Stabilizing tauopathies

By Kai-Jye Lou, Staff Writer

Researchers at the **University of Pennsylvania** have found that low doses of the microtubule stabilizer epothilone D, a failed cancer compound from the Kosan Biosciences unit of **Bristol-Myers Squibb Co.**, could have utility in neurodegenerative tauopathies like Alzheimer's disease and frontotemporal dementias.¹

Neurodegenerative tauopathies are characterized by the presence of neurofibrillary tangles in neurons, which are formed by the pathological aggregation of τ proteins. These proteins normally bind to and stabilize microtubules; the loss of this function increases microtubule destabilization, which could impair axonal transport and neuronal function.² Thus, researchers have postulated that restoring microtubule stability could have a therapeutic benefit against tauopathies.³

In 2005, a UPenn group led by Virginia Lee and John Trojanowski reported that the microtubule-stabilizing cancer drug paclitaxel decreased motor deficits in a mouse model of neurodegenerative tauopathy.⁴

The problem, said Kurt Brunden, is that "paclitaxel doesn't cross the blood brain barrier and thus is not suitable for human tauopathies. Thus, our work was focused on identifying and testing microtubule-stabilizing agents that could penetrate the blood brain barrier that might then be efficacious in a transgenic mouse model that shows brain τ pathology."

Brunden is director of drug discovery in the Center for Neurodegenerative Disease Research (CNDR) at UPenn. Lee is director of the CNDR, and Trojanowski is director of UPenn's Institute on Aging and the co-director at CNDR.

The UPenn group's search led to epothilone D, a tubulin-binding polyketide that Kosan and **Roche** had evaluated in Phase II trials for multiple cancers. They discontinued development in 2007 in favor of a second-generation analog with a better safety profile.⁵

Brunden's team showed that mice receiving intraperitoneal injections of epothilone D had higher brain concentrations of the compound than plasma concentrations. In a mouse model of τ -mediated neurodegenerative disease, epothilone D increased both axonal integrity and microtubule density and decreased cognitive deficits compared with vehicle.

Importantly, the doses of epothilone D were lower than those tried

in cancer and did not cause significant weight loss, motor impairment or neutropenia in the mice. Animals in the study received 1 or 3 mg/kg injections of epothilone D. The higher dose corresponds to about 10% of that used to treat prostate cancer patients in a Phase II trial.⁶ In clinical trials, epothilone D side effects included neurosensory toxicity, nausea and vomiting.

Results were published in *The Journal of Neuroscience*.

"Our results would suggest that a much lower dose of epoD than that used in cancer patients might be effective for AD," said Brunden, who is co-lead author on the paper. "Our hope is that this study will encourage Bristol-Myers Squibb, which holds patents to various epothilones, to consider the development of epoD or a related compound for the treatment of AD and related tauopathies."

Bristol-Myers did not respond to requests for comment. However, the pharma did file a patent in 2009 covering the use of epothilone D to treat τ -associated diseases including AD.

Bristol-Myers markets paclitaxel as Taxol to treat multiple cancers. The pharma and partner **Otsuka Pharmaceutical Co. Ltd.**

also market Ixempra ixabepilone, a tubulin-binding agent derived from epothilone B, to treat advanced breast cancer in the U.S. and Switzerland.

Mary Michaelis, a professor of pharmacology and toxicology at **The University of Kansas**, said the data in *The Journal of Neuroscience* paper "add validity to the idea that if you could deliver a microtubule-stabilizing compound into the brain, there is a good chance of helping to preserve synaptic function in neurons."

Bin Zhang, a senior research investigator at UPenn's CNDR, is the lead author on the 2005 paper and co-lead author on *The Journal of Neuroscience* paper. Lee and Trojanowski are

both senior authors on the current paper.

Therapeutic prospects

Although the microtubule-stabilizing effects of epothilone D resulted in clear improvements in the symptoms of neurodegenerative tauopathies, the compound did not have a statistically significant impact on τ pathology in the brain. Thus, researchers contacted by *SciBX* were mixed on whether the compound will also have disease-modifying effects.

Paul Aisen, director of the Alzheimer's Disease Cooperative Study and professor of neurosciences at the **University of California, San Diego**, thinks additional study on epothilone D in the AD setting is warranted.

"Since we have yet to show that any therapeutic approach provides effective disease-modifying activity in AD, we must vigorously explore all plausible leads," he told *SciBX*. "High among the approaches deserving attention is the strategy targeting τ pathology. We hope that this study will lead to clinical development of an antitangle therapy for disease modification in AD."

