Institution: Sheffield Hallam University

Unit of Assessment: 5 Biological Sciences

Title of case study: Public Understanding of Multiple Sclerosis Research

1. Summary of the impact

Research undertaken by Professor **Woodroofe** has impacted on a range of beneficiaries: people with multiple sclerosis (MS), their families and carers, and health professionals, including nurses, physiotherapists and doctors. This has been achieved through an array of innovative dissemination activities involving shared learning among researchers and beneficiaries. Through these activities beneficiaries gained a greater knowledge and deeper understanding of the disease process in MS, which they subsequently shared within their own networks. **Woodroofe's** research on MS has been published in leading international journals making an important contribution to the field and underpinning the impact achieved.

2. Underpinning research

Since her appointment as a senior lecturer at Sheffield Hallam University (SHU) in 1994, **Woodroofe's** research has focused on elucidating the mechanisms underpinning MS pathogenesis with 25 publications on MS and £1.2 million funding (grants 1-12) associated with her research undertaken at SHU from 01.09.1994 to 31.10.2013. Key features observed in the central nervous system (CNS) of people with MS are infiltration of immune cells from the bloodstream and subsequent activation of resident macrophages (microglia). This leads to loss of the axonal myelin sheath and the resultant clinical symptoms experienced by people with MS. **Woodroofe** was one of the first to report high levels of inflammatory chemokines, key mediators of cell migration, in the CNS of post-mortem MS cases (reference 1; grant 1) and identification of their receptors on infiltrating cells (references 2, 3; grant 3). *In vitro* work confirmed the functional importance of chemokines: they induced expression of matrix metalloproteinase 9, an enzyme linked to breakdown of the blood brain barrier (references 4, 5; grants 2, 4, 8).

In collaboration with Buttle (University of Sheffield) a related class of enzymes, ADAMTSs (**a** **d**isintegrin **a**nd **m**etalloproteinase with **t**hrombo**s**pondin motif), was investigated and their expression in the CNS of people with MS demonstrated. As these enzymes degrade the extracellular matrix in the brain, this expression would have a knock-on effect on chemokine binding and cell migration (grant 7). ADAM17, a related enzyme involved in protein shedding from the cell membrane, was investigated in post mortem MS brain, in endothelial cell cultures and in an animal model of MS (the latter in collaboration with Prof Azzouz, University of Sheffield and Dr Bolton, Bristol University) (Grants 5, 6, 9,11). Preliminary studies indicated that the enzyme was increased in inflammation in MS and a rodent model of MS. A potential treatment, siRNA knockdown designed to reduce the level of the enzyme, was assessed for therapeutic effects in the mouse model; this showed a small but significant delay in onset of clinical symptoms. The results were presented by **Woodroofe** at The European Glia meeting, Berlin, Germany (06/2013).

Research involving patients with MS, in collaboration with consultant neurologists at Sheffield Teaching Hospitals (STH), demonstrated the *in vivo* importance of chemokines in MS (reference 6, grant 10). Patients in clinical relapse had raised chemokine levels in their blood. One chemokine which was vital to monocyte recruitment into the brain (CCL2) was decreased in the cerebrospinal fluid in MS; it was suggested that this occurred because the chemokine was retained within inflammatory lesions in the brain, as reported in the post-mortem studies described above (references 1, 2, 3). In collaboration with NHS consultants in Sheffield, a study was undertaken of isolated white blood cells from MS patients who had received one of five prescribed treatments for relapses. The responses of these cells to chemokine-induced migration were assessed *in vitro* (grant 12) and a trend was seen for reduced migration in cells from patients treated with Natalizumab, an anti-adhesion molecule monoclonal antibody which has proven effective in reducing relapse rates *in vivo.*

Woodroofe was appointed at SHU in 1994 as a Senior Lecturer; promoted to Principal Lecturer in 2004 and awarded a personal chair, Professor of Neuroimmunology in 2001.

References to the research (Citations listed are from Scopus, updated 1/10/2013)

1. Simpson JE, Newcombe J, Cuzner ML, **Woodroofe MN**. (1998) Expression of monocyte chemoattractant protein-1 and other beta-chemokines by resident glia and inflammatory cells in multiple sclerosis lesions. Journal of Neuroimmunology, 84, 238-249. DOI: 10.1016/S0165-5728(97)00208-7 (**259 citations**).

