Institution: University of Aberdeen

Unit of Assessment: 8 (Chemistry)

Title of case study: Targeting Tau protein as a treatment for Alzheimer's disease

Period when the underpinning research was undertaken: 2015-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
John Storey	Chair in Pharmaceutical Industrial Chemistry	2001-present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

A joint venture between the University of Aberdeen and TauRx Pharmaceuticals Ltd has made considerable progression towards a novel treatment for Alzheimer's disease (AD), with John Storey leading the chemistry team. Importantly it has also been shown that, in patients receiving the drug as monotherapy for 9 months, the rate of brain atrophy was reduced to that reported for normal elderly controls. Storey's research has enabled elucidation of the drug's mode of action, allowing a drastic reduction in the prescribed dose required for patients with significant enhancements in safety and tolerability, together with a greatly reduced environmental impact from patient excretion. Two new synthetic methods have also been developed that negate the need for toxic heavy metals during synthesis. Significant income generation has been realised for the companies engaged in production [*text removed for publication*]. Storey's research and subsequent intellectual property (IP) [*text removed for publication*] in the REF period) has resulted in approximately [*text removed for publication*] spend with patent agents. The IP has also played a key role in TauRx's ability to raise funds [*text removed for publication*] and its recognised status as an innovative leader in Neurodegenerative Disease Management, creating over 100 new research and development (R&D) jobs in the UK.

2. Underpinning research (indicative maximum 500 words)

Approximately 500,000,000 people have some form of cognitive impairment. Despite considerable research efforts to find a treatment for the disease, world regulatory authorities have approved only five drugs to date, none of which have stopped disease progression. Moreover, these drugs are gradually being delisted, having shown poor-risk benefit profiles. In 2019, France removed state funding for drug treatments for dementia, citing little or no clinical benefit.

Professor Storey, Chair of Pharmaceutical Industrial Chemistry at the University of Aberdeen (UOA) is Head of Technical for TauRx Pharmaceutical Ltd (spin out company from UOA), leading a team of 26 chemists, working closely alongside TauRx's biologists, behaviourists, mathematicians and the clinical trial team. Storey and his research team have developed the company's portfolio of drug candidates, in particular the design and analysis of tau aggregation inhibitors (TAIs). Unlike the vast majority of large pharmaceutical companies and academic groups, the Aberdeen team's approach to tackling dementia has not been to target beta amyloid, but rather to concentrate on the disaggregation of tau protein[R1-5]. Several lines of evidence indicate that aggregation of tau protein is central to neurodegeneration in AD and BvFTD.

In 2008, TauRx commenced phase II trials, as previously reported, demonstrating that methylthioninium (MT), delivered in its oxidised chloride salt form methylene blue (MB), targets and disrupts the formation of tau protein tangles. However, problems with bioavailability, tolerability and side effects of the first forms of the drug (such as vomiting, diarrhoea), were encountered and therefore, a new drug candidate was sought. In 2012, Storey's team developed and tested a new form of MT — the molecule leuco-methylthioninium

bis(hydromethanesulphonate) known as LMTM (market name, LMTX), a new chemical entity, which delivered the same moiety of the compound into the bloodstream as MB but with much improved bioavailability, tolerability and safety[R1,R2]. This development formed the basis of three patents[P1-3].

As reported in REF2014, TauRx was granted permission to proceed with two worldwide large double-blind, dose-ranging phase III clinical trials in mild/moderate AD patients in February 2013, with an amendment to the protocol occurring in October 2013. Although the LMTM provided patients with measurable benefits[R1-3], the dosage regime was found in 2016 to be incorrect[R2] showing that only approximately 9% of the original dose was required for efficacy (16 mg/day instead of 200 or 250 mg/day). As a consequence, a third phase III trial was initiated in 600 subjects in Nov 2017 using a low dose of LMTM (16 mg/day)[R2,S8]. This much lower dose has clear benefits for patients, with far fewer side effects and greater safety. There is also a huge environmental benefit, as far less of the drug would need to be manufactured and consequently excreted by the patients into the environment.

The initial synthesis route of LMTM (developed in 2012) used commercially sourced methylene blue (MB) as the starting material. However, the process involved in MB production necessitates the use of two chromium(VI)-based oxidation reactions and an iron reduction step, producing large quantities of highly environmentally contaminating Cr and Fe waste, both of which are becoming banned around the world for large scale chemical production. To avoid this problem, and to move away from MB as the starting material, Storey's group (during the REF period) have pioneered two new synthetic approaches to LMTM, avoiding the use of heavy metals, environmentally damaging reagents and high dilution conditions thus meeting modern regulatory expectations. These routes are now being used to make clinical supplies[P2&3].

