

Tangles to Tau to Treatment

The story of tau research

A major breakthrough in the treatment of Alzheimer's disease has been revealed by scientists at the Alzheimer's Association International Conference on Alzheimer's Disease (ICAD 2008) in Chicago, Illinois. An international clinical trial sponsored by TauRx Therapeutics has indicated for the first time that it appears to be possible to substantially reduce the progression of Alzheimer's by targeting the neurofibrillary tangles originally discovered in 1907 by Alois Alzheimer.

This first encouraging evidence supporting the clinical efficacy of a tau-based treatment will have an important impact on scientific approaches to the disease which have been dominated by the rival β -amyloid theory for the last 20 years.

As far back as 1984, Professor Claude Wischik was working in Cambridge UK under the direction of Sir Martin Roth and Sir Aaron Klug. At Roth's instigation, Wischik began a research project with Klug at the MRC Laboratory of Molecular Biology (LMB) in Cambridge to discover the structure of the paired helical filament (PHF) of which the Alzheimer tangle is composed, using techniques for which Klug had won a Nobel prize. Wischik discovered that the polymer is composed of a short segment of the microtubule-associated protein tau in 1988.

This work also led to the discovery that it was possible to dissolve PHFs isolated from the Alzheimer's brain with pharmaceutically viable compounds which act as Tau Aggregation Inhibitors (TAIs).

The tau protein normally functions inside nerve cells to stabilize nerve connection fibres (axons), by binding to microtubules which are the backbone of these axons. The Wischik research team showed that at an early stage of the disease, there is tangle-based destruction of nerve cells in the hippocampus of the brain, and that tau aggregation first appears in the brain's cortex some 20 years before the clinical impact on the person becomes severe.

The strong correlation between tangles and dementia, and genetic evidence for the role of tau aggregation in a wide range of neurodegenerative disorders due to mutations in the tau gene, suggested that a drug which blocks tau aggregation could possibly be useful in the treatment of Alzheimer's.

To investigate and prove the principle, Wischik's team developed a novel form of methylthioninium chloride (MTC, now trademarked as rember™), an old chemical substance which has been used clinically for many years to treat urinary tract infection and methaemoglobinaemia, and one of a class of pharmaceutically viable diaminophenothiazines with activity against the tangle filaments.

The team showed that this drug dissolves the tangle filaments (PHFs) isolated from the Alzheimer's brain, and blocks abnormal tau aggregation in specially engineered cells - without interfering with the normal function of tau. Working with Professor Franz Theuring at the Charite Hospital in Berlin, the team demonstrated that the drug reversed tau pathology in transgenic mice, and also reversed cognitive and other behavioural deficits. These results are being presented for the first time at ICAD 2008 (Harrington et al., Melis et al., Zabke et al.)

Following their discovery of selective Tau Aggregation Inhibitors (TAI's) in 1996, the diaminophenothiazine drug class was patented for the treatment and prevention of Alzheimer's disease in US, European Union and other jurisdictions.

Wischnik moved with his team to take up a Chair in Mental Health at the University of Aberdeen in 1997 where work continued in the laboratories of the Institute of Medical Sciences.

Wischnik teamed up with Dr K M Seng in 2002 to found TauRx Therapeutics as a company incorporated in Singapore with the mission to develop new treatments and diagnostics for a range of neurodegenerative diseases based on its technology platform. The company is managed in Singapore, but its research is conducted in Aberdeen, Berlin, Warsaw and Paris.

Wischnik is the Executive Chairman of TauRx, which undertakes clinical development and commercialisation, and of WisTa Laboratories which owns and manages the discovery platform.

Because of the prior history of clinical use of MTC, its well established clinical safety record, and extensive available preclinical safety pharmacology, the UK regulatory authorities granted permission for the Company to conduct a Phase 2 trial in up to 400 subjects for up to 2 years of treatment in 2004. This was conducted in 16 centres in the UK and one centre in Singapore. The study was designed as a 24-week exploratory, dose-range finding, parallel design, double-blind, randomised, placebo-controlled trial of TAI monotherapy followed by a 60-week blinded active treatment extension, conducted in 321 AD subjects of mild or moderate severity. A nested molecular imaging study of the brain was conducted in 100 of the mild AD subjects after 18 to 24 weeks of treatment in parallel.

