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Identification of selective anti-trypanosome agents from compound library LOPAC

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Abstract

Sleeping sickness disease (human African trypanosomiasis) is still a major health threat to a large number of people in 36 countries of sub-Saharan Africa. Currently, the estimated infection cases in these areas are between 300,000 and 500,000. *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are the pathogens of sleeping sickness in humans. These parasites live and proliferate mainly in the blood and tissue fluids of the infected mammals and are transmitted by tsetse flies (*Glossina spp.*). The disease starts from a bite by an infected tsetse fly and goes through an initial stage, where trypanosomes multiply in the bloodstream and the lymphatic system. The disease will progress quickly without effective treatment, and the trypanosomes will cross the blood-brain barrier and invade the central nervous system eventually. In the late stage, patients will show a variety of neurological symptoms and often exhibit characteristic signs such as an alteration of the circadian sleep/wake pattern, which is how the disease is named “sleeping sickness”. The disease will result in wasting of body tissue, coma, and ultimate death. There is an urgent need to develop better chemotherapeutic agents for the treatment of trypanosomiasis. Exploring the new application of existing medicines is a new trend in drug development field. There are multiple advantages of this strategy. First, the manufactory of these agents is mature already. Second, the toxicity profiles of the existing medicines are well established, which can be used to guide the new clinical testing if their anti-trypanosomiasis activity is identified. Third, multiple administration routes of the medicines are well-developed which may include the oral administration formulation. Oral administration route is very critical for the treatment due to the limited medical resource at sub-Saharan Africa area. Our group has developed and validated an easy operating high throughput screening (HTS) cell proliferation assay with *T. brucei* cells, and two mammalian cell lines. Sigma-Aldrich provides a LOPAC compound library (about 1300 chemicals), which consist of all the current clinical medicines and drug candidates in clinical trials, which are used for the high throughput screening process. The results from the screening are summarized.