Institution: Lancaster University

Unit of Assessment: 8 Chemistry

Title of case study: Uncovering how the drug galantamine works contributes to its availability on the NHS for use in early stage Alzheimer's disease

1. Summary of the impact

The drug galantamine (Reminyl) received approval for the treatment of early stages of Alzheimer's disease in 2001. However it was not made available on the NHS until March 2011, the effective onset date for the impact. The decision as to whether a treatment is available on the NHS is made by the National Institute of Health and Care Excellence (NICE), who sought additional clinical data and a rationale for the action of the drug. The mechanism of action was elucidated by Lancaster researchers that included chemists and biomedical scientists. These results were part of Alzheimer's Society's campaign to convince NICE to make the drug available on the NHS for early stage Alzheimer's. The resulting impact was direct, enhancing the quality of life for 100,000s of Alzheimer's patients (318,000 galantamine prescriptions were dispensed in the UK in 2012 [8]), with indirect impact on spouses, immediate family, and carers. The impact continues as new patients come into the pool.

2. Underpinning research

Alzheimer's disease (AD) is characterised by dementia involving loss of memory, mood changes, and problems with communication and reasoning. Pathological changes include a shortage of the transmitter substance acetylcholine and the deposition of protein plaques and neurofibrillary tangles in the brain, leading to the death of nerve cells and a reduction in brain function. The plaques contain a central deposit of the 39-43 amino acid peptide β-amyloid (or Aβ), which accumulates in the form of numerous 'amyloid' protein fibrils. This accumulation is widely thought to be an important step in the early stages of development of AD. Inhibiting aggregation of Aβ or blocking its neurotoxic effects are considered to be important approaches for developing treatment.

In 2004, chemists (Thomas Huckerby, Reader in Spectroscopy) and biomedical scientists (David Allsop, Chair in Neuroscience; Nigel Fullwood, Senior Lecturer; Frances Martin, Senior Lecturer) developed a collaborative research programme to investigate potential inhibitors for the aggregation of the amyloid peptide Aβ responsible for plaque formation in Alzheimer's disease. This built on Huckerby's long-standing research in nuclear magnetic resonance (NMR) spectroscopy with applications to biological systems, a notable sustained contribution being structural characterisation of polymeric chemical species present in connective tissue (see list of references cited in the major review by Huckerby [4]). This research continues to thrive [5]. Indeed, NMR spectroscopy is now a strategic research area for Lancaster involving significant investment with a view to developing an internationally-leading centre for solid state NMR. Investment includes two world-class Chair appointments, Mark Smith (materials science focus, see e.g. [6]) and David Middleton (biomolecular structure and interactions, see e.g. [7]), and University commitment to securing a 600 MHz solid-state NMR instrument through matched funding.

The research collaboration initially investigated members of the nicotine alkaloid family of chemicals. It was already known that L-(-)-nicotine itself was active – smokers are slightly less susceptible to developing Alzheimer's' – and in "Alzheimer's" mice, plaque densities were reduced by administration of L-(-)-nicotine. This prompted comparative solution NMR studies, combined with other tests which indicated, surprisingly, that the enantiomeric D-(+)- form (inactive at nicotinic receptors) showed identical binding to histidine residues in the amyloid peptide [1]. Both enantiomers inhibited aggregation and reduced the cell toxicity of Aβ. It appeared that this was thus due to weak, relatively non-specific binding, possibly involving the anti-oxidant and/or metal-chelating properties of the alkaloid rather than a chiral interaction. Inhibitor studies using NMR spectroscopy were then extended to other small molecule species including the known Alzheimer's drug, galantamine.

Galantamine appears to have multiple actions as a drug. It was known to have an inhibitory effect on the enzyme acetylcholine esterase (AChE), thereby increasing the level of the neurotransmitter acetylcholine in the diseased brain to improve memory and cognition. However, the effectiveness of galantamine treatment did not entirely correlate with its AChE activity, suggesting an additional unknown mechanism of action.

Lancaster chemistry research on galantamine showed clear concentration-dependent inhibition of

aggregation of Aβ by galantamine, *in vitro*. In complementary biological research, various cell toxicity assays showed that galantamine also reduced the cytotoxicity induced by Aβ. NMR spectroscopy involving a combination of 1D and 2D approaches was employed to identify the locations and 3D-shape of all 16 proton sites to reveal the galantamine conformation in solution. Following on, difference NMR spectroscopy was employed to ascertain whether galantamine interacted with Aβ in solution. The results (perturbations in the proton shifts) revealed a fast-exchange interaction of galantamine with Aβ involving histadine residues on Aβ, explaining the effects of the drug on Aβ aggregation and toxicity [2]. These results suggest that galantamine may not act purely as a symptomatic treatment for AD. The drug possibly had *disease-modifying* effects, due to the neuroprotection afforded against Aβ aggregation and toxicity. A significant inference arising from this research is that the drug should be prescribed as early as possible to check or even reverse the course of the disease.