The results of this study are as follows: on the primary outcome measure, ADAS-cog (Alzheimer's Disease Assessment Scale cognitive subscale), treatment with rember™ at 60mg tid produced clinically relevant, significant benefit as compared to controls at 24 weeks in moderate subjects (effect size -5.5 ADAS-cog units, $p = 0.0208$), and with respect to the control arm at 50 weeks in both mild and moderate subjects (effect size -6.8 ADAS-cog units, $p < 0.0001$). This efficacy profile was supported on the MMSE (Mini-Mental State Examination), and on non-cognitive outcome measures at both 24 and 50 weeks. As a first approximation to supporting disease modifying efficacy, treatment with rember™ at the 60mg tid dose produced a significantly larger effect size at 50 weeks than at 24 weeks implying an effect on the rate of cognitive decline ($p = 0.0014$). This was confirmed in a mixed effects slope analysis, showing an 81% reduction of long run rate of progression over 50 weeks ($p < 0.0001$). This effect on slope translates into a divergence from controls at the rate of 11 ADAS-cog units per annum: the theoretical on-treatment patient is better off than the patient not on treatment by an extra 11 ADAS-cog units for every year of treatment. The final 84-week analysis confirmed the long term effect of the 60mg dose in subjects remaining on treatment, with apparent decline still not significantly different from baseline at the final assessment, whereas there was significant decline at other doses. In essence, TAI therapy appears to stabilise patients who remain on treatment for at least 19 months.

The brain imaging study confirmed the clinical trial results. This was designed to determine whether TAI treatment with rember™ has the capacity to impact the pathological progression of Alzheimer's as determined by SPECT scan. This measures neuronal function indirectly by measuring regional cerebral blood flow (rCBF) which is tightly coupled to neuronal activity. The study showed that treatment

with rember™ at the 60mg dose altered the trajectory of rCBF decline over 6 months in mild Alzheimer's. That is, the decline seen over 6 months in the control group was eliminated in the group receiving rember™ treatment. The efficacy of rember™ was shown to be greatest in those brain regions characterised by the most severe tau aggregation pathology, namely the hippocampus and the entorhinal cortex, the regions first affected in the Braak staging system. Amyloid plaque pathology is relatively sparse in these regions, particularly at the mild stage of the disease. This result is being presented publically for the first time at the ICAD 2008 (Staff et al.), along with similar findings in hippocampus from a smaller FDG-PET study (Murray et al.).

The brain scan efficacy of rember™ was found to anticipate clinical evidence of efficacy by some 6 months in mild Alzheimer's cases. This creates the potential both for early detection of treatment responders and demonstration of efficacy at a stage of Alzheimer's when standard clinical instruments are insensitive and confounded by cognitive reserve and practice effects. The fact that the greatest effect on pathology could be seen in the regions affected earliest in Alzheimer's raises the possibility that rember™ could be used in early stage prevention of Alzheimer's, well before significant neuronal destruction occurs in the brain regions essential for memory and before symptoms become apparent.

In the search for disease-modifying approaches to Alzheimer's disease the field has been dominated by the β -amyloid cascade hypothesis. According to this hypothesis, the formation of aggregates of the β -amyloid protein that are found in β -amyloid plaques in the brain is considered to play a central role in causing clinical dementia. However, β -amyloid plaques are poorly correlated with dementia, and the clinical results of this approach have so far proved to be disappointing, with smaller effects on the ADAS-cog scale than available symptomatic treatments.

The TAI results reported at ICAD 2008 provide the first support for the hypothesis that a treatment approach based on tau aggregation pathology could delay the progression of cognitive decline in both mild and moderate Alzheimer's. This now requires confirmation in a larger Phase 3 trial. There are well established correlations between tau pathology and both clinical severity and neuronal destruction in Alzheimer's. The evidence for clinical efficacy of TAI therapy in mild Alzheimer's and supporting physical evidence of efficacy in the brain regions affected earliest and most severely in the disease is entirely consistent with these correlations. The efficacy shown in these regions raises the possibility that treatment targeting the tau aggregation cascade that underlies Alzheimer's tangle may be an important component of the long term management and prevention of Alzheimer's disease.