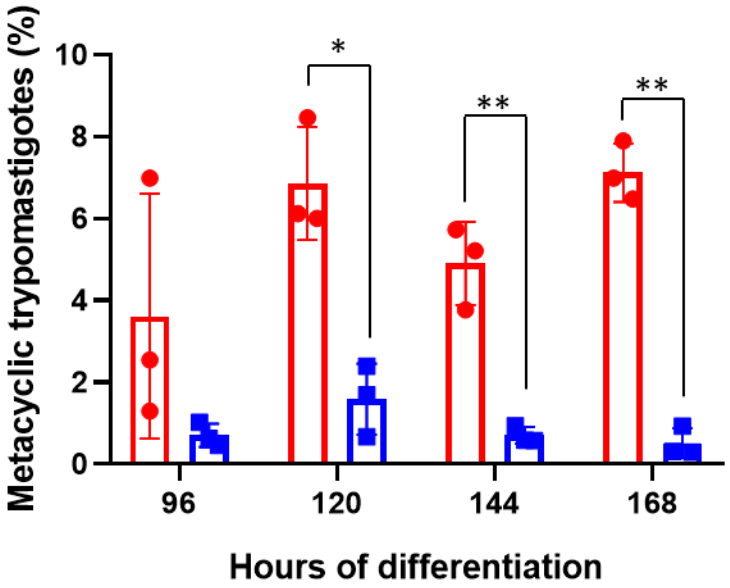


Infectivity (epimastigotes)

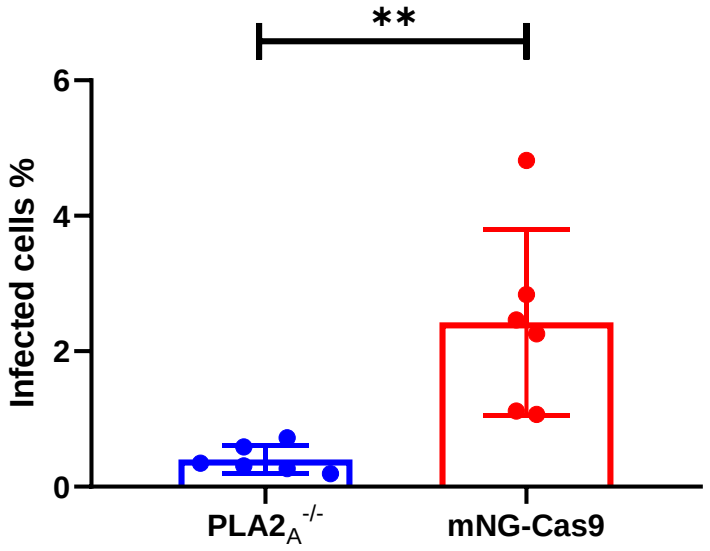


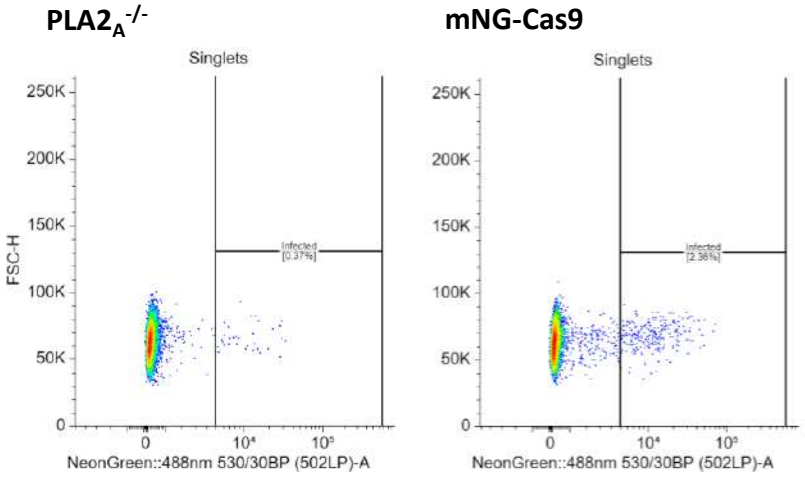


Metacyclogenesis



Infectivity (TCT)



