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TauRx global phase 3 trial in Alzheimer's disease with tau aggregation inhibitor LMTX

There have been 19 phase 2/3 clinical trial failures in 15,000 AD subjects to date, all aiming to reduce amyloid pathology. The Tau theory has offered an entirely viable alternative conceptual framework, largely ignored for the last 20 years.

The filaments of the Alzheimer neurofibrillary tangle are made of a truncated fragment from the repeat domain of tau. This truncated fragment can catalyse the conversion of normal soluble tau into aggregated oligomeric and fibrillary forms which, in turn, can infect neighbouring neurons. Initiation of tau aggregation requires it's binding to a non-specific substrate to expose a high affinity tau-tau binding domain and is self-propagating thereafter. The initiating complex is most likely formed as a consequence of age-related degradation of endosomal-lysosomal processing (ELP) of neuronal proteins, particularly of membrane proteins from mitochondria. Tau pathology begins in the late 40s and affects 50% of the population over the age of 45. Unlike amyloid load, Tau pathology is highly correlated with cognitive decline in post-mortem epidemiological studies and with FDG-PET imaging deficits, correlations also confirmed with new tau-selective PET ligands.

Methylthioninium (MT), the first identified Tau Aggregation Inhibitor (TAI), reverses the proteolytic stability of the tau oligomers/filaments, facilitates their proteolytic clearance and reduces the load of tau pathology in transgenic tau mouse models. A phase 2 clinical trial in 321 subjects with mild/moderate AD demonstrated a reduction of 85%±30% in the rate of disease progression as measured by ADAS-cog over 12 months and prevented progression of functional imaging deficits. The chloride salt of oxidized MT (MTC) has dose-dependent pharmaceutical limitations. A superior stabilized reduced version of the molecule (leuco-MT, LMTX) has been developed, that has greater tolerability and better absorption at higher doses. Two global phase 3 trials are currently underway in 22 countries. Recruitment of the 1,500 subjects in these trials is expected to be completed by 3rd quarter of 2014, with first data read-out in 2016.

Biography

Claude M Wischik is board certified in psychiatry and Professor of Old Age Psychiatry at the University of Aberdeen, Scotland. A pioneer in Tau research, Professor Wischik's work on Tau pathology began in 1985 in the laboratory of Sir Martin Roth, who was the first to correlate tangles with Alzheimer's dementia, and later with Sir Aaron Klug (Nobel Laureate) at Cambridge University. Prof. Wischik subsequently discovered the Tau protein compositional structure of the Alzheimer tangles and established that it was possible to dissolve tangles with pharmaceutically viable compounds that act as Tau Aggregation Inhibitors. He also demonstrated a direct link between clinical dementia and Tau aggregation at the biochemical level, irrespective of ß-amyloid load in human brain. As TauRx Chairman, Prof. Wischik has led the company to its present stage, has developed its portfolio of projects to the phase 3 clinical level and has worked with his Singaporean colleagues to raise ~$150m to date.

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