Institution: University of Aberdeen

Unit of Assessment: 5 - Biological Sciences

Title of case study: Discovery and commercialisation of an entirely new drug for the treatment of Alzheimer's disease

1. Summary of the impact

Pioneering research led by the University of Aberdeen has directly resulted in the development of an investigational medicinal product for the long-term management and prevention of Alzheimer's disease, breaking new ground in the search for effective Alzheimer's treatments. Although not yet commercially available, this drug has already benefited more than 100 patients and their families. A new spin-out company created to develop the drug has created new jobs and attracted more than US$335 million in investment since 2008. Extensive media coverage of the research has generated increased public awareness of the disease and Aberdeen's cutting-edge research and ability to raise investment. *The claimed impact is therefore that a new spin-out company was formed; investments from and collaborations with industry in research and development were generated; and new employment created.*

2. Underpinning research

The World Health Organization estimates that over the next twenty years, the number of people with Alzheimer's disease (AD) will double to 65.7 million. Currently there are no approved drug treatments that can provide a cure for AD - only medicines that can improve symptoms or temporarily slow down their progression in some patients. Major new research undertaken at the University of Aberdeen by Professor Claude Wischik, Professor of Psychiatric Geratology, and Dr Charles Harrington, Senior Research Fellow, forms the basis for an entirely new therapeutic approach to treating AD - one that could effectively prevent disease progression.

Since arriving at Aberdeen in 1998, Wischik and Harrington's work has concentrated on understanding the mechanism of action through which tau pathology, the hallmark of Alzheimer's disease, can be inhibited by compounds. This research began with the development of models of tau aggregation in cells [1] and transgenic mice [2] to test the activity of compound inhibitors *in vivo*. These models and assays were then used to screen further novel aggregation inhibitors, active against tauopathies, such as AD, and also other diseases of protein aggregation, such as Parkinson's disease [3]. This approach was a marked departure from the amyloid-based focus that has dominated AD research and drug development and was based on fundamental biochemical and clinicopathological research conducted by the pair while at the Laboratory of Molecular Biology in Cambridge.

During a double-blind Phase 2 clinical trial (2004-2008) of 321 people with mild AD, it was found that taking methylthioninium chloride three times a day over a period of 50 weeks was successful in slowing down the development of AD by about 81% - with some reported side-effects [4]. Researchers then worked to improve subject-tolerability of the drug and, in 2007, developed the synthesis of the first-ever stable, pharmaceutically acceptable version of the compound [5].

In 2012, this version of the drug entered a Phase 3 programme that is recruiting 1,500 subjects worldwide. This constitutes the first test of effectiveness for the treatment of AD using a tau aggregation inhibitor (TAI), and three Investigational New Drug applications have been filed with the US Food and Drug Administration. Related drugs have been created for pharmaceutical development, and their use has been protected by a number of international patent applications.

The potential of TAIs to treat early AD has also resulted in new streams of research at Aberdeen, including the development of a diagnostic marker to identify AD sufferers before symptoms appear. For this purpose, the research group has developed biological assays to detect compounds that bind to tau pathology *in vitro* [6]. Between 2004 and 2008, more than 170 novel compounds were

created, some of which have demonstrated efficacy in identifying early indicators of AD. On the basis of this research, a formal collaboration was initiated with Bayer Healthcare in May 2010 that continues today with Piramal Imaging.

3. References to the research

[1] 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 TAIs. It also demonstrates that compounds penetrate the cell membrane and provided the basis for screening novel tau aggregation inhibitors. Granted in EU, US, JP, CA, AU, CN, IN, SG, MY, and HK.*

[2] 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. Granted in EU, US, JP, CA, AU, and HK.*

[3] Wischik, CM, Rickard, JE, Horsley, D, Harrington, CR (2007). Inhibitors of protein aggregation. PCT WO2007/110629. *This patent demonstrates a series of compounds that inhibit the aggregation of synuclein as a means for disease modification in Parkinson's disease. Granted in US, AU, and SG.*

[4] Wischik, CM, Wischik, DJ, Storey, JMD, Harrington, CR (2008). Therapeutic use of diaminophenothiazines. PCT WO09/044127. *This describes the phase 2 clinical trial and explains the need to change the formulation to avoid haematological side-effects. Granted in CN and SG.*

[5] 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. The patent has been granted in US, EU, EA, KR, CA, MY, SG and HK.*

[6] Kemp SJ, Storey LJ, Storey JMD, Rickard JE, Harrington CR, Wischik CM, Clunas S, Heinrich TK (2010). Ligands for aggregated tau molecules. PCT WO2010/034982. *In this application, a bioassay was developed to screen ligands to image the tau pathology in early AD.*

Key funding associated with the research

- 1998-2002, Knowledge Transfer Grant from Aberdeen University (£1.2m).
- 2002-13, TauRx has funded all associated staff. TauRx has raised US $335 million (as at August 2013), from investors in S.E. Asia and North America.
- 2010-13, Industrial partnership with Bayer Healthcare/Piramal Imaging (€900,000).

