Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-14 Redirecting the global search for an Alzheimer's cure

1. Summary of the impact

Research by a team at Southampton into amyloid beta protein (Aβ) immunisation to treat Alzheimer's disease has been key to changing the way the global medical community understands and reacts to the disease. The first to observe that Aβ immunisation clears Aβ plaques, the team's studies were pivotal in initiating and informing the safe clinical trial development of 40 immunotherapy agents; investments of $3bn by the pharmaceutical industry; and 30 phase II and phase III studies. The research shaped US government policy on new safety measures for clinical trials and played a leading role in the doubling of UK funding to tackle Alzheimer's.

2. Underpinning research

Driving the global research effort into Alzheimer's over the last two decades was the *Amyloid Hypothesis*: the theory that the accumulation in the brain of amyloid beta protein (Aβ), associated with the subsequent accumulation of tau protein, plays a key role in the cause of the disease by disrupting normal cognitive function.

Animal studies led researchers to believe that peripheral immunisation (via the bloodstream) with Aβ protein may reduce the amount of Aβ in the brain and improve brain function. But until 2000, no one had looked at active Aβ immunisation in the *human* brain. That year the University of Southampton's Memory Assessment and Research Centre (MARC) carried out the first human clinical study of active Aβ immunisation. The team studied the ability of Aβ peptide to provoke an immune response and assessed the safety of the procedure.

In 2003, a Southampton team carried out a follow-up study focused on a single case from the 2000 study. The team comprised James Nicoll, Professor of Neuropathology (2001 to present) and Clive Holmes, Professor of Biological Psychiatry (1998 to present). Their neuropathological examination was the first to demonstrate that Aβ immunisation alters the pathology of Alzheimer's disease by removing Aβ plaques from the brain **[3.1]**. The paper, published in Nature Medicine, was recognised as one of the most notable advances in Alzheimer's disease (Nature Medicine 2006, 12, 612-769) and was quoted by the British Medical Journal as the most highly cited case report (>800 citations to August 2013).

Later that year, the team set up an independent, multi-site, follow-up study of the initial group of subjects. This was done in collaboration with Elan Pharmaceuticals who provided unpublished trial data. Dr Delphine Boche, Lecturer/Senior Lecturer in Clinical Neurosciences (2004 to present), joined the team to examine the clinico-neuropathological findings.

They confirmed that Aβ immunisation alters the pathology of Alzheimer's disease **[3.1, 3.2, 3.3]**. They identified two ways that plaque removal occurs: phagocytosis of Aβ by microglia and the break-up of the plaque build-up into soluble Aβ **[3.1, 3.2, 3.4]**.

The team showed that the effects of employing immunotherapy to attack Aβ plaques in the brain varies widely from one patient to another **[3.3]** and discovered that even complete Aβ plaque removal is not sufficient to halt cognitive decline **[3.3]**. That, in turn, suggested that removing plaques during later stages of the disease is unlikely to benefit the patient, and that early intervention is crucial.

The team demonstrated that immunotherapy reduces the accumulation of tau protein **[3.5]**. They also found evidence, for the first time, of serious side-effects associated with removing Aβ plaques from the brain including an increase in cortical microhaemorrhages (micro bleeds in the brain), an increase in levels of Aβ in the cerebral vasculature and an increase in the activity of microglia cells **[3.6]**. These insights into the pathophysiology occurring after Aβ immunisation have been highly

influential in the development and understanding of the side effects being encountered in current clinical trials **[3.4, 3.6]**.

