**Institution:** University of Aberdeen

Unit of Assessment: UoA1: Clinical Medicine

**Title of case study**: Discovery and development of a new drug for the treatment of dementia.

Period when the underpinning research was undertaken: 2002 – 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: |
|---|---|---|
| Prof Claude M Wischik | Professor of Psychiatric Geratology | 1997 – current |
| Dr Charles R Harrington | Senior Research Fellow | 1998 – current |

**Period when the claimed impact occurred**: ongoing since Aug 2013

**Is this case study continued from a case study submitted in 2014?** No

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

Dementia is a growing global health problem in need of medical treatments. Pioneering research led by the University of Aberdeen has led to the development of the drug, hydromethylthionine, a potential 'game-changer' for the long-term management and prevention of Alzheimer's disease. Building on the initial commercialisation reported in the REF2014 case study, the award-winning company TauRx has expanded its research team from 38 to 68 scientists and attracted investment totalling more than [*text removed for publication*] since August 2013. The claimed impact is the provision of clinical benefit to individuals, growth of an international company with established presence worldwide (creating new employment and a new joint venture) and the demonstration of pharmacologic activity of a new drug for Alzheimer's disease and frontotemporal dementia.

## 2. Underpinning research (indicative maximum 500 words)

There are over 800,000 people with dementia in the UK, and this will rise to over 1 million by 2025. Dementia costs the UK an estimated GBP35 billion every year. Alzheimer's disease (AD) is the most common form of dementia. In younger adults, frontotemporal dementia (FTD) is the second commonest cause after AD. Behavioural variant FTD (bvFTD) primarily affects personality and behaviour but, like AD, progresses to a severe dementia state and death within six to eight years of symptom onset.

Symptomatic treatments in the form of the licensed cholinesterase inhibitors and memantine have been the mainstay of AD treatment for more than a decade, but neither slows progression of the disease. There are still no licensed treatments for any form of FTD. The research undertaken at the University of Aberdeen by Claude Wischik, Professor of Psychiatric Geratology, and Dr Charles Harrington, Senior Research Fellow, has pioneered a new approach to developing a disease-modifying treatment for both AD and FTD, and led to its commercialisation.

Wischik and Harrington's research has concentrated on understanding the development of tau pathology, a feature of both AD and FTD that is closely correlated with the clinical symptoms of dementia. Tau is a protein that normally stabilizes the microtubules which act as the cytoskeleton in neurons and assist in the transport of essential components. In disorders such as AD and FTD, tau protein forms abnormal aggregates and filaments that lead to neuronal death and cognitive impairment. Targeting tau is a significant departure from the amyloid-based focus that has dominated AD research and drug development, but which has failed in many clinical trials over the last decade. The research began with the development of models of tau aggregation in cells [**R1**] and transgenic mice [**R2**] in which to test the activity of tau aggregation inhibitors *in vitro* and *in vivo*. These patented models and assays were then used to screen further novel aggregation inhibitors which have been patented for their use in the treatment of AD, FTD and expanded to

other neurodegenerative diseases of protein aggregation, that include Parkinson's, Huntington's and motor neuron disease [**R3**].

The scientific rationale arising from this research has permitted international regulatory authorities to allow clinical trials of hydromethylthionine, a novel tau aggregation inhibitor synthesised by TauRx chemists at the University. Two large phase 3 trials, recruiting 1700 AD subjects worldwide, were carried out between 2013 and 2015. Although the primary clinical endpoints were not met, the team discovered that hydromethylthionine showed pharmacological activity on both brain structure and function at an unexpectedly low dose [**R4**] and that AD medications interacted negatively with hydromethylthionine [**R5**]. These were critical findings that have allowed further investment to undertake a placebo-controlled trial in drug-naïve AD subjects, that is underway, to confirm efficacy at this dose. Furthermore, hydromethylthionine showed pharmacological activity in a large study of 176 patients with bvFTD [**R6**]. Several research groups and pharmaceutical companies have since followed this lead, by developing their own tau-targeted research programmes. To date, the TauRx programme is the only one to have reached phase 3 clinical trials development.

