Posaconazole and the Septins: Combating Chagas Disease Through Polypharmacology and In Silico Analysis

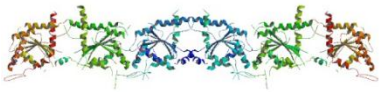

Fig. 1- Septin 2-6-7, a Heterotrimeric GTP-binding protein

PDB ID: 2QAGStructural insight into filament formation by mammalian septins.Sirajuddin, M., Farkasovsky, M., Hauer, F., Kuhlmann, D., Macara, I.G., Weyand, M., Stark, H., Wittinghofer, A., **Journal:** (2007) Nature **449:** 311-315

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Chagas Disease is a major cardiovascular affliction primarily endemic to Latin American countries, affecting millions of inhabitants of Mexico, Central America, and South America. Caused by the insect vector *Trypansoma Cruzi*, Chagas causes fatal cardiac and intestinal disorders in its chronic phase, though its acute phase is largely asymptomatic. While available drugs such as Benznidazole and Nifurtimox are effective in treating acute Chagas, their efficacy in the chronic phase is limited. Furthermore, their toxic properties and numerous side effects have led researchers to investigate improved antifungal compounds that are effective in the chronic phase.

Posaconazole is a promising new experimental compound that is known to be effective in treating mice infected with chronic Chagas. However, the identification of alternative drug receptors within the human proteome may allow us, through medicinal chemistry efforts, to repurpose Posaconazole for increased therapeutic effect. The binding of a drug to these *off-targets* may also help to explain its side effects, saving time and money for researchers evaluating the drug in clinical trials.

The purpose of this project is to evaluate significant human off-targets and their interactions with Posaconazole. By analyzing these interactions in the context of the literature, as well as documented metabolic pathways within the KEGG database, we may be able to suggest novel mechanisms by which Posaconazole can be applied in the treatment of Chagas disease.

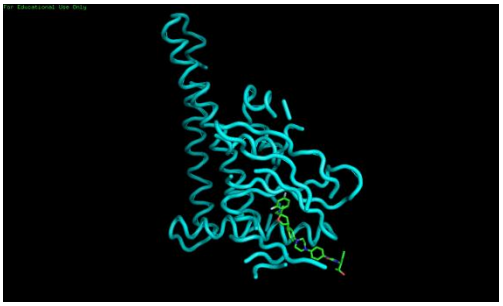

Fig. 2- Posaconazole docked to the Plecstrin Homology (PH) subdomain of Tiam 1

The application of bioinformatics-based methods and databases to this project plays a key role in identifying and analyzing these off-targets. The use of the SMAP algorithm identifies a large list of relevant off-targets within the human proteome- docking software such as AutoDock Vina and visualization tools such as Pymol have assisted in determining binding affinities to these off-targets, as well as specific interactions within their active sites. In this manner, we suggest that Posaconazole may stimulate Septin proteins in the production of filaments that are able to compartmentalize and degrade bacterial pathogens (1). Similarly, the computationally predicted interactions between Posaconazole and the guanine nucleotide exchange factor Tiam 1could stimulate expression of Rac 1 GTPases, known to be correlated with *T. Cruzi* amastigote membrane invasion (2).

Thus, we demonstrate that the *in silico* approach holds great promise in Chagas research, and continue this work in an effort to expedite the search for a permanent cure.

(1) Entrapment of Intracytosolic Bacteria by Septin Cage-like Structures
Mostowy, Serge; Bonazzi, Matteo; Hamon, Mélanie Anne; Tham, To Nam; Mallet, Adeline; Lelek, Mickal; Gouin, Edith; Demangel, Caroline; Brosch, Roland; Zimmer, Christophe; Sartori, Anna; Kinoshita, Makoto; Lecuit, Marc; Cossart, Pascale Cell host & microbe
doi:10.1016/j.chom.2010.10.009 (volume 8 issue 5 pp.433 - 444)
(2) Adriana B. Fernandes, Renato A. Mortara, Invasion of MDCK epithelial cells with altered expression of Rho GTPases by Trypanosoma cruzi amastigotes and metacyclic trypomastigotes of strains from the two major phylogenetic lineages, Microbes and Infection, Volume 6, Issue 5, April 2004, Pages 460-467, ISSN 1286-4579, 10.1016/j.micinf.2004.01.009.