The Immune Response in Chagas Disease: Are cytotoxic CD4 T cells friends or foes?

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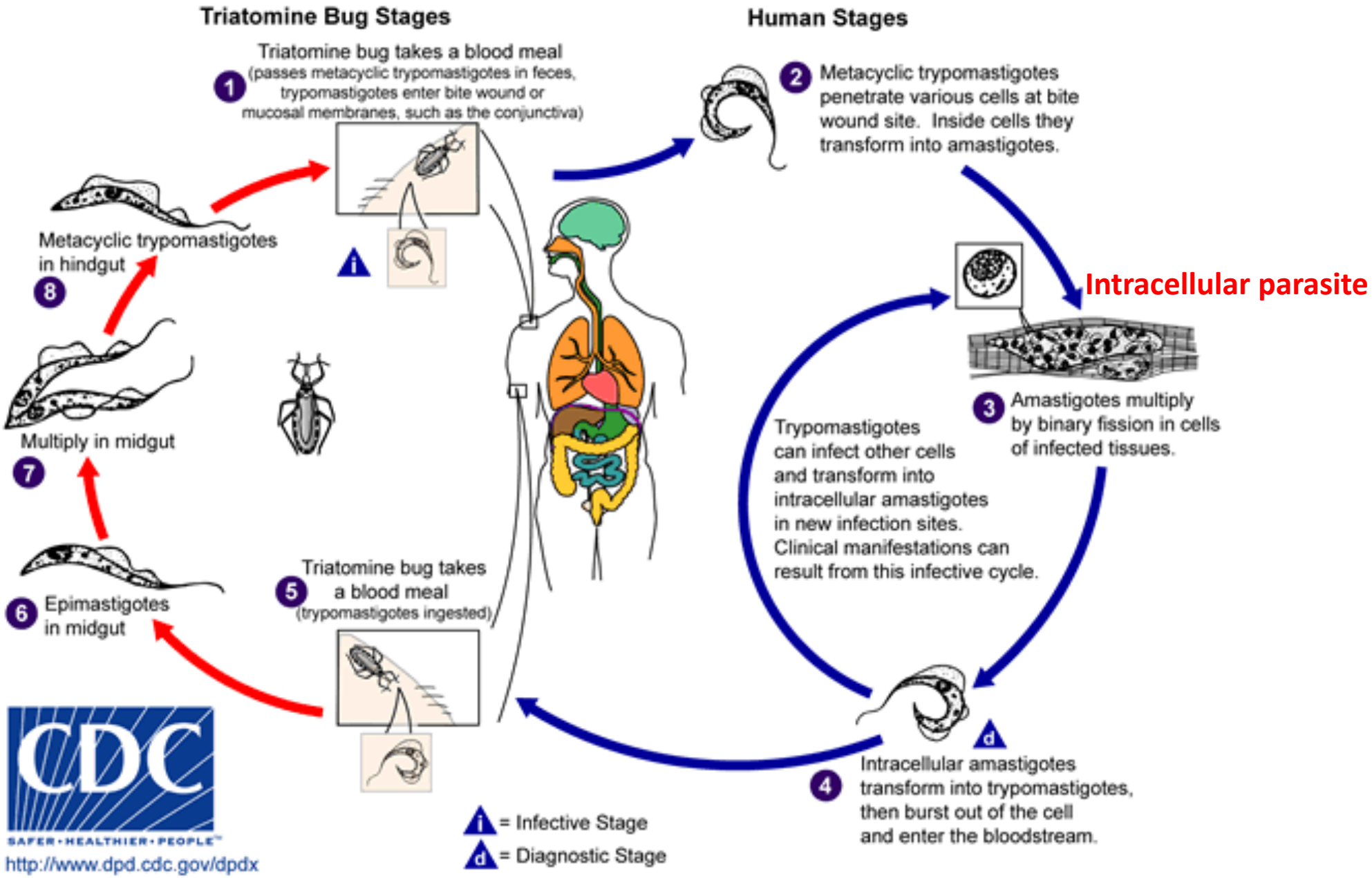
San Diego, April 14th, 2023

