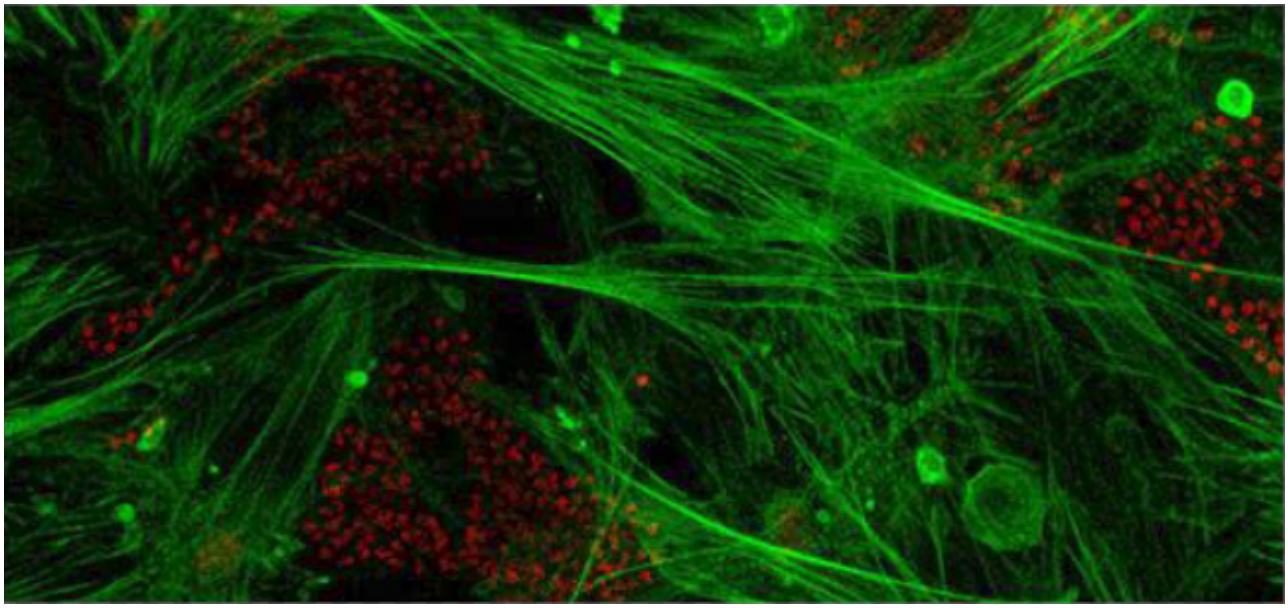
The search for new drug candidates to treat Chagas disease

Chagas disease (CD) is a parasite-born pathology caused by a unicellular microorganism called *Trypanosoma cruzi.* This illness causes a significant morbidity and mortality in the developing world, being endemic in 21 countries across Latin America, representing also a relevant public health problem in non-endemic countries (as Australia, Canada, Japan, Spain, and the United States) mainly in consequence of the immigration of infected people to these regions. CD is one of the seventeen neglected diseases and is primarily transmitted by blood-sucking insects through contact with the feces of infected bugs, deposited on the skin after their blood meal.



Fluorescent miscroscopy image of primary cultures of mouse cardiac cells labeled (in green with phalloidin) infected with Trypanosoma cruzi (stained in red) in vitro.

These insects typically hide in crevices of poorly-constructed homes in rural or suburban areas and thus CD is mainly a poverty-associated disease. Blood, organ transplant, and congenital transmission also occur, and cases of oral transmission through ingestion of food infected by bugs/feces are well documented. CD has two clinical phases: the acute phase that starts as soon as the infection occurs and is usually oligosymptomatic, and may display fever, malaise, facial edema, generalized lymphadenopathy, and hepatosplenomegaly. As result of the immune response, there is a control of the parasite proliferation (but not eradication) and often spontaneously resolves in few weeks. However, some people may present a serious cardiopathy leading to about 5% of death (mostly in children). Next, the infected people move to a second stage called the chronic phase in which the majority keep asymptomatic (indeterminate form). However, years or even decades after the initial infection, untreated individuals may develop a chronic

progressive pathology with about 10% to 30% exhibiting severe heart and/or gastrointestinal disorders that results in death. Today more than 6-8 million people are infected with *T.cruzi*, 7,000 die annually and about 70 million people are at risk of infection only at Latin America. Despite this serious problem, until now only two drugs can be used to treat this pathology: two nitroderivatives named nifurtimox and benznidazole (Bz). Both are far from being ideal since are not active upon the last chronic phase, have several toxic effects (cutaneous hypersensitivity, ringworm, digestive intolerance, bone marrow depression, peripheral neuropathy, hepatotoxicity, anorexia, weight loss, drowsiness or excitability), require long periods of therapy and there is several parasite strains that are naturally resistant against both drugs. Another great concern is that today less than 1% of the chagasic patients have access to the treatment, underlining the urgent need to expand access and accelerate the development of truly innovative safer and more potent medicines to treat CD. In this context, our group is involved in scientific studies using *in vitro* (from Latin: “in glass”) and *in vivo* (from Latin: "within the living") models aiming to identify novel drug candidates and presently we will briefly report some of these results obtained with 14 aromatic heterocyclic compounds named arylimidamides (AIAs) assayed against different strains and forms of *T. cruzi*.

We found that one of the most promising was the m-terphenyl bis-AIA 35DAP073. *In vitro* analysis showed that it was about 26-100 fold more potent than the reference drug (Bz), being also active against those naturally resistant parasite strains. *In vivo* findings using mouse models of acute *T.cruzi*-infection revealed that 35DAP073 induced a dose-dependent action, leading to 96 to 46% reductions in the level of blood parasitism in mice, but unfortunately longer periods of treatment designed to reach parasitological cure demonstrated reversible animal neurological side effects. The combination of this AIA with Bz aiming to reduce drug toxicity and improve efficacy resulted in suppression of blood parasitism in the animal models also providing elimination of toxic effects, besides leading to 100 % of mice survival. Although this combination was not able to cure the infected mice, it resulted in a great reduction of the total parasitism measured by sensitive molecular tools like qPCR (quantitative polymerase chain reaction). Our laboratory results support further investigations of this class of compounds with the aim of developing novel alternatives for the treatment of Chagas disease.

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Publication

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