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Mini Review

Current Challenges and Obstacles to Drug Development for Chagas Disease

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Abstract

Chagas disease is a protozoan infection which was first identified more than one hundred years ago. But even now, drugs to treat the latent and chronic phases of the disease are not available. The success of a drug design is highly dependent on activity and toxicity. In the case of Chagas disease, questions remain as to identifying the best treatment (mainly for the chronic phase), and how new drugs and drug combinations compare to current therapy. The principal priority of this mini-review is to report the enormous difficulty that pharmaceutical chemists encounter in the development of new drugs for neglected tropical infectious diseases, in this case Chagas disease.

Keywords: Drug Development; New Drugs; Chagas Disease; T. cruzi

Introduction

Chagas disease is one of the 17 neglected diseases and was identified 109 years ago by the Brazilian physician and researcher Carlos Justiniano Ribeiro Chagas. Also known as American trypanosomiasis, Chagas disease is endemic in 21 Latin American countries [1-5]. Due to an increasingly globalized world, this parasite has spread to the United States, Japan, Australia, Canada, and even across the European continent [6,7]. It is caused by the hemoflagellate protozoan from the Kinetoplastida order of the Trypanosamatidae family, called Trypanosoma cruzi [2,8,9]. Treatment is restricted to two nitroheterocyclic drugs: nifurtimox (1) and benznidazole (2) (Figure 1). These were discovered during the 1960s and 1970s, respectively [10,11]. Both drugs are more effective in the acute phase of the disease than in the indeterminate and chronic phases [12-21]. Furthermore, there are differences in the efficacies of these drugs in relation to the several strains of T. cruzi [22] (Figure 1).

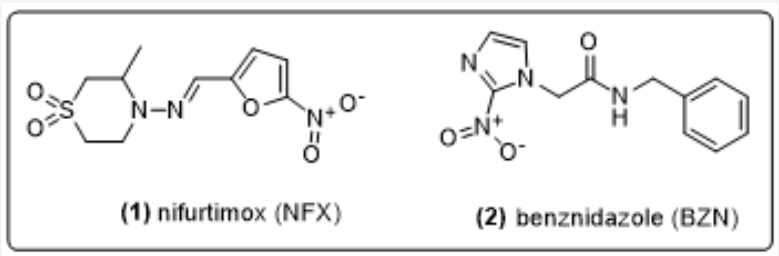

Figure 1: Structures of available chemotherapy agents for Chagas disease: nifurtimox and benznidazole.

Challenges and Obstacles in Research and Development of New Anti-Chagasic Drugs

Medicinal chemistry is a multidisciplinary area involving knowledge related to biology, chemistry, and the medical and pharmaceutical sciences [23]. Medicinal chemists are constantly searching for bioactive compounds for various diseases, including effective compounds for tropical infectious diseases, such as Chagas disease. However, since tropical diseases do not typically

arouse the attention of pharmaceutical companies due to low financial returns (considering the low income of affected people), medicinal chemists are often not motivated to pursue research [24]. The interest of the pharmaceutical industry is extremely important. Characteristics that are indispensable for the search for new lead compounds for Chagas Disease drug development include high activity (< 5μM), low toxicity (ideal selectivity index: >10), and the validation of new molecular targets [25,26]. Overall, neglected tropical diseases (in this case Chagas disease) represent strong obstacles to the development of countries and subsequently maintain the framework of worldwide socioeconomic inequality (Figure 2).

Figure 2: Partnerships must be created for the insertion of lead compounds and/or new drugs.

Scientific Expectations

There is an urgent need for new drugs that have potent activity in the chronic phase of Chagas disease. Concerning toxicity, these drugs need to be safe. If the current medicinal chemistry scaffold continues without a solution, there will be a need for combined drug treatments in the future to decrease blood and tissue parasitology, reduce considerably the percentage of inflammatory infiltrates, and restrict fibrin networks. The optimal experimental protocol is the one that best relates to human response. The data reported in the mini-review published by Scarim and co-workers [27] suggest that for experimental protocol in animals chronically infected with Chagas disease, a treatment with lower doses of benznidazole is more advantageous and can be used as a base to compare new drugs with BZN in the chronic phase of Chagas disease.

Conclusion

More than 100 years after the initial identification of Chagas disease, despite all recent advances and new knowledge about this disease, we still lack an effective treatment against all phases of this disease. Thus, the partnership between governmental and non-governmental institutions with the pharmaceutical industry is extremely important to widen scientific knowledge and research for the treatment of this disease.

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