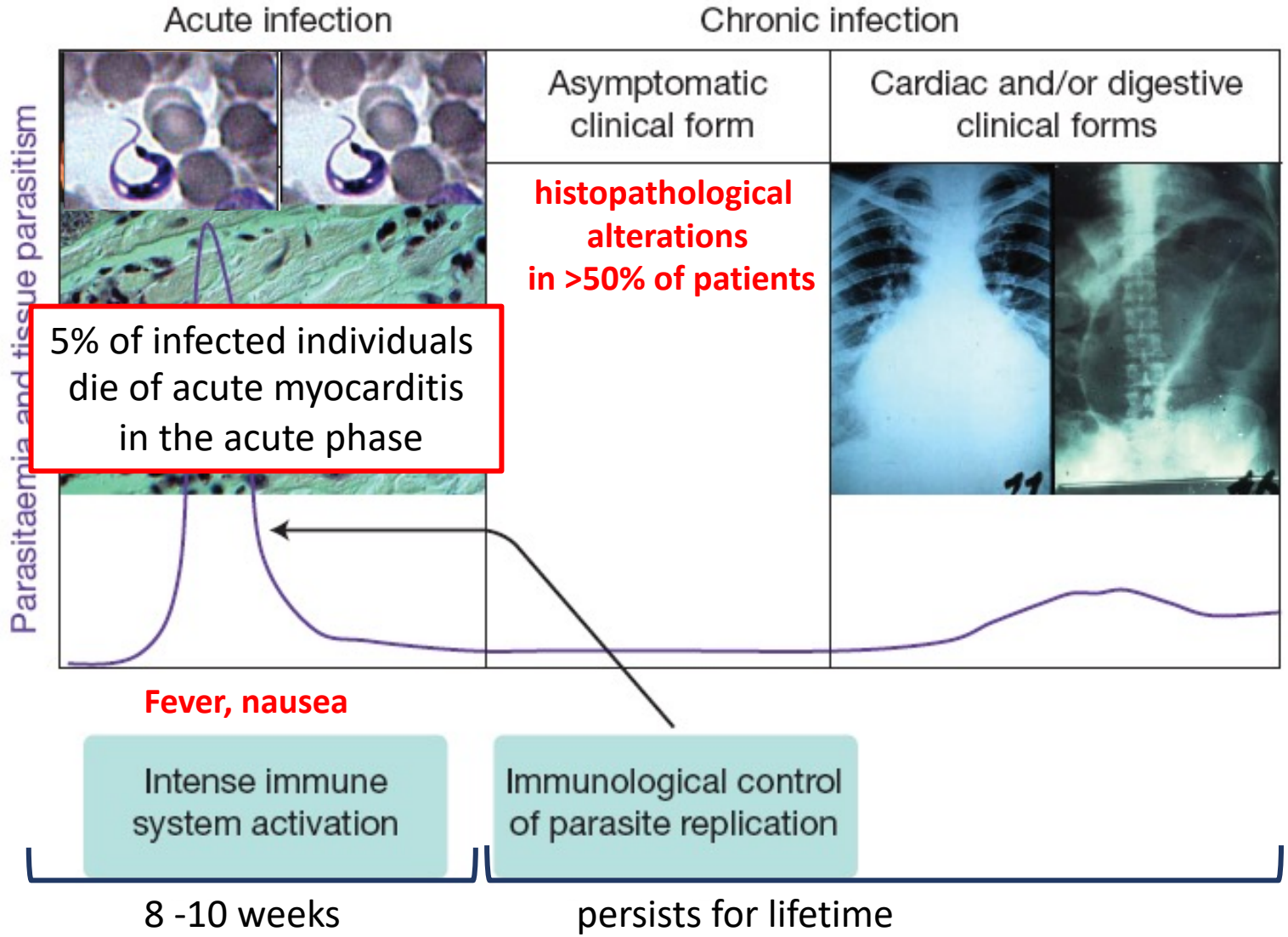
The importance of basic research

- For vaccines
- For novel treatments
- For innovation

The *Trypanosoma cruzi* life cycle



Chagas Disease



≈ 30 % of patients: (CCC)
Chronic Chagas' disease Cardiomyopathy

complex and incompletely understood

No treatment available

Adapted from Junqueira *et al.* (2010) *Expert Reviews in Mol. Med.*12:e29.

Autoimmunity: Molecular Mimicry

Table 1
Molecular mimicry after *T. cruzi* infection.

Host component	*T. cruzi* antigen	Host	Molecular definition
Neurons, liver, Kidney, testis	?	M, R	Mab
Neurons	Sulphated glycolipids	H,R	Mab, sera
47 kDa neuron protein	FL 160	H	rDNA, AS
Heart and skeletal Muscle	Microsomal fraction	H, M	Mab, Serum IgG
Smooth and striated Muscle	150 kDa protein	H, M	Serum IgG
Human cardiac Myosin heavy chain	B13 protein	H	rDNA, Ab T cell clones
Human cardiac Myosin heavy chain	Cruzipain	M	Ab
95 KDa myosin tail	*T. cruzi* cytoskeleton	M	Mab
Skeletal muscle Ca++ Dependent SRA	SRA	H, Rb	AS, serum IgG
Glycosphingolipids	glycosphingolipids	H, M	Serum IgG
MAP (brain)	MAP	H, M	rDNA, AS
Myelin basic protein	*T. cruzi* soluble extract	M	Serum IgG, T cells
28 kDa lymphocyte membrane protein	55 kDa membrane protein	H, M	Mab
23 kDa ribosomal protein	23 kDa ribosomal protein	H	Ab
Ribosomal P protein	Ribosomal P protein	H	rDNA, Ab, SP
38-kDa heart antigen	R13 peptide from ribosomal protein P1, P2	M	IgG1, IgG2
β1 adrenoreceptor M2 muscarinic receptor	Ribosomal P0 and P2 proteins	H	rDNA, Ab, SP
β1-adrenoreceptor M2 cholinergic receptor	150 kDa protein	H, M	Mab
Cardiac muscarinic Acetylcholine receptors (mAChR)	?	H	Ab
Cardiac muscarinic Acetylcholine receptors (mAChR)	cruzipain	M	Immunization with cruzipain
Cha antigen	SAPA, 36KDa TENU2845	M	Ab, T cells

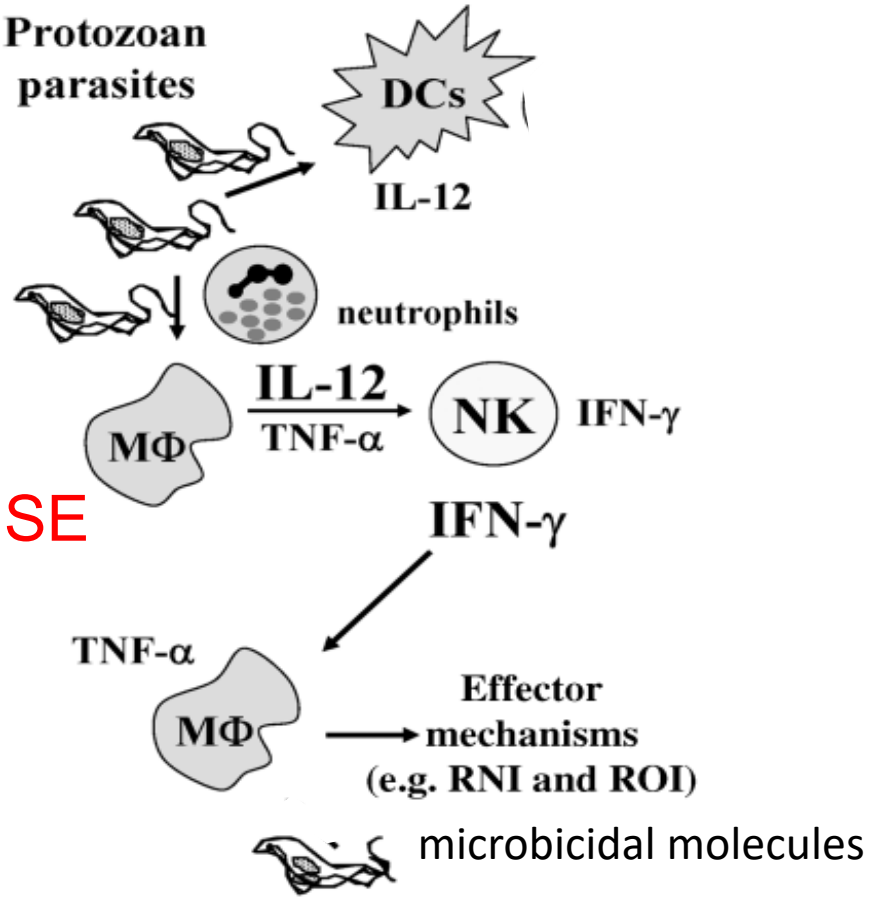
Abbreviations: M, mouse; H, human; Rb, rabbit; R, rat; AS, antiserum; Ab, patient antibody; Mab, monoclonal antibody; rDNA, recombinant DNA; SP, synthetic peptides.
Adapted from Bilate and Cunha-Neto [7].

