Prion-like processing of pathological proteins as a unified basis for pharmaceutical development in neurodegenerative disorders

The molecular pathology of a number of different progressive neurodegenerative disorders are increasingly understood as driven by prion-like processing of an underlying misfolded protein. These now include Tau protein in Alzheimer’s Disease (AD), Synuclein in Parkinson’s Disease (PD), TDP-43 in Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis, and Huntingtin in Huntington’s Disease. Although the overt pathologies differ, there is a common underlying theme at the molecular level of a conformational change that converts a complex functional protein into an oligomeric form (low molecular weight aggregate) which has the capacity to go on recruiting the normal version of the protein into the pathological version. These oligomers are in effect self-replicating at the expense of the normal protein, leading both to loss of function and also to direct toxicity. The oligomers also behave as infectious particles able to propagate the process to otherwise healthy neurons.

The abnormal conformation typically consists of a beta-sheet structure within the critical pathological binding domain. This characteristic conformation offers an opportunity for pharmaceutical intervention. A Tau Aggregation Inhibitor (LMTX*), originally developed for the treatment of Alzheimer’s Disease by selectively blocking the pathological tau-tau binding interaction, has a similar action on TDP-43 aggregates, on Synuclein aggregates and on Huntingtin aggregates. This opens the possibility of developing disease modifying drugs which are able to address a number of distinct neurodegenerative disorders by a common mechanism of action.

Biography
Claude M Wischik holds the Chair in Old Age Psychiatry at the University of Aberdeen in Scotland, and is Executive Chairman of TauRx Pharmaceuticals. He studied medicine in Australia, completed his PhD at the Laboratory of Molecular Biology in Cambridge, and also higher psychiatric training in Cambridge. He was the first to identify Tau protein as the main constituent of the Alzheimer tangle and developed the first Tau Aggregation Inhibitors. He has published 121 papers and holds 11 patent groups based on his work with over 40 individual patents.

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