Institution: University College London

Unit of Assessment: 5 - Biological Sciences

Title of case study: Sodium channels, pain and analgesia

1. Summary of the impact

More than three million people are in pain at any one time in the UK, with inadequate analgesic treatment because of side-effects or lack of drug efficacy. By identifying roles for the voltage-gated sodium channel subtypes Nav1.7 and Nav1.8 in peripheral pain, our research has had a significant impact on the **clinical understanding of human pain disorders** and on the **commercial development of selective analgesics** with fewer side-effects. We have developed and **disseminated several transgenic mouse lines** which are widely used by the pharmaceutical industry. Through media appearances, we have also increased **public awareness of the physiological basis of pain**.

2. Underpinning research

Starting with the hypothesis that genes which are selectively expressed in damage-sensing neurons (nociceptors) might play important roles in pain pathways, research by Professor John Wood's group at UCL (Department of Biology, then Wolfson Institute for Biomedical Research) has discovered and delineated the involvement of two voltage-gated sodium channel subtypes, Nav1.7 and Nav1.8, in peripheral pain.

In 1995, Armen Akopian, a Wellcome Trust-funded post-doctoral fellow in the lab, used a subtractive DNA hybridisation technique to find genes in rat dorsal root ganglia that were not expressed in heart, liver, cortex or cerebellum. In this way, we identified 46 mRNA transcripts that were expressed selectively in neonatal rat dorsal root ganglia (DRG) as judged by Northern blots and *in situ* hybridization **[1]**. Both known (e.g. peripherin, calcitonin gene-related peptide, myelin P0) and novel (e.g. C-protein-like, synuclein-like, villin-like) identifiable transcripts were present in the library. In terms of analgesia research, the voltage-gated sodium channel Nav1.8 (previously known as SNS) was an attractive new target. We then used knock-out mouse technology to show that this channel was important in pain pathways **[2,3]** and, perhaps more importantly, we used the promoter region of Nav1.8 to drive the expression of Cre recombinase to generate knock-out mice that lacked the expression of particular genes only in nociceptive neurons **[4]**. This enabled us to home in on a range of interesting and specific analgesic drug targets.

Using this approach in 2004, Mohammed Nassar, an MRC-funded post-doctoral fellow in the lab, was the first to show that Nav1.7 is a key molecule in peripheral pain pathways in mice **[4]**. We later showed that gain-of-function Nav1.7 mutant channels contribute to human pain **[5]**. Complementarily, in collaboration with Professor Geoff Woods at Cambridge University in 2006, we found that hereditary loss of Nav1.7 function (due to three distinct homozygous mutations in three different families) led to congenital loss of human pain **[6]**. Thus, increased Nav1.7 function leads to increased human pain, whereas loss of Nav1.7 function abolishes human pain.

These important observations focussed the attention of the pain pharmaceutical community on the Nav1.7 channel as a useful and specific analgesic drug target. We have now deleted Nav1.7 in all sensory neurons of mice, which recapitulated the pain-free phenotype of human Nav1.7 loss-of-function mutants, and identified chemical blockers that are potent analgesics in animal models **[7]**.

3. References to the research

[1] Akopian AN, