KINASE INHIBITOR REPURPOSING FOR NEGLECTED TROPICAL DISEASES

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Neglected Tropical Diseases caused by protozoan parasites, like *Trypanosoma cruzi* or *Trypanosoma brucei,* are responsible for millions of infections in developing areas worldwide every year, and are lethal if untreated. Current treatments have serious limitations due to complex administration routes and dosage, severe side effects, and emerging resistance. In order to overcome these drawbacks, the development of new therapies is needed.

Our project is based on kinase inhibitor repurposing as a tool for rapid compound progression in the discovery of new treatments against parasitic diseases. This work is focused on AZD 5438, a small molecule, cyclin-dependent kinase (CDK) and mammalian Glycogen Synthase Kinase-3 (mGSK3) inhibitor with promising results as an antitumor agent and currently in phase I clinical trials. We have generated 83 new analogs based on this chemical structure, and tested them against *T. brucei* and *T. cruzi* responsible for sleeping sickness and Chagas disease, respectively. Toxicity against different mammalian cell lines was also analysed. Compounds that showed potent activity without major cytotoxicity were progressed to rate of kill assays for both parasites. Purified recombinant *T. cruzi* GSK3 was obtained for target validation studies and inhibition analysis was performed for a subset of derivatives. The extensive biological data that we have obtained will be discussed in the context of the structure-activity relationships, as well as future directions of this work.