2. Simpson J, Rezaie P, Newcombe J, Cuzner ML, Male D, **Woodroofe MN** (2000) Expression of the beta-chemokine receptors CCR2, CCR3 and CCR5 in multiple sclerosis central nervous system tissue. Journal of Neuroimmunology, 108, 192-200. DOI: 10.1016/S0165-5728(00)00274-5. (**136 citations**).

3. Simpson JE , Newcombe J, Cuzner ML, **Woodroofe MN** (2000) Expression of the interferon-gamma-inducible chemokines, IP-10 and Mig and their receptor, CXCR3, in multiple sclerosis lesions. Neuropathology and Applied Neurobiology, 26, 133-142. DOI: 10.1046/j.1365-2990.2000.026002133.x. (**138 citations**).

4. Cross AK, **Woodroofe MN** (1999) Chemokine modulation of matrix metalloproteinase and TIMP production in adult rat brain microglia and a human microglial cell line in vitro. GLIA, 28, 183-189. DOI: 10.1002/(SICI)1098-1136(199912)28:3<183 (**87 citations**).

5. Harkness KA, Adamson P, Sussman JD, **Woodroofe MN** (2000) Dexamethasone regulation of matrix metalloproteinase expression in CNS vascular endothelium. BRAIN, 123, 698-709. DOI: 10.1093/brain/123.4.698. (**114 citations**).

6. Mahad, DJ; Howell, SJL; **Woodroofe, MN** (2002) Expression of chemokines in the CSF and correlation with clinical disease activity in patients with multiple sclerosis. Journal of Neurology Neurosurgery and Psychiatry, 72, 498-502. DOI: 10.1136/jnnp.72.4.498 (**81 citations**).

Competitive grants awarded during the period 1994 -2013 (Woodroofe PI on all grants)

1. 1995-1997, The Wellcome Trust (£40,000). Detection of chemokines in MS brain.

2. 1996-1999 The MS Society (£60,000).Expression of chemokines by rat microglia in culture.

3. 1999-2002, The MS Society (£92,000) Expression of chemokine receptors in the CNS in MS.

4. 1999-2003, The MS Society (£99,000) Microglia and matrix metalloproteinases.

5. 2000-2001, Innovative award, The Multiple Sclerosis Society (£25,000). The role of ADAM 17 and urokinase in the pathogenesis of multiple sclerosis.

6. 2002-2005, The MS Society, (£107,000). The role of ADAM17 in the pathogenesis of MS.

7. 2002-2005, The Wellcome Trust, (£240,000). The role of ADAMTS 1, 4 and 5 in the pathogenesis of stroke and multiple sclerosis.

8. 2004-2007, The Multiple Sclerosis Society PhD studentship, (£75,000). Astrocyte expression of chemokines.

9. 2008-2010, Multiple Sclerosis Society, (£103,000). An investigation into the functional role of ADAM17 in MS pathogenesis using viral vector knockdown in vitro and in chronic relapsing Experimental autoimmune Encephalomyelitis (CREAE). 852/07

Funding from clinical consultants at Sheffield Teaching Hospitals Foundation Trust

10. 1999-2002The Royal Hallamshire Hospital, Neurology Department (£50,000). Chemokine expression profiles in patients with multiple sclerosis.

11. 2006-2009, Neurology Department, Sheffield Teaching Hospitals NHS Foundation Trust. (£70,000). An investigation of the functional role of ADAM17 in human astrocyte and endothelial cells.

12. 2007-2009, Sheffield Hospitals Charitable Trust. (£50,000). Effect of immunomodulatory treatment on migration of peripheral blood mononuclear cells from patients with MS to intact and truncated chemokines. (Awarded to Woodroofe and Sharrack at Sheffield Teaching Hospitals NHS Trust).

4. Details of the impact

Professor **Woodroofe** has contributed to impact activities targeted at two non-academic, MS-related audiences: (i) people with MS and their families and (ii) healthcare professionals working with people with MS. Harnessing **Woodroofe's** communication skills, academic expertise and knowledge, these activities enabled beneficiaries to gain a better understanding of the context in which biomedical MS research is undertaken. These activities have helped to shape science communication practice, particularly in relation to MS, informing and stimulating debate, increasing understanding and awareness within the MS patient community and healthcare professionals involved in their treatment.