The two new synthetic approaches have been subjected to a full quality by design critical parameter analysis, suitable for regulatory submission to both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), with the data and methodology transferred to pharmaceutical manufacturing plants in the UK [*text removed for publication*] and Taiwan [*text removed for publication*]. Each synthetic approach has been scaled to approximately 800kg batch size and each site contracted to manufacture a total of [*text removed for publication*] of drug. All development work (analytical and synthetic) took place in the Aberdeen laboratories under Storey's stewardship prior to transfer to manufacturers. This is also the case for the development of the tableted formulation for patient use, which has been manufactured commercially [*text removed for publication*].

In addition to the development of compounds, the Aberdeen chemistry team has played a critical role in the pharmacokinetic analysis[R6] of biological samples from preclinical and clinical studies for regulatory submissions, providing insight into the function of LMTM, as well as its metabolites[R6]. These analyses required the development of new methodology and protocols (measuring down to 0.002 ng/ml) by the Aberdeen team within their GLP/GCP lab (managed by Storey), which is the only facility of its type in a chemistry department in the UK accredited by the Medicines and Healthcare products Regulatory Agency (MHRA) to test both to GLP and GCP compliance standards and it is regularly inspected by the MHRA.

3. References to the research (indicative maximum of six references)

Key patents:

[*text removed for publication*]

Key Research Publications (citations via Scopus):

R1. Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. Gauthier S.; **Storey J.M.D**; Harrington C. R.; and Wischik C.M. *Lancet* (2016); 388(10062): 2873-2884. DOI: 10.1016/S0140-6736(16)31275-2, 221 citations

R2. Potential of Low Dose Leuco-Methylthioninium Bis(Hydromethanesulphonate) (LMTM) Monotherapy for Treatment of Mild Alzheimer's Disease: Cohort Analysis as Modified Primary

Outcome in a Phase III Clinical Trial. Wilcock, G.K.; **Storey J.M.D**., Harrington C.R.; and Wischik C.M. *Journal of Alzheimer's Disease* (2018); 61(1): 435-457. DOI: 10.3233/JAD-170560, 87 citations

R3. Modelling Prion-Like Processing of Tau Protein in Alzheimer's Disease for Pharmaceutical Development. Wischik, C.M.; **Storey, J.M.D**.; and Harrington, C.R. *Journal of Alzheimer's Disease* 2018); 62(3): 1287-1303. DOI: 10.3233/JAD-170727, 17 citations

R4. Alzheimer's Disease-like Paired Helical Filament Assembly from Truncated Tau Protein Is Independent of Disulfide Crosslinking. Al-Hilaly, Y.K.; **Storey J.M.D**.; Harrington C.R.; Wischik, C.M.; and Serpell, L.C. *Journal of Molecular Biology* (2017); 429(23): 3650-3665. DOI: https://doi.org/10.1016/j.jmb.2017.09.007, 26 citations

R5. A Protein Aggregation Inhibitor, Leuco-Methylthioninium Bis(Hydromethanesulfonate), Decreases alpha-Synuclein Inclusions in a Transgenic Mouse Model of Synucleinopathy. Schwab, K.; **Storey, J.M.D**.; Riedel, G.; Wischik, C.M.; Harrington, C.R.; and Theuring, F. *Frontiers in Molecular Neuroscience* (2018); 10:447. DOI: 10.3389/fnmol.2017.00447, 11 citations

R6. Complex Disposition of Methylthioninium Redox Forms Determines Efficacy in Tau Aggregation Inhibitor Therapy for Alzheimer's Disease; Baddeley, Thomas C. ; McCaffrey, Jennifer ; **Storey, J. M. D**.; John K S Cheung [1], Valeria Melis [1], David Horsley [1], Charles R Harrington [1], Claude M Wischik ; *Journal Of Pharmacology And Experimental Therapeutics*,(2015) 352(1), 110-118, DOI: 10.1124/jpet.114.219352, 106 citations

4. Details of the impact (indicative maximum 750 words)

TauRx Pharmaceuticals Ltd is a leader in dementia drug development, targeting cognitive decline resulting from tau aggregates in the brain. The unit's research with the primary beneficiary TauRx, has national and international impact evidenced here by:

(1) Enhanced production and income generation
(2) Improved clinical outcomes for patients
(3) Environmental advantages
(4) International innovation and competitiveness
(5) Job creation and company expansion

1) Enhanced production and income generation for the supply chain: Since 2014, Storey and his research team have achieved several chemistry milestones, modelled upon the first-generation Phase II tau aggregation inhibitor (TAI), 'rember™', and second-generation tau aggregation inhibitor, 'LMTX®', which is now in a phase III clinical trial (Lucidity) in Canada, US, UK and Europe[S8]. Storey leads TauRx's technical section and engages five specialist contractors for GMP manufacture and analysis [*text removed for publication*].

