Membrane Active Chelators (MACs) as Chemotherapueutic Agents for Treatment of Human African Trypanosomiasis (HAT)

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Technology description

Membrane Activated Chelators (MACs) are proprietary neuroprotective drugs [D-PHARM LTD; Rehovot Isreal] that modulate cell membrane metal ion homeostasis by adopting an inactive conformation outside only in the lipid environment of cell membranes. In this environment, the drugs are able to unable to bind metal ions at their elevated non-physiological concentrations, which results in a drug with excellent tolerability. DP-b99, a BAPTA-based lipophilic MAC of calcium, zinc and copper has been safely used in humans (1, 2) and is currently in phase III clinical trails trials for treatment of acute ischemic stroke (D-Pharm Ltd). The safety tolerability and efficacy of related compounds DP-109 and DP-460 has also been demonstrated as these compounds have shown promise in mouse models of Alzheimer's disease and amyotrophic lateral sclerosis (2-6). So why predict that MACs will protect against Stage 2 HAT? It is known that low zinc concentrations or the presence of cell-permeable zinc chelators cause rapid disruption of non-brain human endothelial cells (HUVEC, aorta HAEC, and iliac vein HIVEC). Surprisingly, human BMEC, which comprise the functional unit of the BBB, respond by tightening barrier function (7). We have found that African trypanosomes, the causative agent for human African trypanosomiasis (HAT, also called sleeping sickness) are unable to cross human BMEC that have been pretreated with BAPTA/AM (an intracellular calcium chelator) (8). While BAPTA could theoretically impede/block the development of Stage 2 HAT in patients with early Stage 1 disease and/or protect against PTRE, BAPTA is not suited for use in humans. MACs as chelators of both calcium and zinc should safely fulfill this role. T. brucei also contains Ca2+-binding proteins such as calmodulin (CaM) and other EF-hand proteins (IFH5, Tb-17, Tb24, Tb44) and PKC-like activity (9). Very large Ca2+ reservoirs are also maintained in the acidocalcisome, a unique organelle, which also contains Zn2+. By chelating parasite Ca2+ and Zn2+ MACs might effect growth and/or be trypanocidal (9).

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