4. Details of the impact

In July 2008, Wischik and Harrington presented their Phase 2 trial findings to seismic effect at the International Conference on Alzheimer's Disease (ICAD) in Chicago. Over 2,000 delegates, including scientists, clinicians, people with dementia, family members, and care professionals were among the first to hear the momentous news that Aberdeen's research had provided the first clinical evidence demonstrating that a treatment based on tau aggregation pathology may delay the progression of cognitive decline in both mild and moderate Alzheimer's. To understand the immediate impact of this news, one needs to remember that up until then the search for effective Alzheimer's treatments had focused on amyloid-based treatments with generally disappointing

clinical results. The Aberdeen research suggested not only an alternative approach but one that had already shown positive clinical results. [a]

Aberdeen's Communications Team says, "This was the University's biggest ever news story, leading the national and international network news across the world and generating awareness and responses from the families of sufferers and charity organisations involved in the area of research and care of people suffering from dementia" [b]. In the month following ICAD 2008, more than 100 major media outlets reported on Aberdeen's research. On 29/07/08 TAI was the lead story on the BBC and ITN 10 PM TV News and, the next day, was reported in depth on CNN and ABC in America [c].

International awareness of Aberdeen's research since 2008 has contributed to new commercial opportunities. Since 2008, US$335 million of international corporate investment has gone into new TAI research via TauRx Therapeutics Ltd - a University spin-out company where Wischik serves as Executive Chairman and Harrington as Chief Scientific Officer. As well as supporting 40 full-time research positions at Aberdeen, this investment has partially funded the continued employment of six collaborative researchers in Berlin and full funding for another six in Warsaw since 2008. Further funding for positions at Aberdeen has been provided since 2010 by the research-based partnership agreements with Bayer Healthcare and Piramal Imaging. [d]

As a result of the research, at least 20 patents have been published (11 since 2008), with many of these already granted. This demonstrates that the novelty and utility of the research have been acknowledged by patent offices. [e]

In January 2013, the University's business relationship with TauRx was the subject of a special presentation highlighting innovation in life science at the "Managing Innovation" Conference in Warsaw, Poland. The aim of this conference is to boost high tech, academic-commercial innovation in Poland. Wischik addressed an audience that included founders of successful high-tech companies, scientists, entrepreneurs, investors, and funding agency leaders such as Poland's Ministry of Science and Education and its National Centre for Research and Development. [f]

In addition to the 1,500 AD patients being enrolled in the global Phase 3 trials of the Aberdeen-developed medicine, there are also one hundred patients who, since the Phase 2 trials ended in 2008, have been prescribed the medicine by their physician because they have found it has benefitted their quality of life. Among the benefits described by patients using the drug and their families are an improvement in levels of concentration and greater alertness leading to recovered confidence and an ability to cope. [g]

The Aberdeen research has continued to attract both international scientific attention and media headlines since 2008. Wischik presented Aberdeen's ongoing TAI research to fellow leading clinical researchers at the Clinical Trials Conference on Alzheimer's Disease in Monaco in October 2012, and again at the Alzheimer's Disease International Conference in Taipei, Taiwan in April 2013 - a gathering of more than 1,000 medical professionals, dementia experts and national Alzheimer's associations from more than 60 countries. In the wake of these events, the Aberdeen research once again was the subject of reports in the UK's Daily Mail and Daily Express, The Times of India and the Wall Street Journal. [h,i].

Therefore the claimed impact as defined by REF is that: the research affected commerce by creating a new spin-out company, through investment by industry in research and through the creation of jobs.

5. Sources to corroborate the impact

[a] Caroline Cassels. Tau-based AD therapy appears to arrest disease progression, improve cognition in phase 2. Medscape. Aug 01, 2008. http://www.medscape.com/viewarticle/578452

[b] Record of media coverage from ICAD 2008 presentation.

http://www.abdn.ac.uk/clsm/research/ref/taurx-research-media-coverage.php

[c] TauRx Therapeutics website http://www.taurx.com provides information on the development of the Company, the research involved as well as details for patients and their caregivers.

[d] Vice-President of Bayer Healthcare and Board Director of Piramal Imaging, has provided reference for the Industrial Research partnership on diagnostic ligand research. The agreement was announced in a press release of 04 June 2010: http://taurx.com/press-releases-announcements.html?page=2

[e] Mewburn Ellis LLP have been responsible for filing all patent applications since 2001 and have provided a reference on the new technology and inventive processes that have been developed. The subject matter includes three major categories: proprietary therapeutic agents or methods of synthesising them; diagnostic agents and enabling technologies such as proprietary assays or systems. The costs of patent prosecution, which have totalled £3.3 million since 2008, have been borne by the creation of the spin-out company.

[f] Second International Conference on Managing Innovation, Warsaw, Poland. January 17-18, 2013. Details of conference :- http://www.nencki.gov.pl/en/article/managing-innovation-2013-1 Presentation made by Professor Wischik at the conference:- http://www.youtube.com/watch?v=2x04Zv_sLTI&feature=youtu.be

[g] The Principal Investigator for the TauRx Phase 2 Clinical Trial has provided a reference for personal clinical accounts from subjects in trial and patients who were subsequently administered named patient supply of drug. This continuation into Phase 3 is based on the enhancement of patient experience and improved well-being for patients. The evidence was presented initially in the findings of the Phase 2 Clinical Trial (http://www.sciencedirect.com/science/article/B7W6D-4T25XX0-K7/2/ae9f39f3a87905d8b0e6257d3fb7b040) and the Phase 3 programme has already started for Alzheimer's disease and behavioural variant frontotemporal dementia (http://www.taurx.com).

[h] Public Relations [financial/public]: Wall Street Journal, November 2012; http://online.wsj.com/article/SB10000872396390443624204578060941988428604.html#articleTabs%3Dcomments

[i] Public Relations [pharmaceutical industry]: PharmaVoice October 2012; p.36-44. "Industry Spotlight: The man, the molecule, the market. Untangling Alzheimer's mystery". http://www.pharmavoice.com/archives/article.esiml?id=2567