Editorial

Chagas Disease Treatment: From New Therapeutic Targets to Drug Discovery and Repositioning

Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, currently affects millions of people worldwide although it is only endemic in America. Chagas is considered a neglected tropical disease because it afflicts the low-income and poorest populations in developing regions of the Americas, particularly in remote, rural areas where infrastructure such as adequate housing, sanitation and clinical resources are limited. In addition, governments pay scarce or no attention to this health problem.

Benznidazole and nifurtimox, both discovered more than 50 years ago, are the only two drugs available to treat Chagas disease and not only present severe side effects but also are ineffective in the chronic phase of the disease when most of the patients are diagnosed. Recent efforts to develop new treatments for Chagas disease, including posaconazole repositioning and the prodrug of ravuconazole (E1224) trial, have been unsuccessful and remark the urgent need to develop new therapeutic alternatives. The scientific effort must be focused in finding simple, safe and effective drugs that directly target the parasite without harming the patients.

It is known that the identification of reliable molecular targets for drug development is challenging, with high rates of failure at the stage of validating potential candidates. Thus, we propose in this Special Issue to revise different potential drug targets of the parasite *T. cruzi* and to explore the latest advances in drug design and drug repositioning.

The first review introduces the challenges of Chagas disease and evidences the requirement of new therapies to treat it. Egui *et al*. [1] focus on the immunologic profile associated with the clinical status and evolution of Chagas disease patients as wells as the effectiveness of the current treatment including different biomarkers to monitor the *T. cruzi* infection.

In the next revisions, different metabolic pathways and proteins are explored as therapeutic targets against the parasite *T. cruzi*, and the final two reviews include the latest strategies to identify new potential targets.

Alonso *et al*. [2] explore the bromodomain-containing proteins as potential targets in protozoa since some of these proteins are essential for viability and diverge from the mammalian ones, which are also approach in their review.

Cordeiro [3] describes the importance of the NADPH producing enzymes in biosynthetic processes as well as in the neutralization of reactive oxygen and nitrogen species. He propose them as potential targets, highlighting the role of glucose-6-phosphate dehydrogenase and the cytosolic malic enzyme.

Schoijet *et al*. [4] propose the signal transduction pathway in trypanosomatids as a novel therapeutic target, particularly the cAMP signaling pathway. The authors shed light in phosphodiesterases (PDEs) as druggable target, because of the prominent roles they play in the life cycle and the essentiality for parasite survival. Despite they are highly conserved enzymes, authors highlight the potentiality of differential inhibition from their human orthologs and suggest the drug repositioning approach as a promising strategy to find inhibitors among the numerous drugs against human PDEs that are available in the market.

Sangenito *et al*. [5] introduce the aspartyl peptidase inhibitors used to treat the infection with the human immunodeficiency virus (HIV) as a drug repositioning strategy. Co-infection of patients with HIV with other microorganisms, such as protozoan parasites, is common and the use of HIV peptidase inhibitors evidenced a decrease both in prevalence and incidence of these co-infections. Indeed, several of these inhibitors have been tested in *T. cruzi* showing multiple pathophysiological effects on the parasite.

Talevi *et al*. [6] present the thiol-polyamine metabolism, a well-known and validated *T. cruzi* target because many of its components are absent or significantly differ from the host homologs offering interesting candidates for a rational design of selective drugs. In this review, the authors critically revise the state of the art of the thiol-

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polyamine metabolism deepening in the pharmacological potential of its components and, properly introducing to the different computer-aided approximations to assist systematic drug repositioning strategies.

Sayé *et al*. [7] propose the most represented family of amino acid and derivative transporters in *T. cruzi* as drug targets, focalizing in proline and polyamine permeases. This family is absent in the human host and their members are responsible of the acquisition of relevant nutrients for the survival of the parasite. The review also discusses the latest advances in drug repositioning strategy applied to these transporters.

Saavedra *et al*. [8] explore new fields in drug target development and open new interrogations about target prioritization. The authors analyse the fundamentals of Metabolic Control Analysis and kinetic modelling of metabolic pathways and apply them to the trypanothion metabolism of *T. cruzi*. They conclude that the enzymes with the highest pathway control are the most convenient targets for therapeutic intervention, leaving under discussion if the agreed criterion of gene essentiality is enough to guarantee a valid target.

Last, Salas-Sarduy *et al*. [9] introduce the initiative made by public-private programs for drug discovery against Chagas disease. This strategy consists in taking advantage of the resources invested by the pharmaceutical industry in other commercial areas allowing the evaluation of libraries of millions of low-molecular weight synthetic compounds. These strategies require high-throughput screenings and setting up of robust enzymatic assays to identify and validate small molecule inhibitors, a matter as well addressed by the authors.

Recognizing that Chagas disease requires urgent attention is the first step to develop new alternative treatments with less toxic effects, and this Special Issue is responding directly to this need.

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