A new approach to chemotherapy : drug-induced differentiation kills African trypanosomes

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Author(s) Wenzler, Tanja; Schumann Burkard, Gabriela; S. Schmidt, Remo; Mäser, Pascal; Bergner, Andreas; Roditi, Isabel; Brun, Reto
Author(s) at UniBasel Mäser, Pascal ; Brun, Reto ; Wenzler, Tanja ;
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Human African trypanosomiasis (sleeping sickness) is a neglected tropical disease caused by Trypanosoma brucei spp. The parasites are transmitted by tsetse flies and adapt to their different hosts and environments by undergoing a series of developmental changes. During differentiation, the trypanosome alters its protein coat. Bloodstream form trypanosomes in humans have a coat of variant surface glycoprotein (VSG) that shields them from the immune system. The procyclic form, the first life-cycle stage to develop in the tsetse fly, replaces the VSG coat by procyclins; these proteins do not protect the parasite from lysis by serum components. Our study exploits the parasite-specific process of differentiation from bloodstream to procyclic forms to screen for potential drug candidates. Using transgenic trypanosomes with a reporter gene in a procyclin locus, we established a whole-cell assay for differentiation in a medium-throughput format. We screened 7,495 drug-like compounds and identified 28 hits that induced expression of the reporter and loss of VSG at concentrations in the low micromolar range. Small molecules that induce differentiation to procyclic forms could facilitate studies on the regulation of differentiation as well as serving as scaffolds for medicinal chemistry for new treatments for sleeping sickness.
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