Cunha-Neto et al. Autoimmunity Reviews 10 (2011) 163–165

The immune response against infection with *Trypanosoma cruzi*

Pathogen Associated Molecular Paterns (PAMPs)

INNATE RESPONSE

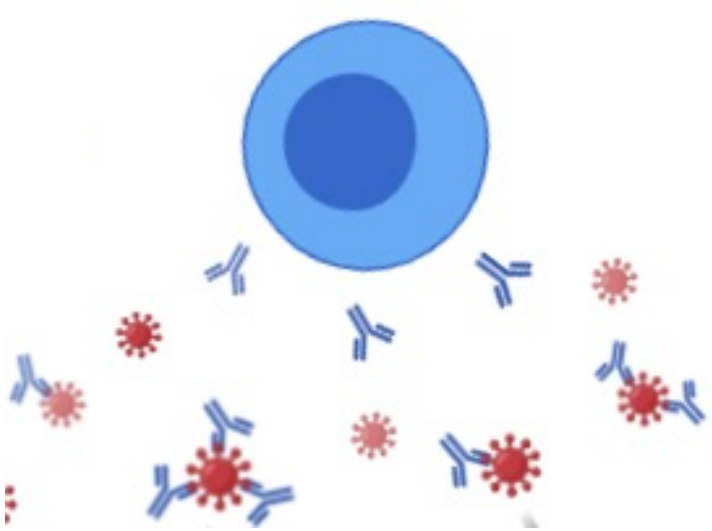


ACQUIRED RESPONSE

Adapted from Gazzinelli R.T. *et al* 2004 *Immunol. Rev.201: 9–25*

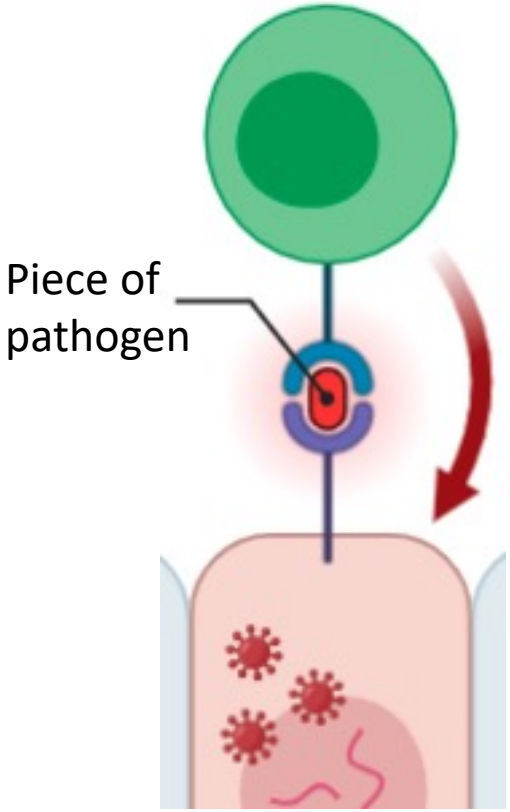
Lymphocytes: cells of the acquired immune response

B cells



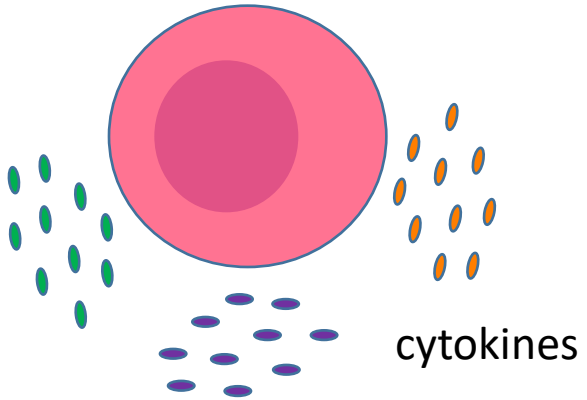
Produce antibodies

CD8 T cells



CYTOTOXIC CELLS - CTL
(kill infected cells)

CD4 T cells

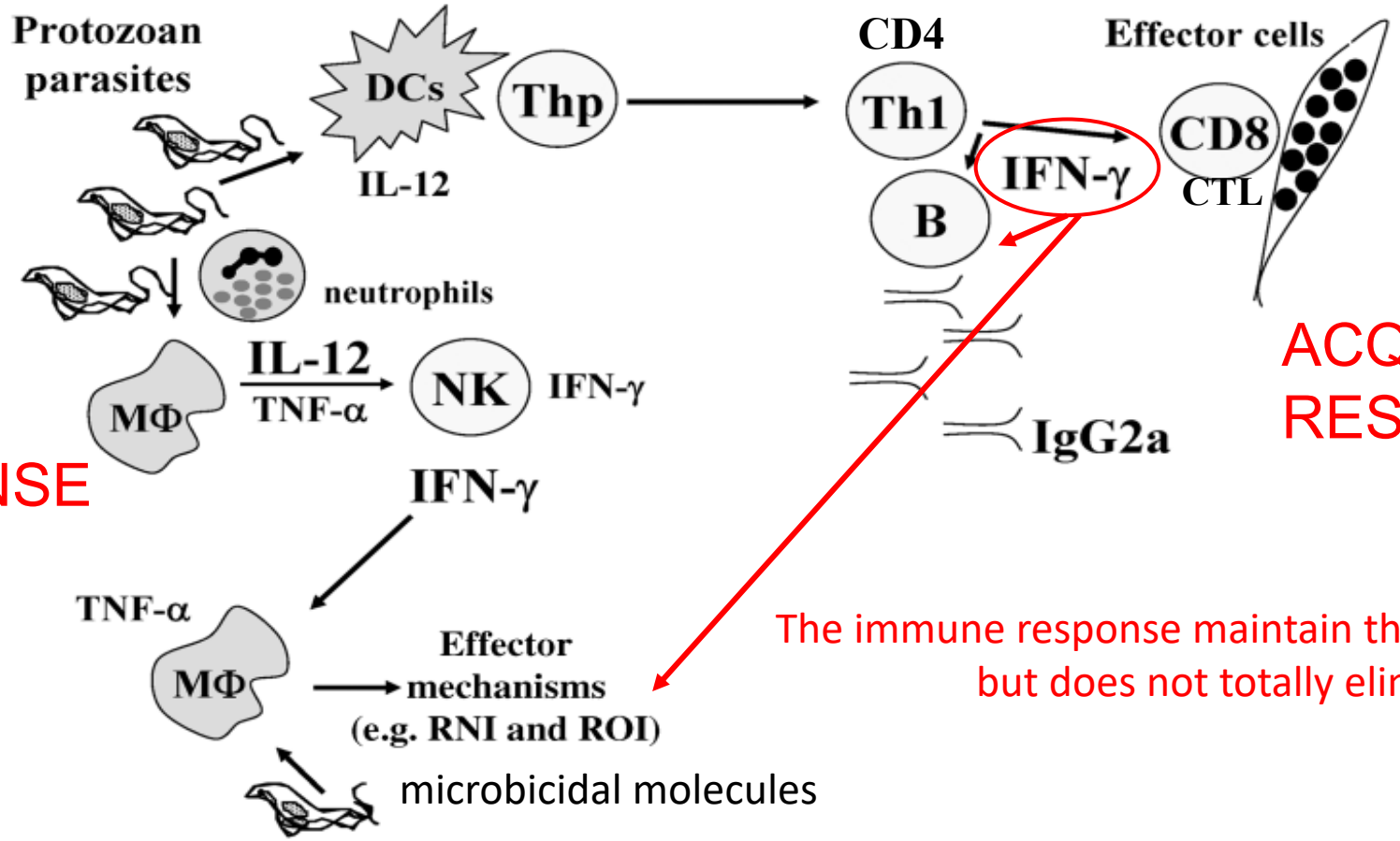


HELPER CELLS (Th)
(Produce soluble factors)

Known mechanisms of host defense against infection with *Trypanosoma cruzi*

Pathogen Associated Molecular Paterns (PAMPs)

INNATE RESPONSE

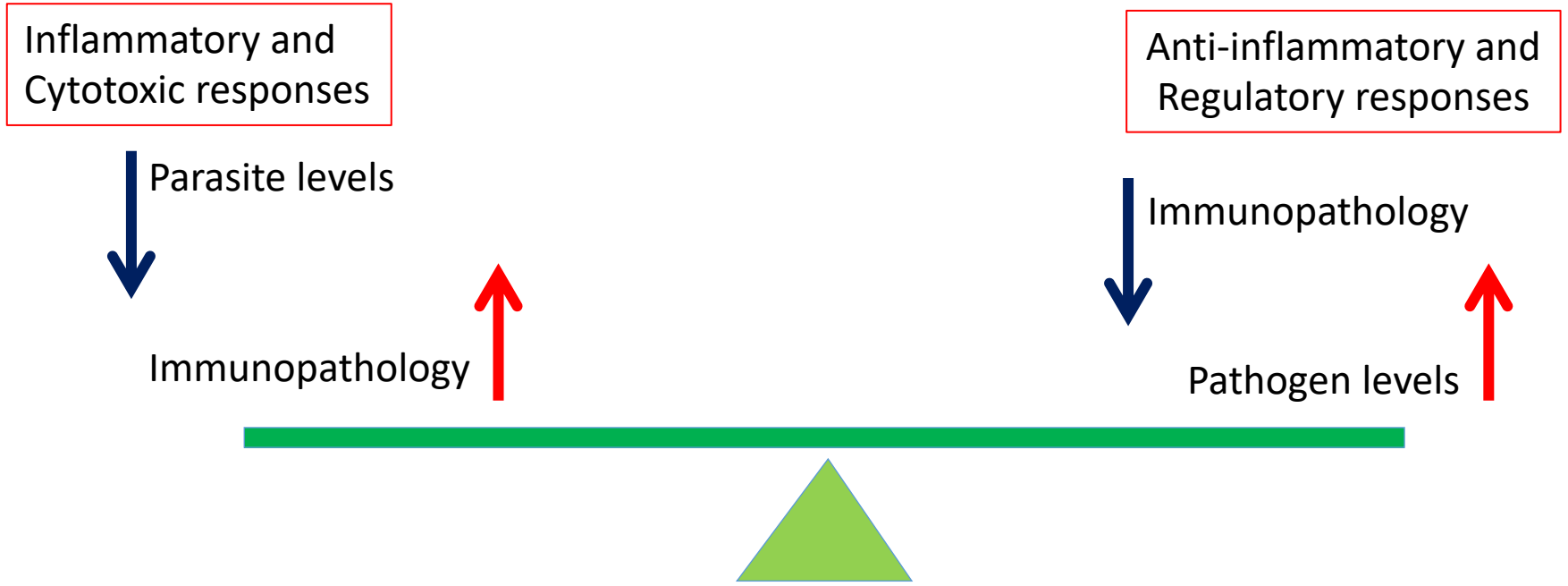


ACQUIRED RESPONSE

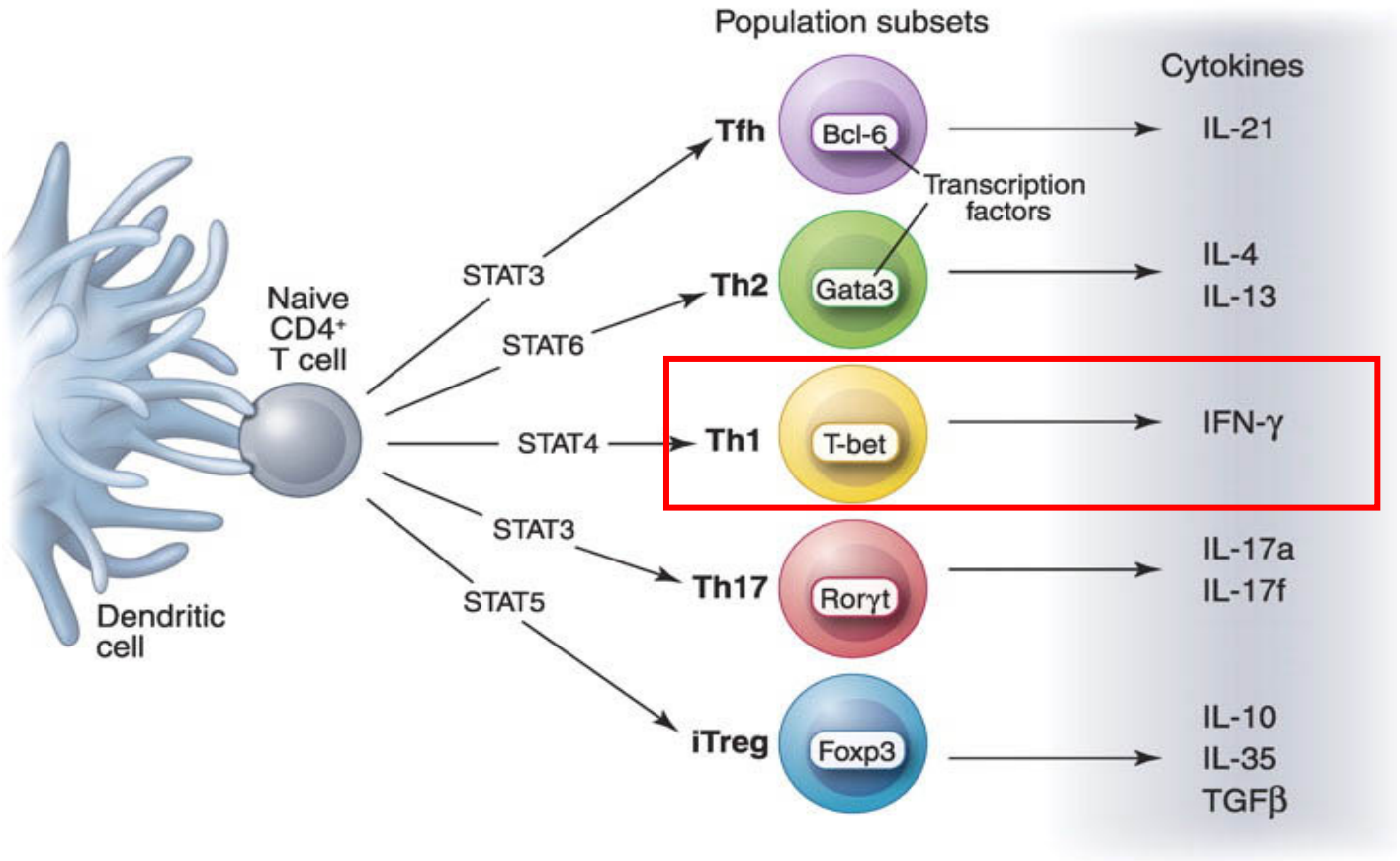
The immune response maintain the parasite in check, but does not totally eliminate it

Adapted from Gazzinelli R.T. *et al* 2004 *Immunol. Rev.201: 9–25*

Control of pathogen load & minimize tissue damage



Different Th (CD4 T cell) subsets



Can CD4 T cells also become cytotoxic?

O'Shea & Paul, *Science,* 2010

frontiers | Frontiers in Immunology

YES!

REVIEW
published: 27 April 2022
doi: 10.3389/fimmu.2022.867189

The Era of Cytotoxic CD4 T Cells

Mara Cenerenti[1,2†], *Margaux Saillard*[2,3†], *Pedro Romero*[2,3] *and Camilla Jandus*[1,2*]

- Steady-state IEL in the gut
- Infections (viral, intra-cellular bacteria, chronic and acute)
- Autoimmune diseases
- Cancer

eLife 2022;0:e74636. DOI: https://doi.org/10.7554/eLife.74636

Cytotoxic CD4$^+$ T cells driven by T-cell intrinsic IL-18R/MyD88 signaling predominantly infiltrate *Trypanosoma cruzi*-infected hearts

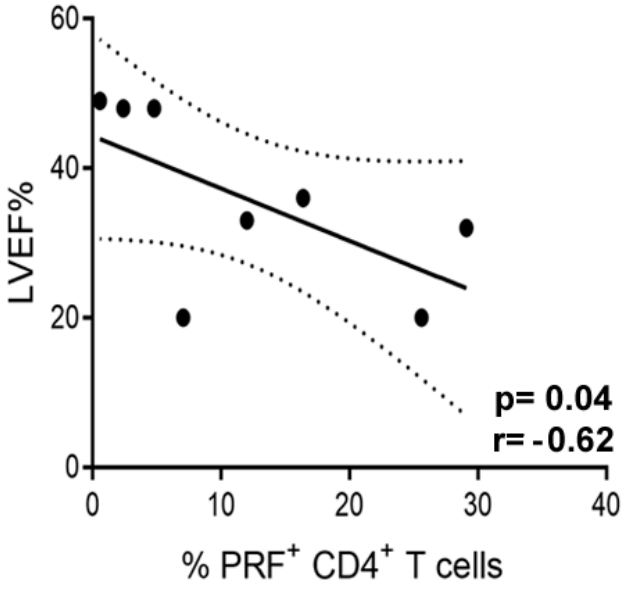
Carlos-Henrique D Barbosa[1†‡], Fábio B Canto[1†§], Ariel Gomes[1†#], Layza M Brandao[1], Jéssica R Lima[1], Guilherme A Melo[1], Alessandra Granato[1¶], Eula GA Neves[2], Walderez O Dutra[2], Ana-Carolina Oliveira[3], Alberto Nóbrega[1], Maria Bellio[1]*

