The TAU of PD

By Lev Osherovich, Senior Writer

An Australian team has shown that loss of microtubule-associated protein- τ leads to accumulation of toxic intracellular iron, a shared feature of Parkinson's disease and Alzheimer's disease.¹ The findings could mean that companies developing AD therapies that target the aggregated protein will need to be mindful of iron levels.

Microtubule-associated protein- τ (MAPT; TAU; FTDP-17) is a structural component of the cytoskeleton that helps neurons move proteins to distant synapses. In AD, TAU becomes hyperphosphorylated and forms large aggregates called neurofibrillary tangles that are thought to hasten the destruction of neurons.

Recent findings have suggested that TAU aggregates are present in PD as well, but exactly how TAU contributes to the disease has been unclear.²

Now, a team led by Ashley Bush, professor of pathology at **The University of Melbourne**, has found that the soluble form of TAU normally functions in a pathway that helps to export excess iron and that this process goes awry in the brains of PD patients and in mice lacking Tau.

"The findings pertain as much to Alzheimer's disease as Parkinson's disease," said Bush. Indeed, he expects TAU aids the normal function of amyloid precursor protein (APP), a key AD player that his team has previously shown to aid the detoxification of iron.³

The findings add support for **Prana Biotechnology Ltd.**'s strategy of treating AD, PD and other neurodegenerative diseases by trapping excess metals.

Metal health

The team's first clue that TAU deficiency could play a role in PD came from studying the postmortem brains of patients with PD. The group found that the substantia nigra—the dopaminergic brain region most affected by PD—had higher levels of iron and lower levels of soluble TAU than the same region in healthy controls.

The team also examined the brains of aged Tau knockout mice and saw increased iron levels and degeneration of the substantia nigra as well as PD-like motor difficulties compared with what was seen in wild-type control brains.

"TAU knockouts don't develop much of a phenotype prior to seven months," so in previous studies of these mice the PD-like phenotype had been overlooked, said Bush.

He hypothesized that other mouse models of PD also would show Tau abnormalities. Indeed, mice with a chemically induced form of the disease had excess iron accumulation and a shortage of soluble Tau compared with untreated controls.

Bush thinks that one of TAU's normal functions may be to help APP travel to the cell surface, which is where APP facilitates the transport of iron out of the neuron. In primary cortical neurons from Tau knockout mice, iron accumulation was higher and cell surface levels of App were lower than those in wild-type controls.

Finally, Bush's team showed that pretreatment with clioquinol, an iron-chelating compound, protected Tau knockout mice from degeneration of the substantia nigra and cortex compared with no treatment.

Results were reported in *Nature Medicine*.

Bush's findings are in line with the hypothesis that metal accumulation is a central feature of several neurodegenerative diseases, said James Connor, professor and vice-chair of neurosurgery research at **Pennsylvania State University**.

"The idea that some disruption in APP's function [in iron transport] is involved in AD has been around for a while," said Connor. "The argument is that if you disrupt this function of APP or prevent it from reaching the cell surface, there is an accumulation of iron in the neurons."

It is unclear why Tau knockouts initially develop PD-like symptoms rather than AD symptoms. Connor suspects the substantia nigra may be especially sensitive to decreases in the iron-detoxifying activity of APP and thus is the first brain region to show signs of pathology.

The neurons of the substantia nigra use an iron-requiring enzyme to make dopamine, and thus "have a high turnover of iron," said Connor. "These cells may be more vulnerable to deficiency of APP, since they are in an iron-rich area to begin with."

Bush agreed and said older Tau knockouts go on to develop AD-like pathology, including cortical atrophy, increased ventricular area and decreased cognitive functioning compared with wild-type controls.

Iron it out

Study coauthor Robert Cherny, head of research at Prana and an associate professor at the University of Melbourne, said the paper shows that Prana's "approach of re-establishing metal homeostasis is applicable across a range of neurodegenerative disorders."

Prana's lead compound is PBT2, a metal protein-attenuating compound that is in Phase II testing for AD and Huntington's disease. Prana also is developing PBT434, a metal-binding compound that is in preclinical development for PD in a project sponsored by **The Michael J. Fox Foundation for Parkinson's Research**.

Cherny said Prana's compounds work by performing APP's metal-transporting functions, "taking metals from places of excess to areas where they are in deficit, restoring homeostasis."

Bush, who cofounded Prana and is the company's former CSO, said his next steps are identifying metal-binding compounds that have high specificity for iron and testing them in animal models of PD.

His findings could serve as a caution for companies developing AD therapeutics that lower levels of aggregated TAU—either directly or indirectly.

In the former group is **TauRx Pharmaceuticals Ltd.** Its rember methylthioninium chloride, a dye that binds to TAU aggregates, has

completed Phase II testing to treat AD. The company is planning to advance a related compound called LMTX into Phase III testing. TauRx did not respond to queries by *SciBX*.

Among the companies with compounds that indirectly affect TAU is **reMYND N.V.**, a spinout of the **Catholic University Leuven** that has preclinical compounds that reduce the toxicity of TAU aggregates in cell culture models of AD.

CSO of drug discovery Gerard Griffioen said reMYND's compounds likely work by modulating vesicular trafficking and, in addition to decreasing levels of TAU aggregates, may also offset the toxic effect of TAU deficiency seen by Bush.

Bush's study shows "that in addition to TAU having a gain of toxic function in neurodegenerative disease, the soluble form has an important function itself," said Griffioen.

"Many people, including us, are focused on TAU aggregation and the toxic process around that. But here they show that TAU function is important

for iron export. This holds lessons for the field. If you are thinking about degrading or removing TAU as a therapeutic approach, you have to be careful because you might affect other things, such as iron export."

Griffioen said that a potential solution is to focus on preventing TAU from aggregating in the first place rather than on eliminating TAU aggregates that have already formed.

The findings reported in *Nature Medicine* are unpatented.

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COMPANIES AND INSTITUTIONS MENTIONED

Catholic University Leuven, Leuven, Belgium
The Michael J. Fox Foundation for Parkinson's Research, New York, N.Y.
Pennsylvania State University, University Park, Pa.
Prana Biotechnology Ltd. (ASX:PBT; NASDAQ:PRAN), Melbourne, Victoria, Australia
reMYND N.V., Leuven, Belgium
TauRx Pharmaceuticals Ltd., Singapore
The University of Melbourne, Melbourne, Victoria, Australia

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