Funding for the research included a Project Grant (£120k) [3] from the Alzheimer's Society on which Allsop was the Principal Investigator with Huckerby, Fullwood, and Martin as Co-Investigators. Huckerby was assisted in the study by a project student, Robert Millichamp. Other researchers at Lancaster University included Research Associates Susan Moore and Leanne Cooper, who provided electron microscopy expertise and capability.

Complementary research focussing on the effects of galantamine on apoptosis induced by Aβ in cell models was carried out by Brian Austen and his co-workers at St. George's Hospital Medical School, London. This contribution is part of the study reported by Matharu et al. 2009 [2].

3. References to the research

[1] Moore S. A., Huckerby T. N., Gibson G., Fullwood N. J., Turnbull S., Tabner B. J., El-Agnaf O. M. A., and Allsop D. (2004) *Both the D-(+) and L-(-) enantiomers of nicotine inhibit Aβ aggregation and cytotoxicity*. Biochemistry 43, 819-826. DOI: 10.1021/bi035728h.

[2] Matharu B., Gibson G., Parsons R., Huckerby T.N., Moore S. A., Cooper L. J., Millichamp R., Allsop D. and Austen B. (2009) *Galantamine inhibits β-amyloid aggregation and cytotoxicity*. J Neurol. Sci. 280, 49-58. DOI: 10.1016/j.jns.2009.01.024.

[3] Alzheimer's Society project grant "*Effects of galantamine (Reminyl) and other acetylcholinesterase inhibitors on β-amyloid aggregation and toxicity*", David Allsop (PI), with co-applicants Thomas Huckerby, Nigel Fullwood and Francis Martin, 2006-2009. £122,000. This grant was awarded by Alzheimer's Society in open competition, following scientific peer-review and a presentation by David Allsop and Thomas Huckerby to an interview panel of fellow scientists and lay members of the Society.

Development / background research prior to impact

[4] Huckerby T.N. (2002) *The keratan sulphates: structural investigations using NMR spectroscopy,* Progress in Nuclear Magnetic Resonance Spectroscopy 40, 35-110. DOI: 10.1016/S0079-6565(01)00040-1.

Current research in NMR spectroscopy

[5] Lauder R. M., Huckerby T., Nieduszynski I. and Sadler I. H. (2011) *Characterisation of oligosaccharides from the chondroitin/dermatan sulphates: 1H and 13C NMR studies of oligosaccharides generated by nitrous acid depolymerisation,* Carbohydrate Research 346, 2222. DOI: 10.1016/j.carres.2011.06.033.

[6] Bonhomme C., Gervais C., Folliet N., Pourpoint F., Diogo C. C., Lao J., Jallot E., Lacroix J., Nedelec J.-M., Iuga D., Hanna J. V., Smith M. E., Xiang Y., Du J. and Laurencin D. (2012) *Sr-87 solid-state NMR as a structurally sensitive tool for the investigation of materials: antiosteoporotic pharmaceuticals and bioactive glasses*, J. Am. Chem. Soc. 134, 12611. DOI: 10.1021/ja303505g.

[7] Middleton D. A., Madine J., Castelletto V. and Hamley I. W. (2013) *Insights into the molecular architecture of a peptide nanotube using FTIR and solid-state NMR spectroscopic measurements on an aligned sample*, Angewandte Chemie.52, 10537. DOI: 10.1002/anie.201301960

4. Details of the impact

Approximately 500,000 people are currently affected by Alzheimer's Disease in the UK. An

estimated 62,000 people develop the disease each year, of which the majority are in the early stages of the disease. Prior to the date of onset of the impact (March 2011), the three anti-cholinesterase drugs, Aricept (donepezil), Reminyl (galantamine) and Exelon (rivastigmine), although clinically approved much earlier, were not available on the NHS for early stage Alzheimer's. The decision as to whether any treatment is available on the NHS is made by the National Institute of Health and Care Excellence (NICE). NICE considered that the drugs offered insufficient patient benefit to justify their cost and sought additional longer-term clinical data and a rationale for their action [9].

