

Opinion

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Advances in the Neglected Chagas Disease: Drug Targets and Trypanocide Compounds



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Opinion

In the world of Biosciences, studies on neglected diseases must be taken into account. In this sense, Chagas disease, a parasitic infection commonly named American Trypanosomiasis affects millions of people all over Latin America. Presently, the number of international infected people estimated by the World Health Organization (WHO) amounts to 7 to 8 million and more than 10.000 deaths are assumed to happen yearly [1]. The disease has also emerged as a public health problematic elsewhere in non-endemic countries of the world due to transmission of etiologic agent, *Trypanosoma cruzi* by people migration [2,3]. Typically, it is spread by triatomine vectors. However, transmission also succeeds by organ transplantation or blood transfusion, from mother to newborn, and rarely due to eating or drinking contaminated aliments [4-8].

Notwithstanding, Chagas disease cannot be eradicated due to the presence of infected wild triatomines in unceasing contact with domestic cycles favoring the incidence of new cases, it could be likely to interrupt *T. cruzi* transmission in a vast region and to get rid of this disease as a public health problem with strong reduction in the burden of this disease [9]. Moreover, in this milieu, and regarding that there is no effective vaccine currently in rehearsal to combat this neglected disease, current chemotherapy is not suitable, is expensive and is still centered on the nitroaromatic compounds benznidazole and nifurtimox that provide both unsatisfactory results and substantially toxic side effects. So, the finding and investigation of novel ways to challenge this neglected disease is a key priority.

In addition, currently, once the disease has progressed to the chronic stage there is no effective drug. Furthermore, in the last years, children treatment was difficult due to the absence of these drugs in pediatric version. However, solid dispersions have been recently presented as alternative drug delivery system to improve the chemotherapy of Chagas disease and pediatric oral liquid suspension containing Benznidazole was

easily prepared, being an interesting alternative for optimizing the pediatric treatment of the disease [10,11].

The advancement in the biologic and biochemical scientific knowledge of *T. cruzi*, in the last decades has increased the identification of multiple targets for Chagas' disease chemotherapy [12]. Amid the best encouraging targets for trypanocidal drugs, ergosterol biosynthesis pathway [13] and cruzi pain [14], the major cysteine protease (CP) of *T. cruzi*, have been pointed out. Regrettably, recent clinical trials investigating the administration of posaconazole and ravuconazole to chronic indeterminate Chagas disease patients revealed their lowliness compared to the standard drug Benznidazole [15].

In view of the information extended in the previous years and aimed to obtain more efficiency and less secondary effects, a rational approach for the fast development of new trypanocidal chemotherapy would be focused on K777, the cysteine proteinase inhibitor (CPI) near to enter to clinical trials, and founded on the clinical evaluation of combination of known drugs with existing anti-*T. cruzi* agents [16]. Besides, by using nuclear magnetic resonance spectroscopy, mapping of the inhibitor binding modes on the main active site, was used for compounds screening aimed at fast evaluation of enzyme-inhibitor interactions, facilitating lead compounds identification followed by structural studies [17]. Recently, directed evolution in drug-sensitive yeast was addressed for the rapid discovery of Chagas disease drug targets [18].

On the other hand, top series of xanthine have been recently identified as clinical candidate for Chagas disease [19]. In addition, trypanothione biosynthesis, thiol-dependant redox and polyamine metabolism, the glycolytic, glycogenogenic, pentose phosphate, lipidic and polyisoprenoid biosynthetic pathways, and the enzymes from biosynthetic glycol conjugates pathways have been studied. Several specific enzymes from these biosynthetic pathways such as hypoxanthine-guanine-

phosphoribosyl-transferase and farnesyl-pyrophosphate synthase, among others, have also been broadly studied in *T. cruzi*. Novel synthesized anti-*T. cruzi* compounds with or without specific single or multi-target assigned have been described in detail [12]. Although the identification of new anti-Chagas disease agents is not only focused on target-based drug design and its derivatives and on synthetic or natural products screening [20] but also in old ones rediscovered as new drugs against Chagas disease [21-24], despite all the new data available, an appropriate drug has not been still identified.

In addition, the synergism of drugs such as Nx and buthionine sulfoximine has been demonstrated by in vitro and in vivo testing [24]. However, human research is required to ratify these results. Likewise, potential use of amiodarone and dronedarone was proposed [25]. Similar results could be expected with the combination of itraconazole and allopurinol [26], Bz and posaconazole [27], Bz and itraconazole [28], as well as Bz and allopurinol. The relevance of exploring the potential of the combination of treatments with currently available compounds to specifically treat Chagas disease was emphasized by the results obtained.

Currently despite some progress in preclinical studies has been developed, there is no yet an ideal drug or formulation for human treatment. A major problem in the evaluation of potential Chagas disease therapeutics is the lack of tools availability. Indeed, there is still an urgent need to discover a better biomarker capable to determine the efficacy of potential chemotherapeutics in treated patients [29]. Over the last few years, the Drugs for Neglected Diseases initiative (DNDi) has defined and implemented in collaboration with partners from the pharmaceutical industry, an early discovery strategy. It consists in a medium- to high- throughput phenotypic assay to accelerate the screening of compound libraries against kineto plastids, to identify a new class series for further development into preclinical candidates [19]. Unfortunately, trypanocide therapy with Bz in patients with established Chagas' cardiomyopathy significantly reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration through 5 years of follow-up [30].

In conclusion, advances on anti-Chagas disease agents focused to specific parasite targets as their metabolic pathways or specific enzymes has been recently reviewed in detail [12]. Regarding all the data achieved in the last years, a rational approach for the fast advance of novel trypanocide chemotherapy would be focused on drugs ready to enter to clinical trials [31], on new scaffolds [32] and on the clinical evaluation of drug association with existing trypanocidal agents to get extra effectiveness and fewer secondary effects.

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