(i) Public engagement activities:

MS Life is an annual event organised by the MS Society, with exhibitions and talks on MS-related topics, including research, held in Manchester (2008, 2009 and 2012) and in Gateshead (2010). **Woodroofe**, together with Professors Baker, QMC London and Amor, Free University, Amsterdam, developed a '**meet the scientist**' stand using their underpinning research in MS to engage the public in activities designed to promote understanding of the damaging processes occurring in the brain in MS patients and how current treatments act on these processes. The 'meet the scientist' stand was presented at all four MS Life events with over 3000 delegates over two days attending each event (source 1). A small field laboratory, including microscopes, brain tissue slides, and pipettes and reagents for cell culture, was installed to give 'hands on' experience of a research laboratory. Posters explaining aspects of MS and its treatments were on display and a brain model that could be disassembled and reassembled was used to aid learning. At a knitting event in 2012, participants produced woollen neurons and brain cells, which were incorporated into a large tapestry display, serving as a focal point this created an environment conducive to reciprocal learning (source 6).

The key to the success of these events was the sharing of information among scientists and participants, informing and stimulating discussions, and increasing understanding and awareness. In addition to participants benefiting from increased understanding of MS research, researchers also gained insights into participants' attitudes to, and experience and knowledge of, biomedical science. An on-line survey conducted by the MS Society in 2012 revealed that the 'meet the scientist' stand received the highest proportion of positive comments (29%) from the event, scoring the top-rating within the survey. The field laboratory activity was sponsored by the British Society for Immunology at Cheltenham Science Festival (06/2011). A spokesperson commented: '*Thank you very much for coming along to support MS: the big knit. It was brilliant to have you there to answer people's questions properly and to really explain and show them with the microscope what happens in MS*' (source 2).

Buddy/Partnership Scheme: Woodroofe's research group was one of the first to pilot the MS Society Buddy scheme, which provided an opportunity for people with MS to engage in the practice of science and to inform and shape future research questions. The scheme was rebranded as 'The

MS Society Research Partnership' and in 2008, three people with MS were partnered with the **Woodroofe** group (Grant 9). The MS partners commented that they welcomed gaining increased knowledge of MS; it was a two way communication, in that researchers also gained from learning about their clinical condition (source 3). These exchanges stimulated debate by raising understanding and awareness of research knowledge and insights into MS. This scheme was awarded the Association of Medical Research Charities award for best public involvement programme in 2009 (sources 7 and 8).

(ii) MS healthcare professionals in Sheffield region

In 1994, **Woodroofe** initiated collaborations with consultant neurologists specialising in MS. At this time there was limited MS research within Sheffield Teaching Hospitals, despite there being a large population of people with MS in the region (2,900 patients). Working with service providers, these collaborations encouraged the mutual sharing of expertise promoting further opportunities for researchers to engage with patients. Six MS-related papers have been published with **Woodroofe** as main author with clinicians as co-authors, evidence of the impact of the research on clinicians within Sheffield. An annual MS conference aimed at nurses, physiotherapists, GPs and neurology clinical trainees in Sheffield has been established by a consultant neurologist (source 4). In 2009, 2010 and 2011 **Woodroofe** and her research group were invited to present their research to around 100 delegates at each event. One delegate commented '*These presentations were a key part of all the meetings and contributed substantially to their success. In addition, Professor **Woodroofe** displayed an impressive enthusiasm to communicate her understanding of MS and her research results and its practical implications for people with MS'* (source 5).

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

1. National Programme Lead Physiotherapy, MS Society UK, London. (Comment on MS Life event).

2. Science Officer, British Society for Immunology, London. (Comment on Cheltenham Science Festival event).

3. MS Society Research Network member and previous 'buddy' with MS. (Comment on Woodroofe's contribution to the buddy scheme).

4. Consultant neurologist, Sheffield Teaching Hospitals NHS Foundation Trust and organiser of the annual MS Conference in Sheffield. (Comment on Woodroofe's contribution).

5. Delegate at annual MS Conference in Sheffield. (Comment on Woodroofe's contribution).

6. http://www.mssociety.org.uk/ms-resources/ms-life-2012
(Video showing delegates comments on the MS Life event).

7. http://www.acnr.co.uk/may_june_09/ACNRMJ09_awards.pdf (MS Society award).

8. http://www.twocanassociates.co.uk/routemap/monitoring-projects.php#casestudy1 (details of the buddy scheme).