



Preclinical study shows how commonly prescribed drugs for Alzheimer's disease interfere with the activity of the tau aggregation inhibitor hydromethylthionine

ABERDEEN, Scotland and Singapore, 04 March, 2020 – Today, TauRx Therapeutics announced the publication of a study in an Alzheimer's disease (AD) mouse model which demonstrates that drugs currently used to manage the symptoms of the disease interfere with the activity of a drug with an entirely unrelated mode of action. The preclinical research, published online in *Current Alzheimer Research*¹ (abstract available [here](#); manuscript available [here](#)), showed that prior treatment with rivastigmine (an acetylcholinesterase inhibitor) negatively affected the pharmacological activity of hydromethylthionine which acts on the tau aggregation pathology of AD.

The only treatments currently approved for AD, acetylcholinesterase inhibitors and/or memantine, provide temporary symptomatic benefit but do not affect long-term disease progression. Despite their limited efficacy, most clinical trials investigating new disease-modifying treatments have allowed patients to continue taking symptomatic treatments at stable doses. The assumption has been that they do not interfere with disease-modifying efficacy because the mode of action is unrelated to that of the symptomatics. However, the new preclinical study indicates this assumption is likely to be incorrect and may have reduced the chances of success of clinical trials with new drugs.

Researchers compared the effects of hydromethylthionine given alone or as an add-on therapy to rivastigmine in a mouse model of AD engineered to develop tau pathology². This is a hallmark of AD in the brain, characterised by neurofibrillary tangles, disrupted synapses, and decline in memory and learning ability. The study showed that long-term pre-treatment with rivastigmine eliminated the memory-enhancing effects of hydromethylthionine by interfering with a broad range of effects on different transmitter systems and cellular compartments at multiple levels of brain function. Preliminary results from a study testing memantine in the same way showed similar interference.

The study data indicate that the interference results from the brain adapting to the activating effects of symptomatic drugs by downregulating multiple neuronal systems. Since the downregulation is not determined by the mode of action of hydromethylthionine, the researchers conclude that symptomatic drugs might also interfere with other drugs tested in clinical trials in AD regardless of their intended therapeutic target.

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These data are consistent with the significant reduction in the treatment effects of hydromethylthionine seen in patients taking the drug as an add-on to symptomatic treatments compared to its effects when taken alone in two large Phase 3 trials in mild-to-moderate AD.^{3,4} The results support the idea that disease-modifying treatments should be tested alone to avoid interference by symptomatic treatments.

Professor Gernot Riedel, lead author of the paper and Professor of Systems Neuroscience at the University of Aberdeen commented: “This study shows that the difference in hydromethylthionine treatment effects between monotherapy and add-on therapy that was reported recently⁵ can be reproduced preclinically in an AD mouse model. How the brain responds to hydromethylthionine is different according to whether or not the brain has been exposed to symptomatic treatments. Our findings may help explain why so many other clinical trials testing disease-modifying treatments as add-on therapy have failed so far.”

Prof. Claude Wischik, of the University of Aberdeen and executive chairman of TauRx Therapeutics Ltd. commented: “The concentration-dependent treatment effects were reduced by half in the add-on patients compared with those receiving hydromethylthionine as monotherapy. We were able to see this difference clearly in the clinical trials because the treatment effects of the drug on cognitive decline and brain atrophy are much larger than anything seen to date. These results suggest that disease-modifying clinical trials should be conducted as monotherapy to improve chances of success and thereby offer new hope to patients and caregivers.”

For further information on the *Current Alzheimer Research* visit:

<https://benthamscience.com/journals/current-alzheimer-research/>

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About hydromethylthionine (LMTM)

TauRx’s tau aggregation inhibitors (TAIs) have arisen from nearly 30 years of research. TAIs work by preventing the tau aggregation process responsible for the “neurofibrillary tangles” that were originally discovered by Alzheimer and that cause dementia, thereby potentially slowing and even arresting memory loss.⁶ Professor Wischik and colleagues originally discovered that tangles are composed of tau protein and that the process can be blocked by drugs.⁶ The first-generation TAI, rember[®] was a patented, highly-purified version of methylthioninium chloride (methylene blue), which produced initial evidence of clinical efficacy in a Phase 2 trial in mild-to-moderate AD. Hydromethylthionine is

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a stable reduced form of methylthioninium, which is better absorbed, has better brain penetration and is better tolerated than methylene blue. It is therefore active at a much lower and safer dose than was needed for methylene blue. A 12-month placebo-controlled clinical trial is currently ongoing at 150 sites in US and EU.

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. The company 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, hydromethylthionine, targets aggregates of abnormal fibres of tau protein that form inside nerve cells in the brain that give rise to 'tau tangles'. TauRx's headquarters are in Singapore and its primary research and operational facilities are based in Aberdeen. For more information, please visit: <http://www.taurx.com>.

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