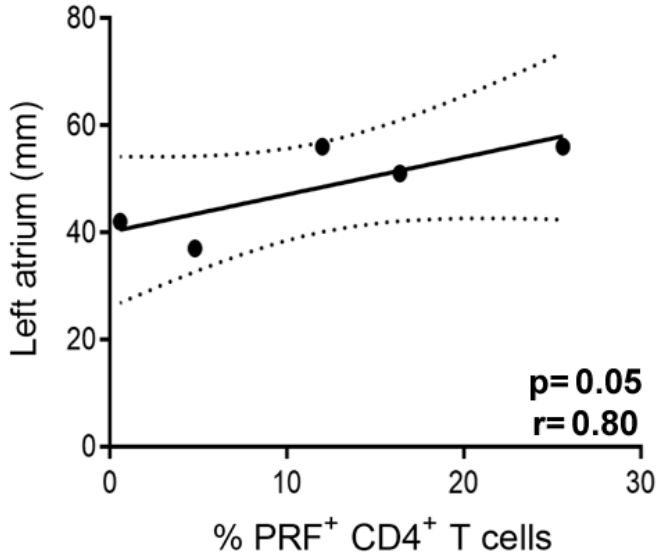
➔ CD4CTLs is the predominant subset among $CD4^+$ T cells infiltrating the infected heart

➔ The adoptive transfer of $CD4^+GzB^+$ T cells increases survival of susceptible mice to acute infection (anti-inflammatory role?)

➔ The frequency of circulating $CD4^+PRF^+$ T cells is higher in chronic patients with Chagas Disease

The frequency of CD4^{+}PRF^{+} T cells correlates with cardiomyopathy





But, a correlation does not imply causation!

Barbosa CH *et al.*, eLife, 2022

Almeida *et al.*
Journal of Translational Medicine (2022) 20:551
https://doi.org/10.1186/s12967-022-03761-5

Journal of Translational Medicine

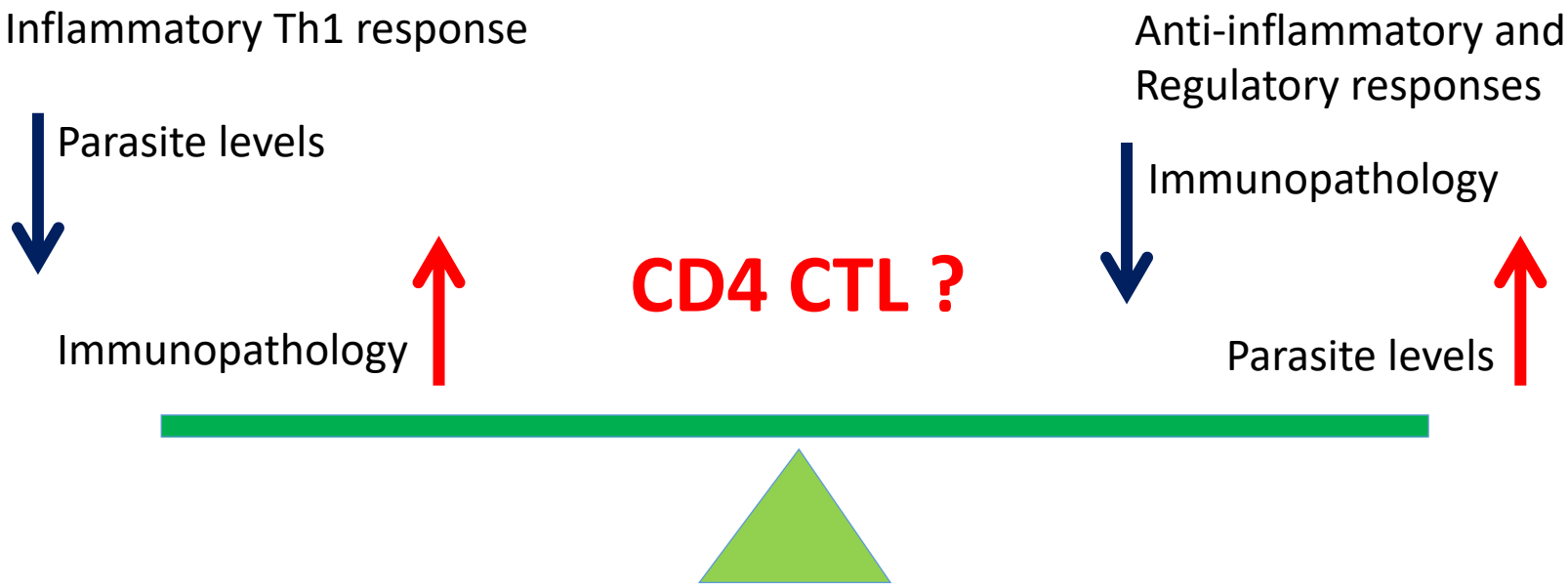
RESEARCH Open Access

Chagasic cardiomyopathy is marked by a unique signature of activated CD4^{+} T cells

Gregório Guilherme Almeida[1], Inga Rimkute[2], Isabela Natália Pascoal Campos do Vale[1], Thomas Liechti[2], Priscilla Miranda Henriques[1], Ester Roffe[3], Fernanda Fortes de Araújo[4], Manoel Otávio da Costa Rocha[5], Silvana Maria Elói Santos[6], Olindo Assis Martins-Filho[4], Dragana Jankovic[7], Alan Sher[7], Andrea Teixeira-Carvalho[4], Mario Roederer[2] and Lis Ribeiro do Valle Antonelli[1*]

