Phenotypic high-throughput screening identified potent Trypanosoma inhibitors with ability to cure Human African Trypanosomiasis

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The current anti-trypanosomal therapies suffer from problems of toxicity, inadequate efficacy hence there is an urgent need for safer, more efficacious and 'easy to use' oral drugs. Novartis carried out whole cell based high-throughput screening using ~2 million compounds and obtained ~28,000 hits showing > 50 % growth inhibition against *Trypanosoma brucei brucei* at 10 µM concentrations. Further reconfirmation, removing cytotoxic hits and cheminformatics analysis for drug-like properties resulted in ~1,000 tractable hits with Tbb IC_{50} < 10 µM. Biological characterization using reversibility and kill kinetic profiling helped to group them in to 'cidal' and 'non-cidal' compounds. Following chemical hit triaging 36 chemical series were identified; further 7 chemical series were prioritized on the basis of cidality, broad SAR, metabolic stability and efficacy against clinical isolates. Tool compounds from all the chemical series were subjected to early efficacy testing using blood stage mice model, wherein they significantly reduced parasitemia, followed by either complete or partial cure. One of the series was prioritized for lead optimization to address brain penetration and other pharmacological properties. This led to successful identification of a lead compound which completely cured trypanosoma infection in brain stage mice model. Mechanisms of action studies on this series revealed 20S proteasome as the target for this series. Characterization of hits in disease relevant assays and early animal efficacy studies helped in identification of promising chemical series which had the ability to cure HAT in both blood and brain animal models.