Institution: University of Aberdeen

Unit of Assessment: 8 (Chemistry)

Title of case study: Development of treatments & diagnostics for Alzheimer's disease

1. Summary of the impact

Alzheimer's disease (AD) affects one in seven of the population over 60 years of age, and represents an increasing burden on worldwide medical and care resources. Treatments currently available are symptomatic. Despite pharmaceutical industry efforts there has been little indication of a marketable product for long-term treatment.

To address this problem, a joint venture was established in 2001 between the University of Aberdeen and TauRx Pharmaceuticals. A team was created of chemists, biologists, animal behaviourists, working together with a clinical trial team. A drug effective against the progress of AD based on the compound methylene blue was synthesised and scaled up within the Chemistry Department (led by Professor John Storey), with a quality that was proved acceptable through successful phase two clinical trials (2006-8), and is now used in phase three clinical trials which are due to complete in 2015. Several other drug candidates have also been developed and evaluated in pre-clinical and phase one clinical studies that show promise. Collaborations with commercial pharmaceutical companies have as a result led to the manufacture of significant quantities of drug medicines for TauRx Pharmaceuticals based on IP generated within the Chemistry Department and these drugs have been used in clinical trials and for named patient supply (c. 60 patients). This has resulted in increased commercial revenue for these companies and the creation of new employment.

2. Underpinning research

From the outset of the research in 2001, the development of a candidate drug for treatment of AD required an integrated team of medicinal chemists, analytical chemists and scale-up / development chemists. Unlike the vast majority of large pharmaceutical companies and academic groups, the Aberdeen team's approach to the Alzheimer's problem was not to use beta amyloid, but rather concentrated on the disaggregation of tau protein – in 2001 this approach was distinctive and arguably unique.

Clinical trials and investigations cannot take place without a fully developed and potentially efficacious drug candidate. The purity of such drugs has to meet the criteria of the Pharmacopeia and competent regulatory authority guidelines for each region. The challenges to be met by the Chemistry team were to discover a suitable drug candidate and follow-on molecules for future clinical development, and to prepare the drug to a purity commensurate with a pharmaceutical product. This required the team to develop a synthesis suitable for scale up, and to develop suitable testing and analytical protocols for both products and impurities. Work continued to then transfer this technology to facilities capable of scale up to Good Manufacturing Practice (GMP) regulations operated in Europe (by Lonza), in the UK (Shasun Pharma Solutions) and in the USA (Bohringer). Working with the team of chemists based in Aberdeen, this material has then been formulated suitable for use as a final pharmaceutical product.

A suitable drug candidate was identified early in the project. The molecule in question, methylene blue (methylthioninium chloride), was commercially available as a dye. The quality of this material was very variable and did not meet regulatory standards for an active pharmaceutical ingredient (API). Despite a number of attempts by various chemical companies worldwide over the years to synthesise this molecule to a suitable level of purity in order to treat other medical indications (malaria, cancer staining, urinary tract infection etc.), this goal had proved elusive.

The design of a new, efficient and high yielding synthetic approach was therefore required in order to unlock the true potential of this molecule as a drug and to make a clinical trial possible. Two new

innovative routes were devised and taken from milligram scale through to 10-litre scale in the laboratories in Aberdeen. This involved the design and establishment of a scale-up laboratory within the Department of Chemistry with 2, 5 and 10 litre reactor vessels; such a facility is relatively rare within a Chemistry department. Furthermore, the control and understanding of the polymorphic state of the molecule was a regulatory and key component in the successful use of methylene blue as a drug [1].

Early in the project (2003) it became apparent that for TauRx Pharmaceuticals to develop a convincing market position and accrue more value, second generation compounds would also be required. A large number of previously unreported molecules have been prepared which have resulted in a significant patent portfolio [2]. Four of the drug candidates developed have moved into phase 1 preclinical toxicological studies and have already been assessed using a number of highly discriminating animal models. One of these molecules has been fast-tracked through phase one bioequivalence studies and escalating dose / tolerability studies in humans. The design of this molecule centred upon developing a stable reduced form of the methylthioninium moiety (methylene white or leuco-methylene blue). The rationale behind this approach was to provide the molecule in a form with greater tolerability, due to fewer haemolytic and other undesirable side effects [3]. In addition, due to higher solubility and other desirable attributes, a far improved pharmacokinetic profile has been obtained [4]. This molecule has been approved worldwide for two large international phase III clinical trials with 1,500 patients which started in November 2012, and a third phase II/III clinical trial in fronto-temporal dementia.