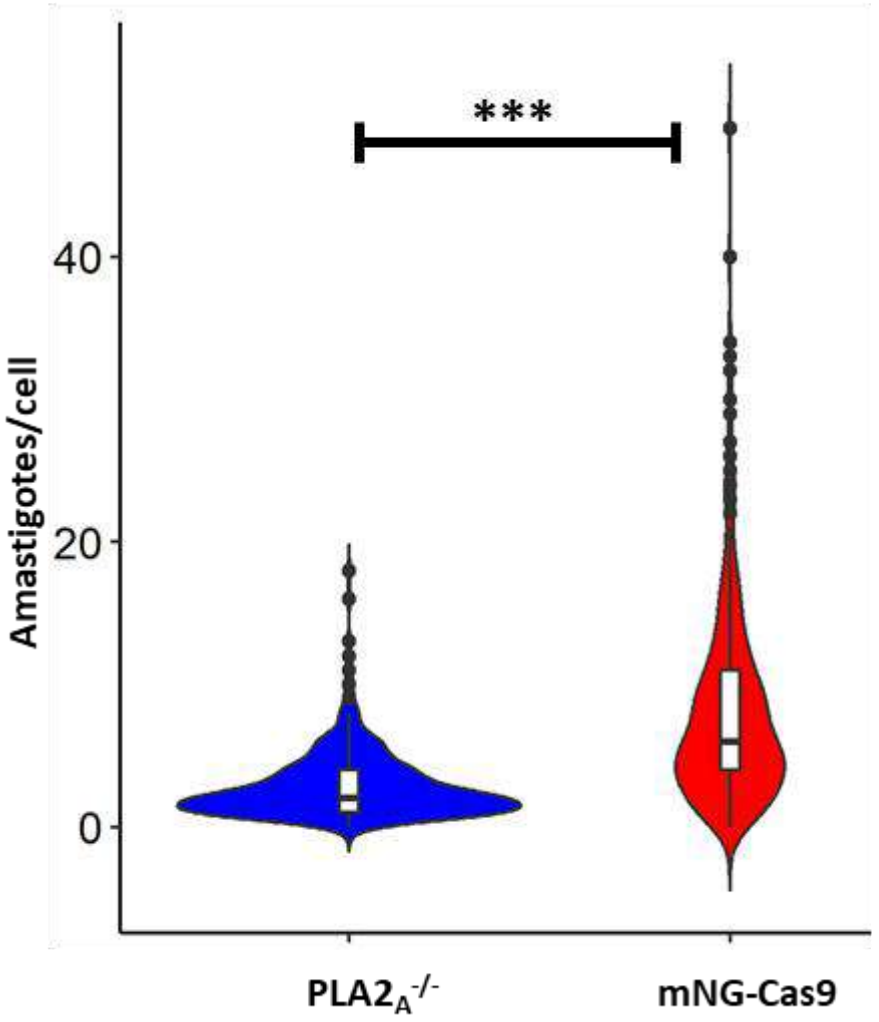


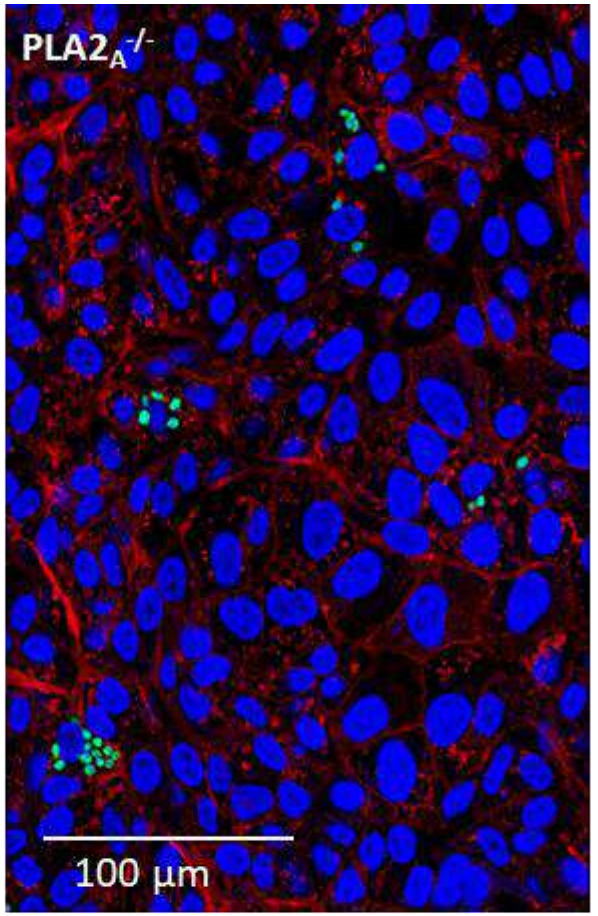
Gabaldón-Figueira et al, unpublished data