2) Improved clinical outcomes for patients: TauRx's initial Phase III clinical trial program[R1,2], which concluded in 2016 involved the second-generation tau aggregation inhibitor, LMTX®, and comprised two clinical trials (TRX-005 and TRX-015) in Alzheimer's disease and a further trial (TRX-007) in behavioural variant frontotemporal dementia (bvFTD; neurodegenerative orphan indication) in 1890 patients. Study TRx-015 was the first study to report promising results on clinical and brain imaging endpoints at doses of 150 and 250 mg/day. After receiving LMTM as monotherapy for 9 months, the rate of brain atrophy was reduced to that reported for normal elderly controls. The low dose of 8 mg/day appeared to show the same benefit as the higher doses, indicating previously unrecognised absorption and efficacy properties of LMTX® [R2]. This was a highly important finding, as it meant that dosing in the currently ongoing trials[S8] could be reduced to lower levels (16 mg per day compared to 200-250 mg/day), thereby improving patient safety, drug tolerability[S4] and significantly reducing side effects. [*text removed for publication*]. In addition to the patients being treated with LMTM in clinical trials, there are now a substantial number of patients around the world being supplied with the drug under a named-patient supply protocol and gaining significant benefit[S4].

3) Environmental advantage: With the development of two new synthetic strategies to LMTM avoiding the use of toxic heavy metals (Cr and Fe) and avoiding high dilution reaction conditions,

clear environmental benefits have been achieved in terms of process waste minimisation. Furthermore, reducing dosing from 200 or 250 mg/day to 16 mg/day) has vastly reduced drug excretion from patients into the environment eliminating concerns related to long-term environmental impacts on watercourses and sewage treatment facilities due to the antibacterial properties of the drug, an important consideration when seeking market authorisation. Vastly lower doses for patients also mean much lower volumes of drug need to be synthesised with clear environmental benefits.

4) International innovation and competitiveness: The quality of the underlying science has enabled TauRx to continue to raise considerable external investment. Since August 2013, the company has raised almost [*text removed for publication*]. In recognition of the continued expansion of their innovative approach, in 2019 TauRx received the highly prestigious Frost & Sullivan Asia Pacific 'Neurodegenerative Disease Management Technology Innovation Award' in recognition of visionary innovation, with the company's low-cost therapeutic and diagnostic Alzheimer's solutions being 'poised to revolutionise the market.' Frost & Sullivan Excellence Awards recognise companies in a variety of regional and global markets for demonstrating outstanding achievement and superior performance[S6]

[*text removed for publication*] patent attorney to TauRx stated, '*Storey's contribution to the IP assets which underpin TauRx has gone well beyond helping devise the inventions covered by the patents. Prof. Storey and his team provided additional experimental evidence, and Prof. Storey personally interviewed and provided declarations to the United States Patent and Trademark Office (USPTO) examiners. There is no doubt that this contribution was instrumental in leading to the withdrawal of the objections and achieving the grant of patents which are a key part of the exclusivity strategy of the Company*.'[S7]

5) Job creation in the UK and overseas: The expansion of the TauRx's drug synthesis portfolio and scaling up of drug manufacturing capabilities by Storey at specialist contractors such as [*text removed for publication*] has been instrumental in job creation and retention. In addition to creating and securing jobs for 26 chemists within the Department of Chemistry (continuously during the REF period) at the University of Aberdeen, (Funding from TauRx to JS since 2014 for the Tau Chemistry research project [*text removed for publication*] a further 40 staff now manage the clinical development of TauRx's drug candidates at Tau's Aberdeen office and 68 other employees are involved in R&D at the University of Aberdeen as well as across the UK, Germany and in Singapore[S5]. [*text removed for publication*]

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1 Letter from [*text removed for publication*] outlining importance of the Tau project
S2 Letter from [*text removed for publication*] outlining importance of Tau chemistry project to [*text removed for publication*]
S3 Letter from [*text removed for publication*] outlining importance of Tau project to their company
S4 Letter from Physicians from the UK, Birmingham and Solihull Memory Assessment Service, NHS indicating the importance of Tau treatments and research
S5 Letter from (CBO TauRx) outlining the importance of chemistry to the company and its growth
S6 Frost & Sullivan Asia Pacific award database: http://www.apacbp-awards.com/results.html
S7 Letter from [*text removed for publication*] patent attorney outlining importance of chemistry contribution to TauRx's patent portfolio and storey's contributions
S8 *"Safety and efficacy study evaluating TRx0237 in subjects with mild Alzheimer's disease". ClinicalTrials.gov. 2 November 2015, Phase 3 trial details,* https://clinicaltrials.gov/ct2/show/NCT01689233