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

The quality of the research is deemed to be at least of 2* quality as corroborated by the following patents and peer-reviewed, international publications (with Google Scholar **citations**):

[**R1**] **Wischik, CM, Horsley, D, Rickard, JE, Harrington, CR** (2002) Materials and methods relating to protein aggregation in neurodegenerative disease. PCT WO2002/055720. *This patent describes a model of tau aggregation in cells that is sensitive to tau aggregation inhibitors (TAIs). It also demonstrates that compounds penetrate the cell membrane and provided the basis for screening novel TAIs. It was subsequently included as part of a peer-reviewed article in the Journal of Biological Chemistry (Harrington et al., 2015). Granted in EU, US, JP, AU, CA, CN, HK, IN, MY, and SG.*

[**R2**] **Wischik, CM, Rickard, JE, Horsley, D, Harrington, CR,** Theuring, F, Stamer, K, Zabke, C (2002) Materials and methods relating to protein aggregation in neurodegenerative disease. PCT WO2002/059150. *Despite having the same title as [1], this patent is distinct and describes the creation of a transgenic mouse model of AD in which compounds can be tested in vivo. It has been used to demonstrate efficacy of methylthioninium in decreasing the tau pathology in brains and improving learning memory. It was subsequently published as part of peer reviewed articles in Cellular and Molecular Life Sciences and Behavioural Pharmacology (Melis et al., 2015a,b). Granted in EU, US, JP, AU, CA, AU, and HK.*

[**R3**] **Wischik, CM, Harrington, CR, Rickard, JE, Horsley, D**, **Storey, JMD**, Sinclair, J, Marshall, C, Baddeley, TC (2007). 3,7-Diamino-10H-phenothiazine salts and their use. PCT WO2007/110627. *This patent describes the manufacture of a stable reduced form of drug having improved absorption and tolerability features and demonstrates their use in treatment of AD and other tauopathies. It was subsequently included as part of a peer reviewed article in the Journal of Biological Chemistry (Harrington et al., 2015). The patent has been granted in EU, US, JP, AU, CA, CN, EA, HK, ID, IL, IN, KR, MY, and SG.*

[**R4**] **Schelter BO**, **Shiells H, Baddeley TC**, Rubino CM, Ganesan H, Hammel J, **Vuksanovic V, Staff RT, Murray AD**, Bracoud L, **Riedel G**, Gauthier S, Jia J, Bentham P, Kook K, **Storey JMD**, **Harrington CR, Wischik CM** (2019) Concentration-dependent activity of hydromethylthionine on cognitive decline and brain atrophy in mild to moderate Alzheimer's disease. J. Alzheimer's Dis. 72:931-946. (**14**) https://doi.org/10.3233/jad-190772 *This paper describes the pharmacological activity of hydromethylthionine at a low dose to be confirmed from an ongoing phase 3 trial in AD subjects.*

[**R5**] **Riedel G**, Klein J, Niewiadomska G, Kondak C, Schwab K, Lauer D, Magbagbeolu M, Steczkowska M, Zadrozny M, Wydrych M, **Cranston A, Melis V, Santos RX**, Theuring F, **Harrington CR, Wischik CM** (2020) Mechanisms of anticholinesterase interference with tau aggregation inhibitor activity in a tau-transgenic mouse model. Current Alzheimer Research 17, 285-296. (**6**) https://dx.doi.org/10.2174%2F1567205017666200224120926 *This paper describes the interference of acetylcholinesterase inhibitors on the cognitive benefits of hydromethylthionine in an animal model of AD. These findings support the observations in the phase 3 clinical trials and have implications for all potential new therapeutic compounds in clinical trials.*