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University of Pennsylvania**

The Alzheimer's Disease Cooperative Study was formed by the **National Institute on Aging** and UCSD to research AD therapeutics.

Michaelis thinks the microtubule-stabilizing effects of epothilone D have the potential to slow the progression of the symptoms stemming from a loss of synaptic activity but said it's still unclear whether epothilone D could also affect other targets that would give it disease-modifying effects, such as preventing cell death.

"We still don't have a clear understanding of why cells in Alzheimer's disease are dying, and there are multiple competing theories," said Michaelis. "But if you could slow this degenerative process, you could potentially buy patients several additional years and also improve their quality of life during those years."

Claude Wischik, cofounder and executive chairman of **TauRx Pharmaceuticals Ltd.**, agreed that epothilone may have a symptomatic benefit in AD but doesn't think the microtubule-stabilizing effect will have a clinically meaningful impact on disease progression.

"There is no doubt that there is a loss of microtubules in Alzheimer's, but the question is whether restoring microtubule levels could alter the progression of the disease," said Wischik, who also is a professor of old age psychiatry at **The University of Aberdeen**.

"The issue with a microtubule-stabilizing approach is that it won't affect the formation of toxic τ aggregates, which will continue to accumulate and damage the synaptic terminals," he said. "If you envisage treating patients with epothilone D, you would stabilize the microtubules, but toxic τ aggregates will continue to form and thus the disease will progress at the same rate."

Wischik added that the authors themselves reported that epothilone D did not have a statistically significant impact on τ pathology in the brain.

TauRx has multiple τ aggregation inhibitors in development for AD and other neurodegenerative tauopathies like frontotemporal dementias. Wischik said the company is planning to start a Phase III trial of LMTX in AD but declined to disclose a timeline. LMTX is a second-generation form of the biotech's Rember methylthionium and delivers the same active methylthionium moiety.

Moving to the clinic

Although epothilone D has already been tested in cancer patients, several hurdles remain before the compound could enter the clinic for AD.

For example, both Michaelis and Wischik were concerned about the compound's known cytotoxic effects. Michaelis also thinks developing an appropriate dosing protocol is going to be tricky.

"We can't lose sight of the fact that epothilone D is cytotoxic," she told *SciBX*. "You want to stabilize the microtubules in nerve cells but at the same time it's very easy to cause overstabilization, which could result in these cells losing their ability to grow new synapses. It will be important to study whether microtubule overstabilization is occurring."

"Such a compound would be applicable for use in life-or-death situations such as cancer, but it is not yet clear whether it has a pharmacokinetic and safety profile that would make it acceptable for use in Alzheimer's disease."

**—Claude Wischik,
TauRx Pharmaceuticals Ltd.**

"The question that needs to be addressed is whether doctors would be willing to use such a compound for five years in a patient with Alzheimer's," added Wischik. "Such a compound would be applicable for use in life-or-death situations such as cancer, but it is not yet clear whether it has a pharmacokinetic and safety profile that would make it acceptable for use in Alzheimer's disease."

Brunden's UPenn group now is trying to characterize the effects of epothilone D in additional mouse models.

"Our mouse studies suggest that low doses of epoD are well tolerated, but it is unknown if

similar results will be found in humans," he told *SciBX*. "An unresolved question that we are pursuing is whether epoD will provide benefit in a transgenic mouse with established τ pathology. This is an important question as our initial findings demonstrate an effect during the early stages of diseases, which might be equivalent to the prodromal stages of AD" in which patients may show signs of mild cognitive impairment and memory loss.

Brunden said the work reported in *The Journal of Neuroscience* is not patented. Indeed, clinical development of epothilone D is at the discretion of Bristol-Myers.

"I think it is possible that epoD could be evaluated in humans at doses that would be applicable for AD," said Brunden. "As regards the proper clinical path, this would require consultation with the FDA, as it is conceivable they might require additional Phase I safety testing in addition to what was completed for cancer indications. Bristol-Myers Squibb would have to initiate these discussions and develop the clinical program for AD."

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COMPANIES AND INSTITUTIONS MENTIONED

Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
National Institute on Aging, Bethesda, Md.
Otsuka Pharmaceutical Co. Ltd. (Tokyo:4768), Tokyo, Japan
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
TauRx Pharmaceuticals Ltd., Singapore
The University of Aberdeen, Aberdeen, U.K.
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