Given the very poor diagnosis of Alzheimer's disease in its early stages based upon standard medical examination, and to complement the development of treatments within the group, the parallel development of a molecular imaging agent for early and accurate diagnosis was considered important. This has involved the synthesis of a wide range of novel heterocyclic systems that contain tracers such that they can be used for MRI or PET visualisation. Progress on this project has been good, with a number of compound classes being identified and tested with one patent filed to date [5]. In order to progress this project it became apparent that collaboration with an industrial partner with radio labelling capabilities and imaging technology would be advantageous. To this end a collaboration with the leading diagnostic imaging group for AD in the world (Bayer-Schering, Berlin) has been established. This collaboration involves chemical discovery, ligand design and labelling methodology being undertaken in the Chemistry department in Aberdeen, and the "hot" labelling and animal / human imaging taking place in Berlin. The funding for this collaboration has largely come from Bayer-Schering (£405K per annum) but the outcome of this research will result in joint income for both discovery parties.

Whilst the development of compounds has been a central theme throughout all the chemistry effort, analysis has played a very important role; both for molecules synthesised, and also when these molecules are tested in animals and/or humans. Analysis of biological samples is demanding, and new methodology and protocols have been developed, validated and the data obtained used in support of regulatory submissions for clinical trial approvals worldwide. To achieve these outcomes GLP, GCP and GMP laboratories have been set up and accredited by the MHRA in Aberdeen and inspected on three occasions, the only chemistry department in the UK boasting all three accredited analytical laboratories within a university.

All Chemistry research activities have taken place in, or have been directed from, the Chemistry Department at the University of Aberdeen, led by Professor John Storey, who joined the University of Aberdeen in 2001, and was promoted to Professor in 2010. Storey is responsible to TauRx Pharmaceuticals for drug synthesis, design and scale up, and leads a team of 17 research fellows and research assistants on this project (as of 31st July 2013).

3. References to the research

1. T.Rager, A.Geoffroy, R.Hilfiker, J.M.D.Storey, "*The crystalline state of methylene blue: a zoo of hydrates*", Phys.Chem.Chem.Phys., (2012), 14, pp 8074-8082.,

2. S.Clunas, J.M.D.Storey, J.E.Rickard, D.Horsley, C.R.Harrington, C.M.Wischik (2010) "*3,6-Disubstituted Xanthylium Salts*" WO/2010/067078

3. C.M.Wischik, J.E. Rickard, C.R. Harrington, D. Horsley, J.M.D. Storey, C. Marshall, J.D. Sinclair, T.C. Baddeley, "*3,7-diamino-10h-phenothiazine Salts and their Use*", WO2007/110627

4. C.M.Wischik, D.J. Wischik, J.M.D.Storey, C.R.Harrington, "*Therapeutic Use of Diaminophenothiazines*": WO2009/044127

5. S.J.Kemp, L.J.Storey, J.M.D.Storey, J.E.Rickard, C.R.Harrington, C.M.Wischik, S.Clunas, T.K.Heinrich, "*Ligands for Aggregated Tau Molecules*." WO/2010/034982.

4. Details of the impact

The major impact of research conducted in the Chemistry department relates to commercial impact with regard to the bio-pharmaceutical industry and impact on practitioners and services. The generation of a pure drug was made possible through the development of new synthesis routes that made the launch of phase 2 clinical trials possible. Based on the research outcomes, and as a result of the Phase 2 trials, TauRx was able to raise £320 million in external investment, now employs 17 chemists, 5 biologists, and 14 clinicians. In relation to chemistry activities alone TauRx under Storey's supervision is now working in collaboration with 7 companies: Shasun Pharma Solutions (Newcastle upon Tyne, UK), Roberts Chemicals (UK), Lonza Pharma (Visp, Switzerland), Bohinger (USA), Bayer Schering (Berlin), Piramal Healthcare (Newcastle and Berlin), and Almac Sciences (Edinburgh and Craigavon). Through these commercial collaborations, three centres have been established to each manufacture 5 tonnes of the candidate drug as part of the validation campaign based on the patent [4]. Each validation campaign represents an income of £2.5 million for the companies concerned within the REF period. In addition the ongoing manufacture of 400 tonnes between the three sites, to be completed by May 2015 to coincide with completion of the Phase 3 trials, represents a total investment already achieved for these companies of approximately £35 million.

