



# New Perspectives for Therapeutic Intervention during the Chronic Phase of *Trypanosoma Cruzi* Infection

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## Introduction

The intracellular protozoan parasite *Trypanosoma cruzi* causes Chagas's disease in humans<sup>[1]</sup>. About 5 million to 8 million people are infected by *T. cruzi* around the world<sup>[2]</sup>. Chagas disease has acquired global relevance because is spreading to non-endemic countries<sup>[3]</sup>, representing a significant economic global burden<sup>[4]</sup>. The parasite infects many tissues and the presence of the parasite in peripheral neurons and heart muscle cells may be related to some of the pathological findings in the acute and chronic infection<sup>[5]</sup>. The systemic and tissue-localized immune responses induced during the acute infection are not sufficient to eradicate the pathogen, resulting in chronic infection<sup>[6]</sup>. Approximately 30 to 40% of the infected patients may develop megacolon, heart failure and cardiomegaly during the chronic phase of the disease, even many years after the acute infection<sup>[1]</sup>. Yet, the majority (about 60 to 70%) of the patients that progresses to the chronic phase of the infection remains clinically healthy<sup>[7]</sup>. Recently, results of a multicenter, double-blinded, controlled clinical trial evaluating the efficacy of a trypanocidal drug (benznidazole) to halt the disease progression concluded that this pharmacological treatment did not confer protection against disease<sup>[8,9]</sup>. This suggests that other pathogenic mechanisms, besides the parasite itself, are involved in the progression of the disease<sup>[5,10]</sup>. *T. cruzi* induces a strong immune response against its own molecular components, but the infection also induces a strong immune response to host self antigens<sup>[10]</sup>. Therefore, a malfunction of immune regulatory mechanisms may also be involved in the autoimmune responses during the infection<sup>[11]</sup>. In addition, the immune response to parasite antigens and host self-antigens are not dissociated and occur concomitantly<sup>[10]</sup>, and both should be considered as promoters of tissue lesion during the infection. Nevertheless, one may assume that in most of the chronically *T. cruzi*-infected patients, an effective but regulated immune response is achieved preventing the development of pathology<sup>[2]</sup>. This may be due to the action of CD4+ CD25+ regulatory T cells (Tregs) that may curb the autoimmune response, allowing a partially effective anti-parasite immune response. Recent findings in humans, have shown an increased percentage of Treg cells in chagasic subjects in the indeterminate chronic phase (free of disease) when compared to patients with heart damage, suggesting an important role for Tregs in Chagas disease<sup>[12]</sup>. Studies concerning Tregs and Chagas disease should also consider other Treg marker such as CD15s to discriminate suppressors (CD15s+) versus non-suppressors (CD15s-) regulatory T cells, as the expression of this molecule could be an important prognostic biomarker for disease progression<sup>[13]</sup>. Moreover, it has been recently demonstrated, using a nondepleting monoclonal antibody to CD25 that regulatory T cells may also help to control the adaptive immune response, during the infection in mice<sup>[14]</sup>. The immunomodulatory activity of the nondepleting monoclonal antibody to CD25 encompassed a delayed increase of Treg frequencies and an augmented production of IL-10 by T cells that correlated with less myocardial inflammation in the chronic infection<sup>[14]</sup>. Consequently, there is evidence that the functional activity of Treg cells might be



of crucial importance during the chronic phase of the infection in decreasing tissue destruction and pathology. Therefore, the notion concerning the manipulation of Treg cells by antibodies to CD25 holds promising as a tool to treat pathological outcomes in Chagas disease. In addition, interleukin-2 (IL-2) binds to its high affinity receptor (CD25) and is also involved in the regulatory arm of the immune response by augmenting the proliferation of regulatory T cells<sup>[15,16]</sup>. Low amounts of IL-2 favor the immunoregulatory pathway, whereas high amounts are required for driving effector immune responses<sup>[16]</sup>. The role of IL-2 in the immunoregulatory axis of the immune system is evident in mice and humans where the availability of IL-2 was reduced<sup>[15,16]</sup>. For instance, IL-2R-beta chain knockout mice develop autoimmune inflammatory disease and blocking of IL-2 by *in vivo* treatment with monoclonal antibody to IL-2 accelerates autoimmunity in mice<sup>[17,18]</sup>. Additionally, several polymorphisms in the IL-2 pathway have been linked to type I diabetes and loss of function of Treg biological activities in human studies<sup>[19]</sup>.

### Concluding Remarks

The study of acute and chronic phases of infection with intracellular pathogens, such as *T. cruzi*, allows the elucidation of the mechanisms and conditions that may be targeted to re-program the host immune system by using tools that interfere with components of the regulatory arm of the immune system machinery, thus providing new strategies to treat Chagas disease, besides the use of drugs that only kills the parasite *in vivo*, sterilizing the host. In this regard, the *in vivo* biological activity of nondepleting antibodies to CD25 seems to reinforce rather than inhibit the function of regulatory T cells in mice and humans<sup>[14,20]</sup>. Additionally, new approaches, including *in vivo* administration of IL-2 or complexes of IL-2/anti-IL-2 to increase the numbers and functional activity of regulatory T cells are also desired<sup>[16,21]</sup>. However, it should be noted that more studies, using different strains of *T. cruzi* in combination with distinct strains of mice should be performed in order to better establish this conceptual clinical intervention.

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