In silico repurposing of approved drugs for paracoccidioidomycosis

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Paracoccidioides spp. is a thermodimorphic fungus associated with paracoccidioidomycosis (PCM), the most common systemic mycosis in Latin America. The PCM treatment involves a long-term chemotherapeutic approach and relapses occur at an alarming frequency. Moreover, the emergence of strains with increased drug-resistance phenotypes makes the discovery of new drugs drugs an urgent task. Aiming at repurposing drugs for treating PCM, our group implemented an *in silico* chemogenomics screen on *Paracoccidioides* spp. genomes based on concept that "proteins sharing enough similarity (orthology) have enhanced the probability of share the same ligands". Initially, using the OrthoVenn web platform, we compiled a list of 6743 *P. brasiliensis* proteins (Pb01) with orthologous (E-value ≤ 10-20) in other two isolates (Pb03 and Pb18). Then, protein sequences of the prioritized proteins were aligned against the sequence of drug targets in the DrugBank and TTD databases to screen for drugs that can potentially have anti-PCM activity. Inclusion and exclusion criteria such as drugs approved in phase I of the clinical studies, FDA approved status, sequence identity (≥ 30%), and conservation state of functional amino acid residues were also incorporated in the drug screening. As a result, 254 proteins genes encoding potential *Paracoccidioides* drug targets for a total of 982 approved drugs or drug candidates were identified. Among the combined list of potential drugs targeting PCM proteins, drug such as Sulfamethoxazole, ketoconazole, Itraconazole, Fluconazole, Voriconazole, Rifampicin, already are used in PCM treatment. In doing so, we suggested an array of drugs that are expected to inhibit several metabolic processes, such as protein translation, transport Na+ -K+ -2Cl-, non-depolarising muscle relaxant and imprisonment cell cycle. The drugs identified were distributed within a wide range of classes, including antibiotics (e.g., Sulfoxone), anti-inflammatory agents (e.g. Acetylsalicylic acid), hypertensive agents (e.g., Chlorthalidone), antiepileptic agents (e.g. Vigabatrin,) and anticancer agents (e.g., Bosutinib). Our next step is to screen experimentally these drugs against Pb 01, Pb 03, and Pb18 and develop homology models and molecular docking studies to reveal insights into the molecular basis of drug action.

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