[**R6**] **Shiells H, Schelter BO**, Bentham P, **Baddeley TC**, Rubino CM, Ganesan H, Hammel J, **Vuksanovic V, Staff RT, Murray AD**, Bracoud L, Wischik DJ, **Riedel G**, Gauthier S, Jia J, Moebius HJ, Hardlund J, Kipps CM, Kook K, **Storey JMD, Harrington CR, Wischik CM** (2020) Concentration-dependent activity of hydromethylthionine on clinical decline and brain atrophy in a randomized controlled trial in behavioral variant frontotemporal dementia. J Alzheimer's Dis 75, 501-519. (**5**) https://doi.org/10.3233/jad-191173 *This paper describes the pharmacological activity of hydromethylthionine at a low dose in bvFTD, a disease like AD characterised by tau aggregation.*

**Key funding associated with the research**

1998-2002, Knowledge Transfer Grant from the University of Aberdeen.
2002-21, TauRx has funded all associated staff at the University of Aberdeen. [*text removed for publication*]

The totals awarded during 2013-2021 to each of research groups has been [*text removed for publication*]

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

The impact for this case study falls into three categories: health benefits, commercial impact, and intellectual property.

**Health impact.** Some 1,700 AD patients and 190 FTD patients have been enrolled in three global Phase 3 trials of hydromethylthionine. A further one hundred patients have been prescribed the medicine by their physician under compassionate use, with several noting that it has benefitted both their quality of life and predicted life expectancy. As yet, there is no licensed treatment for any form of FTD, however hydromethylthionine has shown to have potential health benefits for those in the trials. [*text removed for publication*]

**Commercial Impact.** TauRx is the pharmaceutical spin-out that was formed by Professor Wischik with investors from SE Asia in 2002 and is incorporated in Singapore. The company has received the Frost & Sullivan 2019 Asia Pacific Neurodegenerative Disease Management Technology Innovation Award, in recognition of visionary innovation "developing novel treatments for neurodegenerative disease. [*text removed for publication*] This demonstrates the successful creation of a commercial pharmaceutical company funded through the investment and based upon the research carried out at the University of Aberdeen.

A substantial amount of funding has been used to support basic scientific research both at the University of Aberdeen and in other academic research centres in Berlin, Warsaw, Frankfurt and at the University of Sussex. Wischik and Harrington serve as Executive Chairman and Chief Scientific Officer for TauRx, respectively. As well as continuing to support 38 full-time research positions at the University of Aberdeen, this investment has funded the continued employment of six researchers in Berlin, a further six in Warsaw (Aug 2013 onwards), and two scientists each in Frankfurt and at the Open University. Research funding is also provided to a collaborative group at the University of Sussex, with three scientists under the lead of Professor Louise Serpell, focused on determining the precise mechanism of action for lead inhibitory compounds at the molecular level [**S2**]. [*text removed for publication*]

As part of a collaborative research agreement with Prof Serpell at the University of Sussex, the research team have created Alzheimer-like filaments under physiological conditions and demonstrated the mechanism of action of methylthioninium, the first tau aggregation inhibitor originally reported by Wischik and Harrington in 1996.

**Intellectual property.** As a result of the research, more than 30 patent families have been filed, with 13 of these since 2013. [*text removed for publication*] The granting of the many patents demonstrates that both the novelty and utility of the research have been acknowledged by patent offices throughout the world. As well as covering the treatment of AD and FTD, these patents include descriptions of novel uses of compounds for the treatment of mild cognitive impairment and Parkinson's disease and for the use of compounds other than hydromethylthionine. [*text removed for publication*] The group has published 32 research articles in peer-reviewed journals during the period 2014-2020, demonstrating the academic relevance of their research.

The demonstration of pharmacological activity of hydromethylthionine for bvFTD [**R5**] is important since this is an orphan indication having no current treatment and provides a route for accelerated marketing approval.

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

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