

Targeting Trypanosoma brucei Using Antibody Drug Conjugates against the Transferrin Receptor

Authors : Camilla Trevor, Matthew K. Higgins, Andrea Gonzalez-Munoz, Mark Carrington

Abstract : Trypanosomiasis is a devastating disease affecting both humans and livestock in sub-Saharan Africa. The diseases are caused by infection with African trypanosomes, protozoa transmitted by tsetse flies. Treatment currently relies on the use of chemotherapeutics with ghastly side effects. Here, we describe the development of effective antibody-drug conjugates that target the T. brucei transferrin receptor. The receptor is essential for trypanosome growth in a mammalian host but there are approximately 12 variants of the transferrin receptor in the genome. Two of the most divergent variants were used to generate recombinant monoclonal immunoglobulin G using phage display and we identified cross-reactive antibodies that bind both variants using phage ELISA, fluorescence resonance energy transfer assays and surface plasmon resonance. Fluorescent antibodies were used to demonstrate uptake into trypanosomes in culture. Toxin-conjugated antibodies were effective at killing trypanosomes at sub-nanomolar concentrations. The approach of using antibody-drug conjugates has proven highly effective.

Keywords : antibody-drug conjugates, phage display, transferrin receptor, trypanosomes

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