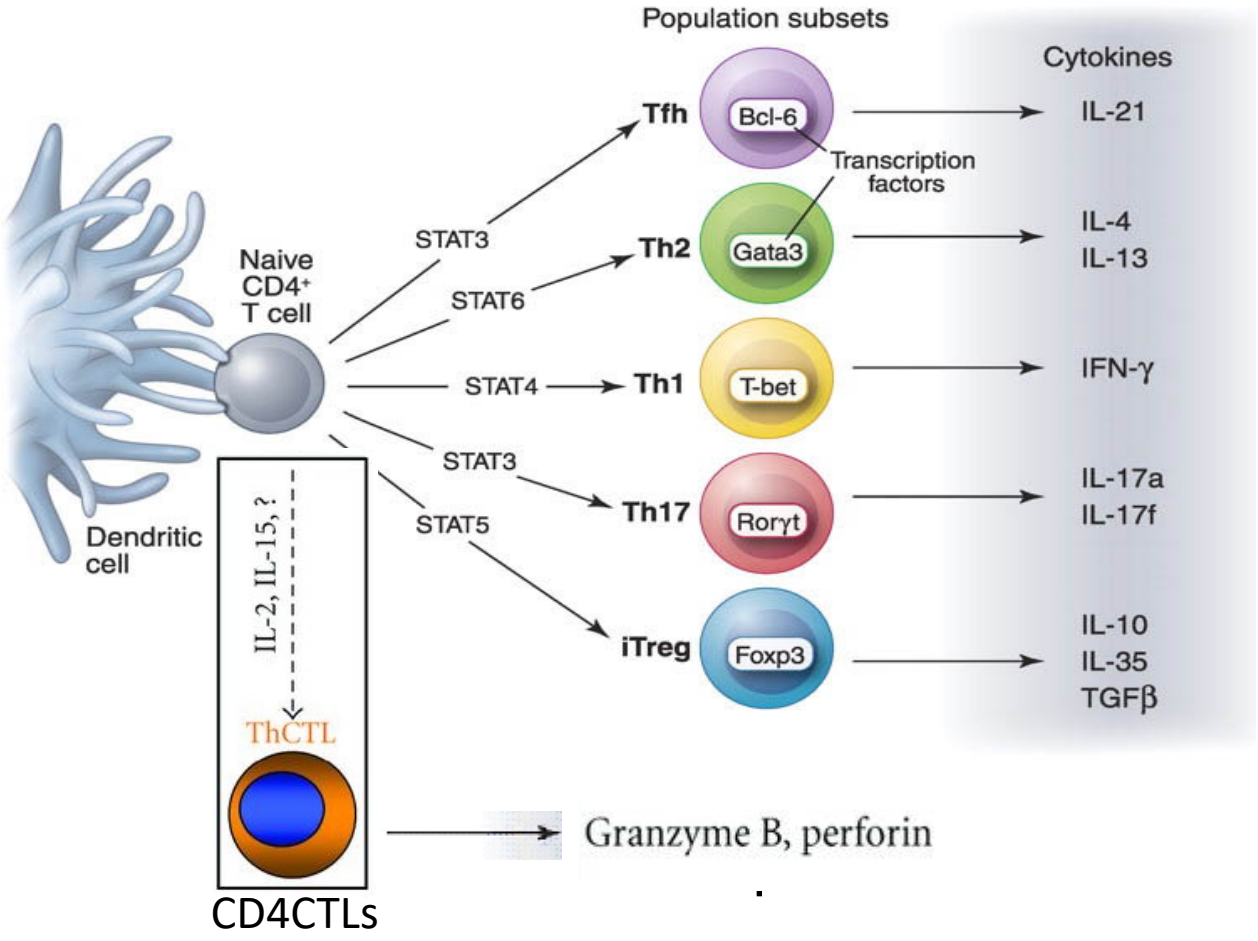
A GrB^{+}PFN^{+}IFN-γ^{+}CD4^{+} T cell population was expanded in Chagas' patients

Role of CD4CTLs during *T. cruzi* infection?



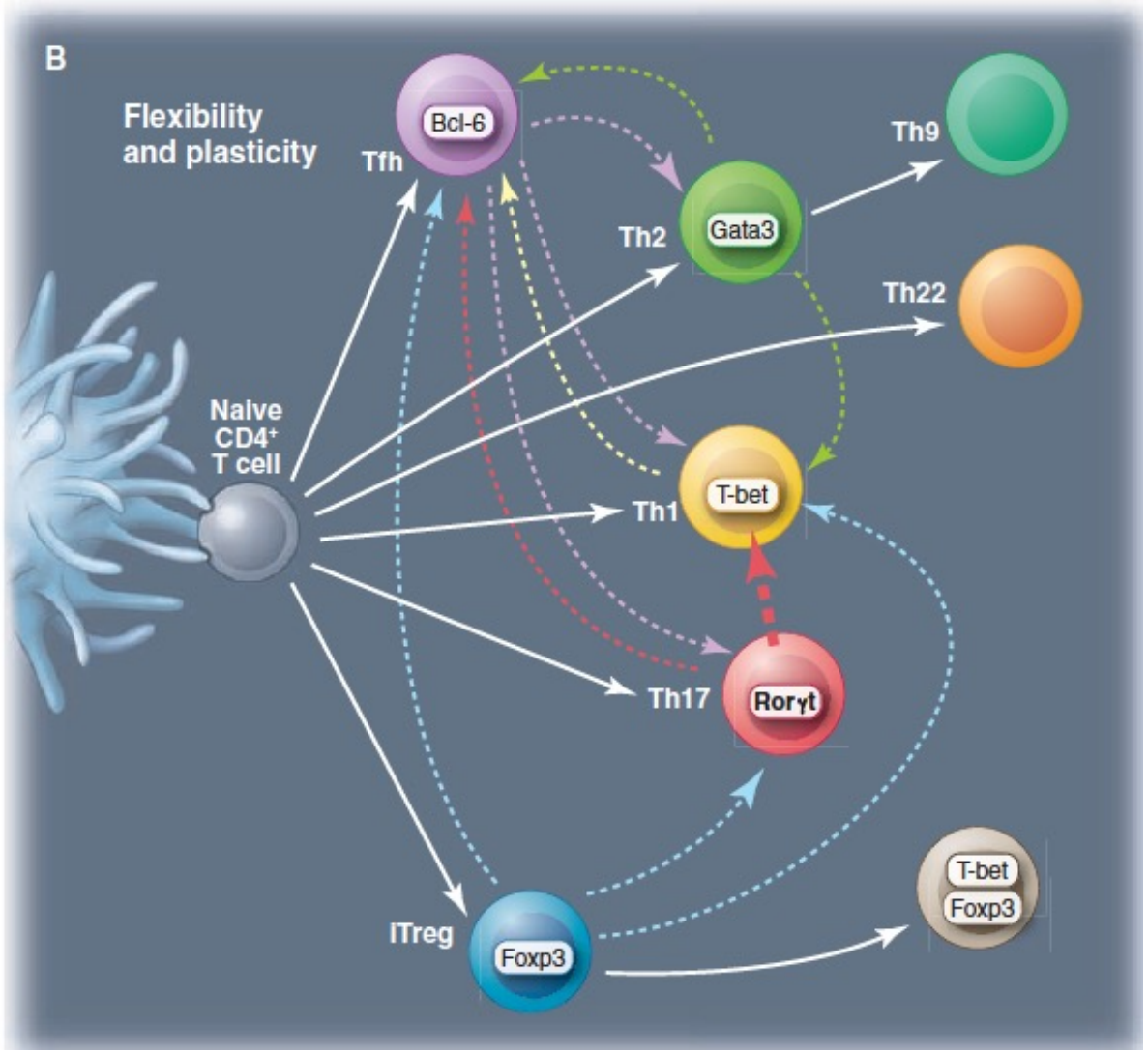
Whether their role is protective or detrimental in promoting cardiomyopathy is still unknown.