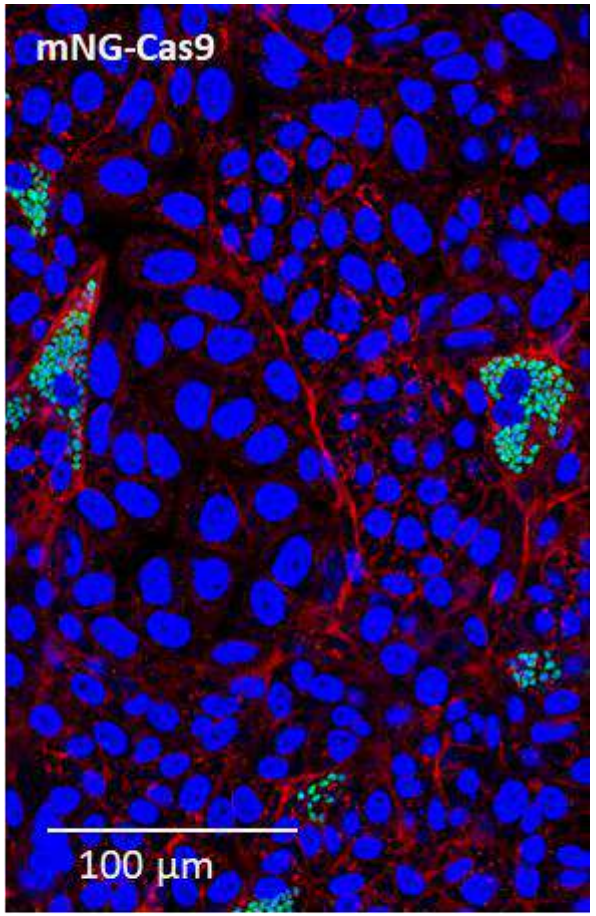
Phenotypic characterization of the PLA2$_A^{-/-}$ line

PLA2$_A$ deletion **hinders metacyclogenesis** and is associated with **a reduced capacity to infect cells and replicate.**