3. References to the research

6 best papers (out of 17 on this topic)

3.1 Nicoll JA, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer's disease after immunisation with amyloid-β peptide: a case report. **Nature Medicine** 2003; 9 (4), 448-52. *[804 citations to August 2013]*

3.2 Nicoll JA, Barton E, Boche D, Neal JW, Ferrer I, Thompson P, Vlachouli C, Wilkinson D, Bayer A, Games D, Seubert P, Schenk D, Holmes C. Aβ Species removal after Aβ42 immunisation. **J Neuropathol Exp Neurol** 2006; 65 (11), 1040-1048. *[144 citations]*

3.3 Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA. Long term effects of Aβ42 immunisation in Alzheimer's disease: immune response, plaque removal and clinical function. **Lancet** 2008; 372, 216-23. *[546 citations]*

3.4 Boche D, Zotova E, Weller RO, Love S, Neal JW, Pickering RM, Wilkinson D, Holmes C, Nicoll JA. Consequence of Aβ immunisation on the vasculature of human Alzheimer's disease brain. **Brain** 2008; 131, 3299-310. *[108 citations]*

3.5 Boche D, Donald J, Love S, Harris S, Neal JW, Holmes C, Nicoll JA. Reduction of aggregated Tau in neuronal processes but not in the cell bodies after Aβ42 immunisation in Alzheimer's disease. **Acta Neuropathol** 2010; 120, 13-20.

3.6 Boche D, Denham N, Holmes C, Nicoll JA. Neuropathology after active Aβ42 immunotherapy: implications for Alzheimer's disease pathogenesis. **Acta Neuropathol** 2010; 120, 369-384.

Grant funding

£67,632 *Alzheimer's Research Trust* (2003-2006) The clinical and neuropathological examination of patients administered with AN1792 vaccine. Holmes C, Nicoll J, Wilkinson D, Jones R, Bullock R, Bayer A.

£236,396 *MRC New Investigator Award* (2006-2009). The mechanisms and consequences of plaque removal following Aβ immunotherapy in human Alzheimer's disease. Boche D (collaborators: Nicoll, Holmes).

£117,306 *Alzheimer's Research Trust* (2006 - 2011) ART/PG2006/4 and extension. Elan Pharmaceuticals Aβ immunotherapy trial: Clinical and neuropathological follow up study. Nicoll J, Boche D, Holmes C.

4. Details of the impact

Alzheimer's disease is a 'ticking time bomb', according to a 2012 report by the World Health Organisation. Globally, an estimated 36 million people have the disease, with associated costs thought to reach $600 billion a year. The number of people affected is expected to more than triple by 2050. There are currently no disease-modifying or preventative treatments for Alzheimer's disease, the most common cause of dementia that affects one fifth of all people over the age of 80. The University of Southampton's research into the disease has fundamentally changed the way the disease is perceived, the theories behind what causes it and, consequently, the development of new vaccination therapies by pharmaceutical companies.

The Southampton team's original finding, published in *Nature Medicine*, that it *is* possible to stimulate the immune system to 'attack', and clear, amyloid plaques encouraged several pharmaceutical companies to continue with the programmes they had been about to abandon. The

Nature Medicine paper was cited as evidence for proof of concept by Elan Pharmaceuticals that immunisation strategies are a valid treatment approach for Alzheimer's in their early US patents in 2004 and 2005. Ensuing financial investment in this treatment concept by the pharmaceutical industry was vast. In 2009, Johnson and Johnson acquired Elan Pharmaceuticals' amyloid immunisation programme for $885m and further financial investment by other pharmaceutical companies followed. The *Nature Medicine* paper and later research findings were cited in more than 40 successful US patent applications **[5.1]** by other pharmaceutical companies, the majority published after 2008. The estimated overall investment in these compounds is around $3bn **[5.2, 5.3]**.

But it was the academics' discovery that, contrary to popular theories of the time, even complete plaque removal did *not* stop, or even slow cognitive impairment associated with established Alzheimer's disease, that had the greatest impact on research into Alzheimer's **[5.4, 5.5, 5.6]**. As a result of these findings, pharmaceutical companies, including Roche and Eli Lilly, switched their focus from trying to find a treatment for the disease once it has taken hold, to finding a preventative treatment. A taskforce convened to advise the Federal Drug Administration on the design of early (pre-dementia) Alzheimer's disease studies, cites the Southampton research as evidence as to why it is necessary to start therapies before the onset of clinical dementia in order for it to have any positive effect **[5.7]**.

