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Hydromethylthionine: Potential of a single drug for multiple neurodegenerative protein aggregation disorders

Following our discovery of a fragment from the repeat domain of τ -protein as a structural constituent of the PHF-core in Alzheimer's disease, we developed an assay that captured several key features of the aggregation process. τ - τ binding through the core τ fragment can be blocked by variants of the Methyl Thioninium (MT) moiety found to dissolve proteolytically stable PHFs isolated from AD brain. The PHF-core tau fragment induces templated proteolytic processing of normal τ , is inherently capable of auto-catalytic self-propagation, can be assembled into characteristic PHFs *in vitro* and assembly can be blocked by MT-like compounds. The potential utility of these compounds for reduction of pathology and reversal of behavioural deficits was confirmed in tau transgenic mouse models using a stable reduced form of the molecule (hydromethylthionine) which is better absorbed and tolerated. Similar benefits have been shown in a synuclein aggregation assay *in vitro* and in a transgenic synuclein mouse model. These findings led to the first clinical trials to test hydromethylthionine therapy in Alzheimer's disease as a way to block this cascade. Although hydromethylthionine appears to be beneficial as monotherapy, there is a negative interaction with standard symptomatic treatments for AD which has now been confirmed in a τ transgenic mouse model. In clinical practice, hydromethylthionine therapy will be optimally useful as first-line monotherapy. The efficacy of hydromethylthionine as a synuclein aggregation inhibitor suggests that it may also be useful in Parkinson's disease and dementia of the Lewy body type.

Biography

Claude M Wischik has completed his Medical degree at Flinders University in South Australia and PhD at the University of Cambridge, UK. He is the Professor of Psychiatric Geratology at the University of Aberdeen and Chairman of TauRx Therapeutics. He has published extensively on the τ -pathology of AD.

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