96h post-infection

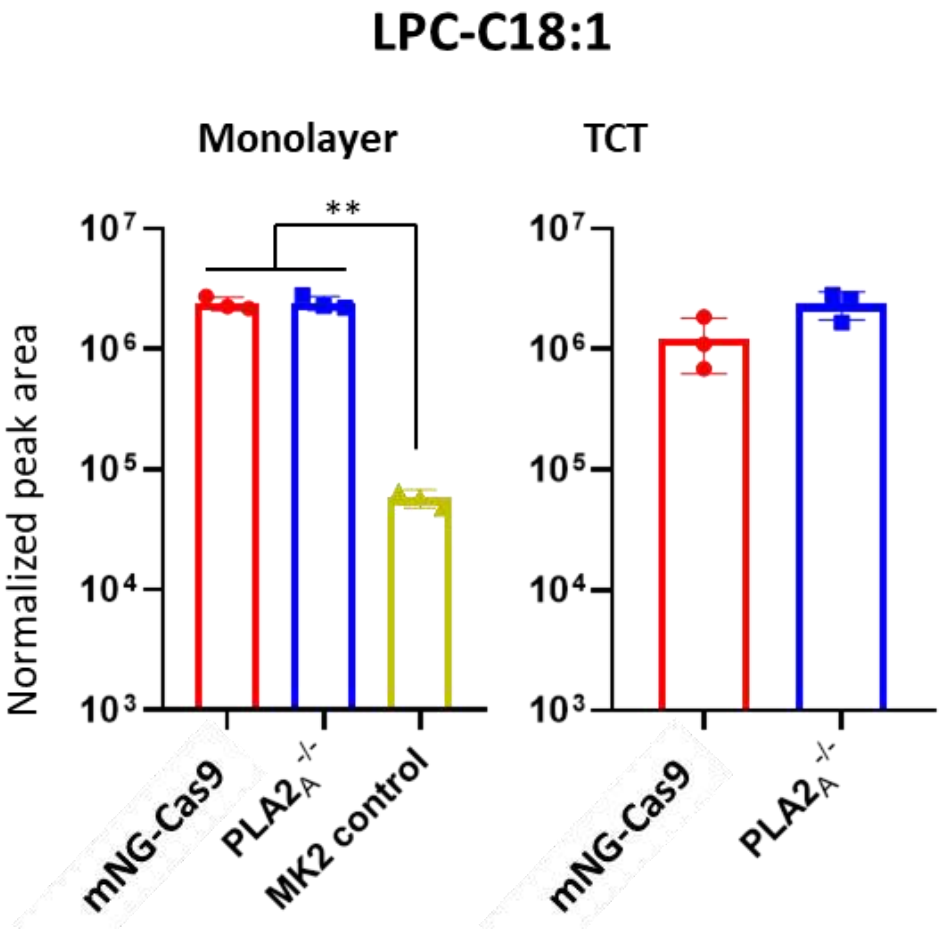


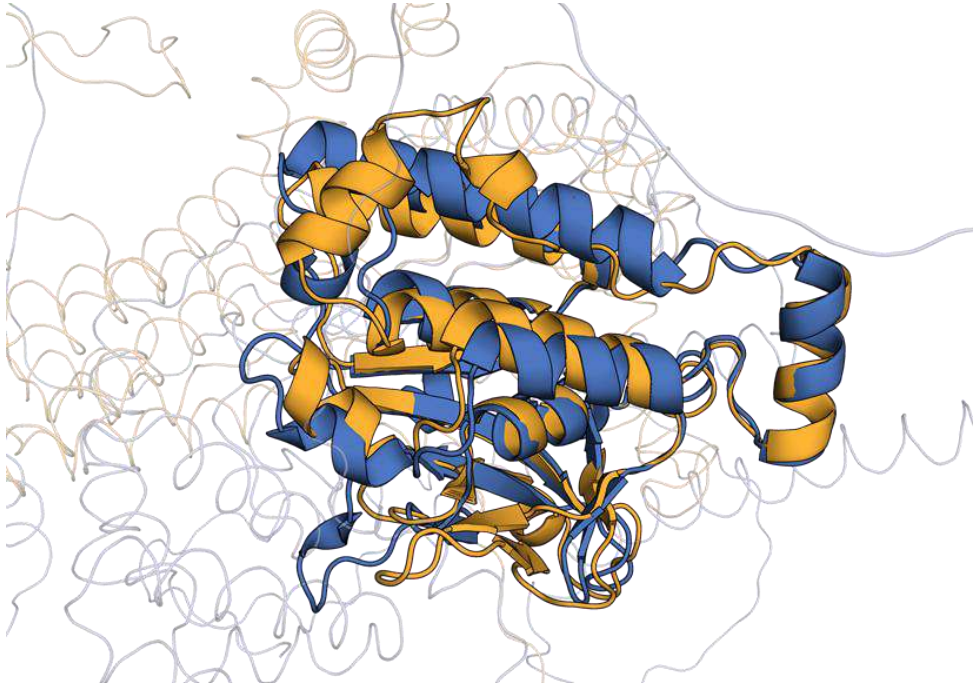




Gabaldón-Figueira et al, unpublished data

Lysophospholipid production in the $PLA2_A^{-/-}$ line



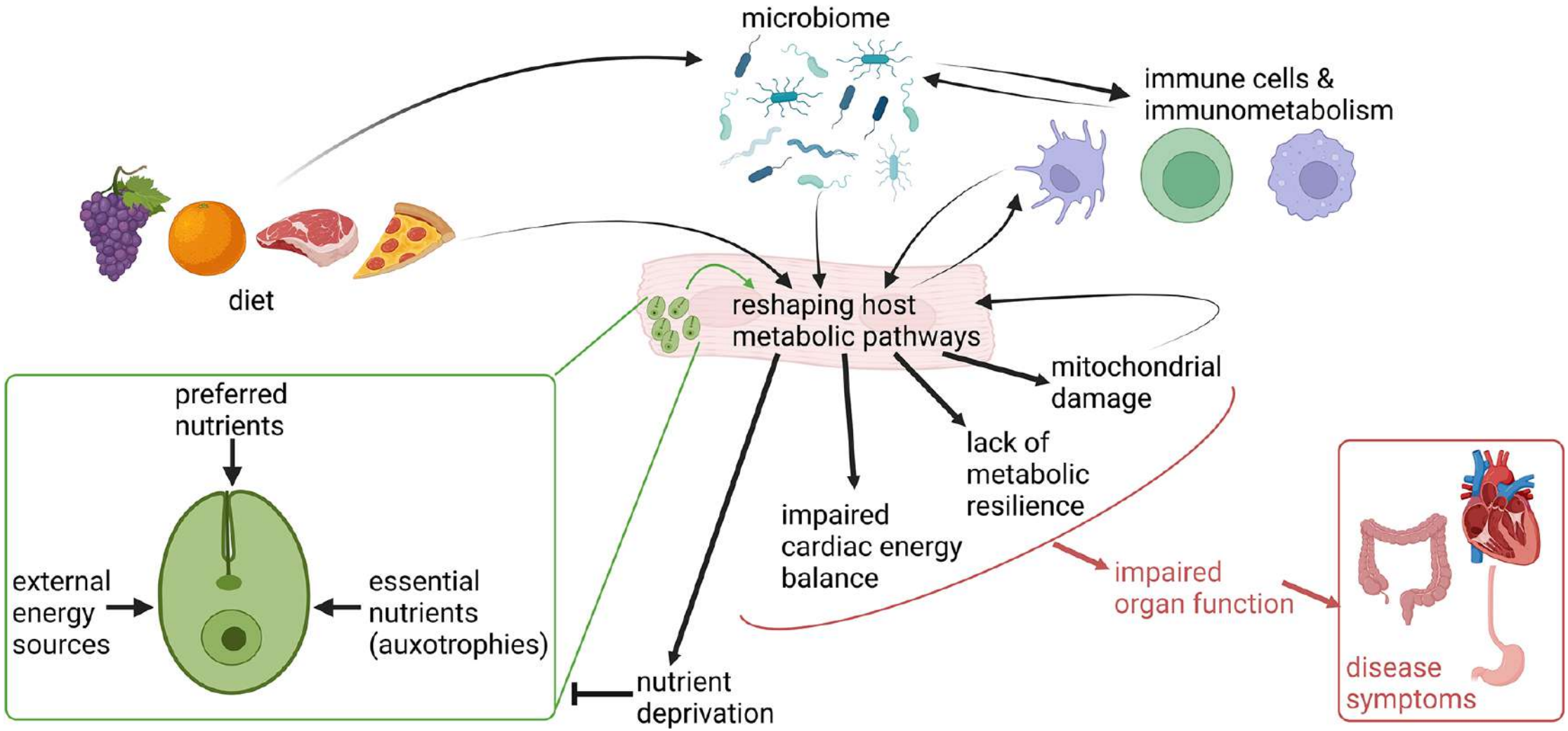


TcCLB.509169.20 / TcCLB.511509.50

- Phenotypic changes are **not mediated by LPC-C18:1 abundance.**
- LPC-C18:1 production is **not dependant of $PLA2_A$ activity**

Gabaldón-Figueira et al, unpublished data

In summary… the big picture is quite complex



Kwakye-Nuako et al, 2024

Take-home messages

- Chagas disease is a complex condition with an unclear pathogenesis.
- The development of chronic disease depends on many different parasite and host-related factors.
- Chronic immune stimulation, metabolic disruption, and tissue-specific dynamics are likely critical in the development of organ damage.
- A balanced response is key to prevent organ damage.
- This balance is influenced by the host's genetic and environmental background.
- Studying the host-parasite relationship can lead to improved biomarkers and therapies.

Further Reading:

1. https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00265-2/fulltext
2. https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1012012
3. https://onlinelibrary.wiley.com/doi/10.1111/pim.12786

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