Human kinase inhibitors as starting points for kinetoplastid drug discovery

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Chagas disease and human African trypanosomiasis represent a significant health problem, particularly in low to middle income countries and have been designated as neglected tropical diseases. Current therapeutics show increasing numbers of treatment failure, have low efficacy, or efficacy against only the acute infection stage, or severe side effects associated with their use. As such, new treatments are urgently needed that meet the Target Product Profiles (TPPs) that have been described by the WHO and the Drugs for Neglected Diseases *initiative* (DND*i*).

Our research began with AZD-5438, an orally active CDK human kinase inhibitor. While our initial efforts focused on the optimization of this scaffold for human African trypanosomiasis, we retrospectively examined the series as a potential *Trypanosoma cruzi* inhibitor. During this process, we uncovered potent inhibitors for both diseases. Further work is ongoing, with a focus on (1) improvement of the drug-like properties for this series, particularly aqueous solubility in a region of the compound that would be solvent exposed; (2) optimization of potency in the *in vitro* assays; and (3) assessment of human kinome selectivity of advanced compounds. This work is being done with an eye to identifying a compound to progress into a proof-of-concept efficacy study.