Shasun Pharma Solutions Ltd has advised that the company had an initial production of 6 metric tonnes of the drug, and has now established a manufacturing capability of 150 metric tonnes per annum, which will potentially increase to 250 metric tonnes per annum. This would see commercial revenues in the longer term reaching several hundreds of millions of pounds. There will also be longer term impact for Shasun UK and Shasun India resulting from increased demand for the drug, both in terms of commercial return and job creation throughout the supply chain [a]. In terms of UK impact the company states "*Should the forecast API demand be recognised, it will not only provide opportunities for Shasun in the UK, but also have significant local impact involving local engineering manufacturing, supply and support requirements for pipework, reactors and filter dryers along with bulk storage tanks and ancillary equipment including increased waste handling and treatment facilities on site. For example, should the API requirement reach 500 metric tonnes per annum, Shashun UK would need to invest in equipment from UK suppliers of up to £10M and procure goods and services from the north East region of up to £5M. Manufacture of the API on this scale could lead to the creation of up to 80 jobs at the Shashun UK site*." [a]

A second manufacturer is Piramal Healthcare (Newcastle upon Tyne, UK). Piramal advise that to meet the requirements of producing tablets at the amounts required for the initial trials the company has engaged nine further employees at its Morpeth facility, with a current project revenue in excess of USD 1 Million for FY 2013 and 2014. The company states that this revenue provides a platform for the company to grow and develop its team. "*Tablet supply is now approaching 1,500,000 with batches released to clinical sites in the UK, Europe, US and Asia, this is truly a program with global reach. We hope very much it will result in a marketed product that provides therapeutic benefits to a patient population that sadly has a current unmet need."* [b]

Supply of raw materials to the drug manufacturers is a crucial component of the impact of the Aberdeen research. Roberts Chemicals Ltd describe the company's role in supply and logistics for

procurement of starting materials. "*The financial impact on Roberts is to have enabled strategic growth planning at a very early stage in the company's development. Critically, the company has been able to promote and market its next generation business model much more forcefully than expected. This has led to an international portfolio of users of its business model-cleverly adapted to the current economic downturn. TauRx are about to undertake a large manufacturing validation campaign at three major pharma companies…….Roberts will supply the starting materials for these campaigns"* [c].

Looking to the future, a potential longer term impact, resulting from the synthetic and analytical chemistry performed in the Chemistry department under Storey's supervision relates to the clinical trials of the drugs developed. The Birmingham and Solihull Mental Health NHS Foundation Trust has direct clinical experience with methylthioninium chloride (MTC) and leuco-methylthioninium bis(hydromethanesulfonate) (LMTM) drugs developed in the TauRx project, and is involved in clinical trials. The Trust confirms: "*In AD, in addition to extracellular deposition of b- amyloid protein, there is also intracellular aggregation of tau protein. Several lines of evidence indicate that aggregation of tau protein is central to neurodegeneration in AD. .Numerous laboratory studies show that MTC, when administered in various forms, is effective in disaggregating tau protein… Data from a large phase-2 clinical trial of MTC also provides some evidence of benefit in AD. Based on the Phase -2 experience TauRx elected to discontinue clinical studies with MTC and develop leuco-methylthioninium bis(hydromethanesulfonate) (LMTM)*" [d]. As a consequence of the success of these Phase 2 trials, a series of Phase 3 trials were organised which commenced in November 2012. These involve an international trial of 1,800 patients, with the data release scheduled for May 2015. In the opinion of a leading consultant from the trust, "*if LMTM is shown to have the expected efficacy in the Phase-3 AD and FTD studies then it has the potential to be a 'Game Changer' in terms of how we manage these conditions*" [d].

5. Sources to corroborate the impact

(a) President, Shasun Pharma Solutions Ltd – this source corroborates the commercial benefits of the research, to one of the drug manufacturers.

(b) Clinical Trial Services and Site Project Lead, Piramal Healthcare UK Ltd - this source corroborates the commercial benefits of the research, to one of the drug manufacturers.

(c) Managing Director, Roberts Chemicals Ltd - This contact corroborates the impact of TauRx in developing a novel API, which was industrialised and transferred to Shasun Pharma for large scale GMP synthesis. It also impacted positively on the Roberts business model.

(d) Consultant Psychiatrist, Birmingham and Solihull Mental Health NHS Foundation Trust - this source offers corroboration of the benefits of the resrearch findings from the perspective of a medical practitioner treating patients.

(e) Media reports:
Alzheimer's Association, *Four Alzheimer's clinical trials address a variety of treatment targets - amyloid, tau, synapse formation* 29/07/08
http://www.alz.org/national/documents/release_icad_072908_trials.pdf
http://www.express.co.uk/news/health/401853/New-wonder-pill-could-halt-dementia