The mechanism of action for the drug galantamine was elucidated by the research carried out at Lancaster. NICE eventually reversed their earlier decision in Mar 2011 [10] taking into account the additional clinical data, the mechanistic rationale for use of galantamine in early Alzheimer's (Lancaster research), and in response to pressure from various patient and carer groups, clinicians, and most notably from Alzheimer's Society [11-13]. There was an additional argument for the reversal of the initial decision, namely that the initial economic model used by NICE to calculate whether the drugs offered "value for money", did not accurately reflect the hidden economic costs of care outside of hospital. The Alzheimer's Society used Lancaster's research as a part of its campaign, generalising the findings to the entire class of anti-cholinesterase drugs (galantamine, donepezil, and rivastigmine). The clinical studies revealed that patients with "mild" i.e. early stage Alzheimer's did indeed benefit from these drugs. Lancaster's basic research (in which NMR spectroscopy played a crucial role) provided the mechanistic evidence for the disease-modifying effects of the drug galantamine, thus rationalising the clinical results.

The policy change by NICE has led to direct impact, enhancing the quality of life for 100,000s of Alzheimer's patients (over 300,000 galantamine prescriptions alone were dispensed in the UK in 2012 [8]). This in turn would have had a substantial, indirect impact on the lives of spouses, immediate family, and those involved in caring for the sufferers. The impact continues as new patients come into the pool.

The impact is certainly beyond the UK, though this cannot be corroborated. The UK medicines regulatory bodies, which include the Medicines and Healthcare Products Regulatory Agency (MHRA) and NICE, are seen as important standards across the world. The confidence expressed by NICE in the use of galantamine and related drugs in early stage Alzheimer's would have enhanced the use of these drugs in other parts of the world.

The interdisciplinary chemistry-biomedical Lancaster research into the disease-modifying effects of galantamine was directly funded by the Alzheimer's Society over the period 2006-2009. The Society promptly recognised the significance of the results that suggested that treatment should be initiated at the earliest stages of development of Alzheimer's disease. The research and its implications were widely publicised through their printed literature and their website [14-16].

The following quotation from Alzheimer's Society Newsletter 'The Journal of Quality Research in Dementia' [14] refers directly to the Lancaster research:

"*There is an exciting piece of research from David Allsop's group in Lancaster, looking at the potential therapeutic properties of existing acetylcholinesterase inhibitors. These drugs are used currently for treating symptoms of dementia, but there is lack of substantial evidence to show whether or not they may be of therapeutic value in treating disease progression. The results of this current study will highlight important evidence in putting forward an argument in using these drugs in a therapeutic context.*"

The impact case study is supported by a letter [17] from the former Director of Research (2003-2011) of Alzheimer's Society from which the following passage is reproduced:

"The Amyloid β aggregation starts in the brain many years before symptoms of dementia appear in Alzheimer's disease and the search is still on for drugs that can prevent the aggregation early. Prof Allsop's research demonstrating that Galantamine had an additional biochemical activity of inhibiting this aggregation was an important supporting argument at the time of the campaign. It seemed to promise that the drug would likely be efficacious in the early stages of disease. Although not evidenced at the time, this result made it more likely that some of the other cholinesterase inhibitors might also have biochemical effects in addition to the inhibition of

acetylcholine degradation….Together with the critical reviews of existing clinical research it helped win the case for people with dementia and their carers."

5. Sources to corroborate the impact

[8] (a) Prescription Cost Analysis England 2012 report, Health and Social Care Information Centre (www.hscic.gov.uk), published 4 April 2013, accessible at http://www.hscic.gov.uk/catalogue/PUB10610.
(b) Prescription Cost Analysis Scotland 2012, Information Services Division, NHS National Services Scotland, at http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Community-Dispensing/Prescription-Cost-Analysis/.
(c) Prescriptions Cost Analysis Wales 2011, Welsh Government, at http://new.wales.gov.uk/topics/statistics/headlines/health2012/1203281/?lang=en.
(d) Prescription Cost Analysis Northern Ireland 2012, Business Services Organisation, http://www.hscbusiness.hscni.net/services/2437.htm.

Documentation on the new NICE guidelines for AD (March 2011)

[9] NICE Final Appraisal Determination: Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease, 26 May 2006, accessible at http://www.nice.org.uk/nicemedia/live/11599/33725/33725.pdf

[10] http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13419

Alzheimer's Society challenges to NICE recommendations

[11] http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=461

[12] http://www.publications.parliament.uk/pa/cm200607/cmselect/cmhealth/503/503we05.htm

[13] http://www.alzheimers.org.uk/site/scripts/news_article.php?newsID=11

Documented references to Lancaster's research on galantamine by Alzheimer's Society

[14] Alzheimer's Society Quality Research in Dementia, Issue 4, September 2007

[15] Alzheimer's Society Quality Research in Dementia Annual Roundup, 2008-2009

[16] Alzheimer's Society Quality Research in Dementia, Issue 95, February 2010

Letter of support from Alzheimer's Society

[17] Letter of support from Former Director of Research, Alzheimer's Society