Which is the origin of CD4CTLs observed during infection with *T. cruzi* ?



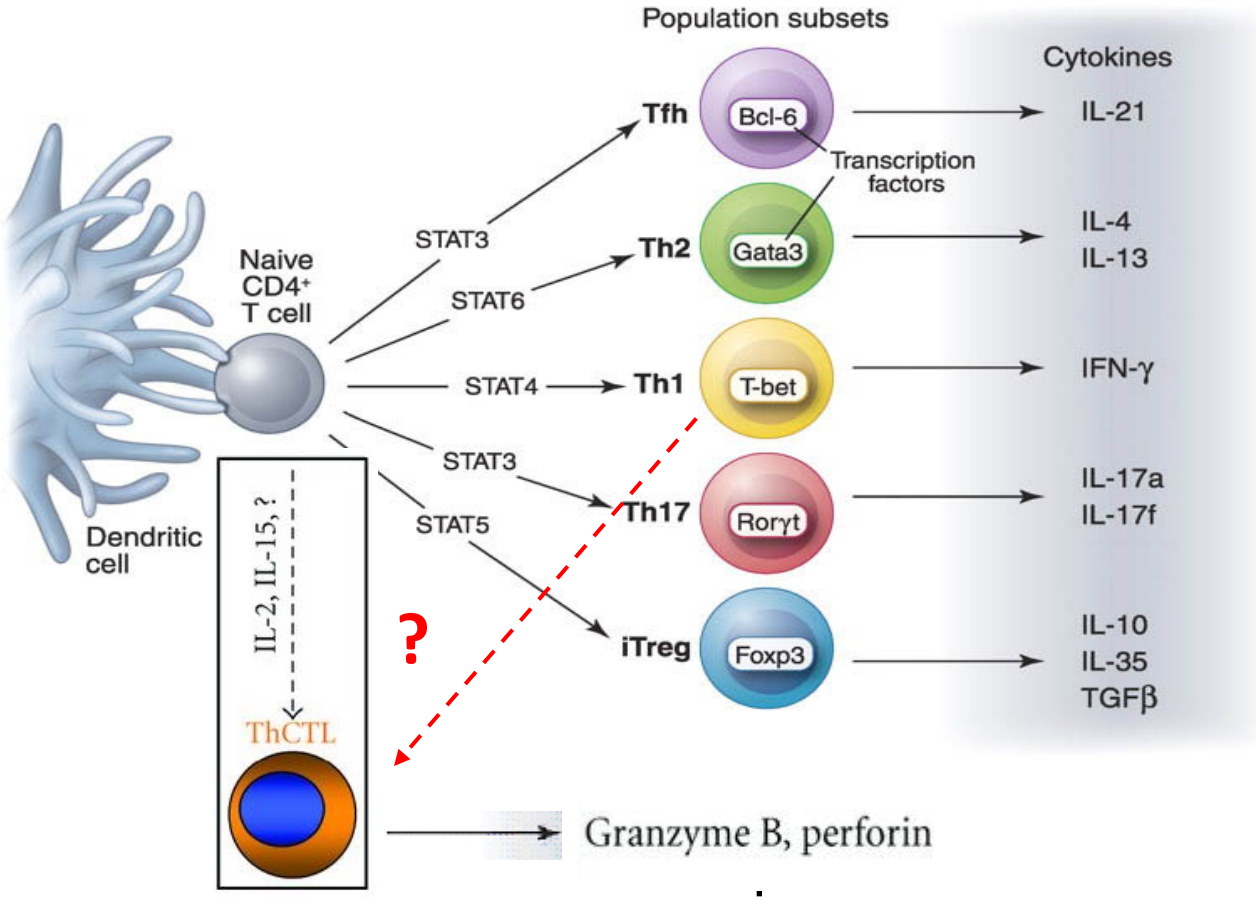
Adapted from **O'Shea & Paul, *Science,* 2010 and Marshall & Swain, *J. Biomed. Biotech*., 2011**

CD4 T cell subset plasticity



O'Shea & Paul, *Science,* 2010

Are CD4CTLs terminally differentiated from Th1 cells?



CD4CTLs

Adapted from O'Shea & Paul, *Science,* 2010 and Marshall & Swain, *J. Biomed. Biotech.*, 2011

Unanswered questions about CD4CTLs in *T. cruzi* infection

- Specificity?
- Memory/Tissue-resident Memory T Cells?
- Induction by vaccination?
- Which factors favor their differentiation?
- Do CD4CTLs found in the acute phase share the same transcriptomic profile of CD4CTLs of chronic patients?
- Are CD4CTLs a type of T regulatory (Tr1) cells?
- Can CD4CTL with a stable phenotype be generated *in vitro*?

T-cell Transfer Therapies

➔ CAR-T cell therapy in cancer (lymphoma)

➔ Treg adoptive cell transfer in organ transplantation and autoimmunity

➔ Transfer of Tr1 cells to prevent graft versus host disease (GvHD) in allogeneic hematopoietic stem cell transplantation (allo-HSCT)

➔ Future T cell therapy for chronic Chagas Disease?

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