Of particular additional importance was Southampton's finding that triggering an immune response that causes the removal of amyloid protein plaques can, in some cases, result in micro bleeds in the brain. This has led directly to changes in ongoing immunotherapy trials to ensure such side effects are mitigated **[5.7]**. Building on these insights into the potential benefits, and risks, of amyloid-lowering therapies is now seen by stakeholders in the Alzheimer's drug development arena, including individuals and families affected by the disease, academic thought leaders, the pharmaceutical industry and the Alzheimer's Association, as amongst the most pressing questions in Alzheimer's research **[5.8]**. Members of the Southampton team have taken on advisory/consultancy roles for the Alzheimer immunisation programmes of the major pharmaceutical companies; Hoffmann-La Roche, Novartis, GlaxoSmithKline, Pfizer, Elan and Janssen. This has led to the inclusion by those companies of methods to monitor and interpret the side effects noted in the trials. This includes in vivo amyloid imaging (PET scans with amyloid ligands) and specific MRI sequences for micro haemorrhages and vasogenic oedema.

In addition, recommendations from the US Alzheimer's Association to the National Institutes of Health in 2011 cited eight of Southampton's publications on this topic **[5.9]**. This led directly to a policy change by the US Food and Drug Administration in 2012 to implement advisory measures for the safe monitoring of patients receiving immunotherapy treatments for Alzheimer's **[5.8]**. These recommendations include: reducing the dose of amyloid-modifying drugs in clinical participants who develop amyloid-related imaging abnormalities (ARIA); increasing the monitoring of study participants in Phase I and early Phase II studies to gain further knowledge about the mechanisms underlying micro haemorrhages; and updating reporting standards for MRIs used to evaluate and monitor for ARIA.

Southampton's research programme has contributed to increasing UK government awareness about the importance of funding further research into Alzheimer's. The Alzheimer's Research Trust organised for the Southampton team to present their findings in the House of Lords, and at a face-to-face meeting with the then Prime Minister Gordon Brown at 10 Downing Street in 2008. Both events were followed a year later by a ministerial summit on dementia on November 15, 2009 at which Prof Holmes chaired round table discussions **[5.10]**. This meeting led to the formation of the ministerial advisory group on dementia research. Subsequently, in March 2012, Prime Minister David Cameron announced a doubling of funding for Alzheimer's disease to £66 million by 2015 and early detection screening **[5.11]**.

5. Sources to corroborate the impact

5.1 USA and World registered patents. www.google.com/search?tbm=pts&tbo=1&hl=en&q=alzheimer+and+nicoll&btnG=

5.2 Menendez-Gonzalez M et al. Immunotherapy for Alzheimer's disease: rational basis in ongoing clinical trials. **Curr Pharm Des** 2011; 17(5) 508-20.

5.3 Sadeghi-Nejad N. The lessons of failure: what we can learn from Bapineuzumab's blow up. Forbes magazine 8/7/12.

5.4 Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical re-appraisal. **Journal of Neurochemistry** 2009; 110, 1129-34.

5.5 *"This award follows a series of papers from the Southampton group that have changed the way many of us think about Alzheimer's disease*" UCL Professor and leader of thought in the Alzheimer field, when presenting a prize to our PhD student (Zotova) at the Alzheimer Research UK annual conference, Leeds, 2011.

5.6 Small SA, Duff K. Linking Abeta and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. **Neuron** 2008; 60, 534-42.

5.7 Aisen PS et al. Report of the task force on designing clinical trials in early (predementia) AD. **Neurology** 2011; 76;280-86.

5.8 USA Alzheimer's Association. Key Alzheimer drug development stakeholders join forces to establish clinical trial safeguards and accelerate discovery. http://www.alz.org/documents_custom/final_aria_news_release_071211_alz-dem_jrnl.pdf. Jul 2011.

5.9 Sperling RA et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. **Alzheimer's and Dementia** 2011; 7:367-85.

5.10 Report of the UK ministerial summit on dementia research. http://www.ilcuk.org.uk/files/pdf_pdf_102.pdf. Nov 2009.

5.11 Prime Minister's challenge on dementia: https://www.gov.uk/government/publications/prime-ministers-challenge-on-dementia