Alzheimer candidate LMTX® inhibits α-sync aggregation in pre-clinical Parkinson's Disease study, published in the *Frontiers in Molecular Neuroscience*

ABERDEEN, Scotland and Singapore, 25th January, 2018 – TauRx Therapeutics Ltd has reported preclinical study results, published online in *Frontiers in Molecular Neuroscience*, showing that LMTM, the active pharmaceutical ingredient in its LMTX® product originally developed for the treatment of Alzheimer's disease, may also be useful for the treatment of Parkinson's disease (PD).[1]

Results from this study in a transgenic model of PD show that LMTM, developed as the first tau aggregation inhibitor for treatment of Alzheimer's disease, may also provide a potential disease-modifying therapy in PD and other synucleinopathies. LMTM works by dissolving and preventing further aggregation of the proteins that are closely linked to neurodegeneration in these diseases. Accumulation of an aggregated form of alpha-Synuclein protein (α-Syn) in brain cells is closely associated with PD and also with dementia with Lewy bodies **(**LBD**).**[2] In the PD form, movement is primarily affected, whereas in LBD the pathology causes hallucinations and progressive dementia.

To test the potential of LMTM in the treatment for these diseases, researchers developed two independent transgenic mouse models of synucleinopathy, named L58 and L62. These models had been fully characterised in an earlier study [Frahm *et al.* 2017[2]] which showed that human α-Syn aggregation was induced in both groups of mice to form abnormal fibrous deposits inside nerve cells in the brain. In the L62 model, which had higher levels of α-Syn aggregation, the brain pathology progressed in an age-dependent manner. Importantly, the mice developed the immobility that is a debilitating feature of PD, as well as other behavioural abnormalities such as lack of directed movement.

When both groups of mice were treated orally with LMTM for just 6 weeks, there was a significant reduction in the amount of α-Syn pathology in multiple brain regions. Treatment with LMTM also restored normal mobility and reversed the other abnormal behavioural features produced by the pathology in these animals. The benefits in movement and behaviour were found to match the effects on pathology closely.

Both models were developed in the laboratory of Professor Franz Theuring of the Institute of Pharmacology, at Charité – Universitätsmedizin Berlin, as part of its long-standing research collaboration with TauRx Therapeutics Ltd. Prof. Theuring said: "This latest trial builds upon the data shown in our earlier alpha-Synuclein study of these mouse models. We already know from studies in Alzheimer's disease that LMTM has encouraging pharmacologic properties and these new data show us a pathway to increasing our understanding of Parkinson's and other neurodegenerative diseases through future LMTM research."

"Continued research in neurodegenerative conditions which support the discovery of potential new treatment options for patients is of the utmost importance," said Prof. Claude Wischik, of Aberdeen University and executive chairman of TauRx Therapeutics Ltd. "As we already have a substantial safety database for LMTM from our recent clinical studies in patients with Alzheimer's disease, the results seen in these animal models open up the possibility of near-term testing of LMTM in patients with PD or LBD, resources permitting. The results also suggest the exciting possibility that a single drug could be used at different doses to treat a range of severely debilitating neurodegenerative disorders, even though they have different underlying pathology at the molecular level."

For further information on the *Frontiers in Molecular Neuroscience* publication visit https://www.frontiersin.org/articles/10.3389/fnmol.2017.00447/full

-ENDS-

About the Study

Both male and female homozygous transgenic mice and wild-type C57BL/6J litters of mice were used in this preclinical trial. In transgenic models, full-length human a-Syn was fused with a signal sequence peptide to promote a-Syn aggregation. Treatment cohorts aged 5–6 months were randomly assigned to groups based upon body weight and dosed with LMTM or vehicle via oral gavage, administered daily for 6 weeks (6 days per week). Brain samples were examined for quantification of α-Syn proteins in brain tissue, as well as immunohistochemistry and stereological cell counting of brain sections. Methylthioninium levels were measured in brain samples by means of a modified dynamic contrast enhanced liquid-liquid extraction method. Animal behavior was assessed in a light/dark box.

TauRx Therapeutics
Innovation in neurodegeneration

About Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects predominately dopamine-producing neurons in an area of the brain called *substantia nigra*, although the pathology can be widespread. Symptoms generally develop slowly over years and differ from one person to another. These may include tremor, slowness of movements (bradykinesia) and limb rigidity, as well as gait and balance problems. The cause remains largely unknown. People with PD experience symptoms later in the disease course when a significant amount of the *substantia nigra* neurons have already been lost or impaired. Lewy bodies (accumulation of abnormal alpha-synuclein) are found *in substantia nigra* neurons of PD patients. Currently, there is no cure for PD. Treatment options vary and include medications and surgery.[3]

Protein aggregation inhibitors

TauRx's tau aggregation inhibitors (TAIs) have arisen from nearly 30 years of research. TAIs work by undoing the tau tangles that cause dementia, thereby potentially slowing and even arresting memory loss.[4] The first-generation TAI, rember® was a patented, highly-purified version of methylthioninium chloride (methylene blue), a compound previously used to treat a variety of conditions. LMTX® is a stable reduced form of methylthioninium which is better absorbed and is better tolerated than methylene blue and has been tested in clinical trials in mild to moderate Alzheimer's disease.

About TauRx Therapeutics Ltd

TauRx Therapeutics Ltd is a member of the TauRx Pharmaceuticals group which is developing technology spun-out from the University of Aberdeen, Scotland, and was established in Singapore in 2002 with the aim of developing new treatments and diagnostics for a range of neurodegenerative diseases. The company's tau aggregation inhibitor, LMTX®, targets aggregates of abnormal fibres of tau protein that form inside nerve cells in the brain, giving rise to 'tau tangles'. TauRx's headquarters are in Singapore and its primary research facilities are based in Aberdeen. For more information, please visit: http://www.taurx.com.

References

1. Schwab K, et al. A protein aggregation inhibitor, leuco-methylthioninium bis (hydromethanesulfonate), decreases-synuclein inclusions in a transgenic mouse model of synucleinopathy. *Front Mol Neurosci*. 2018; 10:447:1–15.
2. Frahm S, et al. Alpha-Synuclein transgenic mice, h-α-SynL62, display α-Syn aggregation and a dopaminergic phenotype reminiscent of Parkinson's disease. *Behav Brain Res*. 2018 Feb 26;339:153-68.

3. Parkinson's Foundation. What is Parkinson's? Available at: http://www.parkinson.org/understanding-parkinsons/what-is-parkinsons. Accessed 15 January 2018.
4. Wischik CM, et al. Tau-aggregation inhibitor therapy for Alzheimer's disease. *Biochem Pharmacol* 2014; 88:529–39.

Media Contacts

Email: taurxpress@hkstrategies.com

Website: http://www.taurx.com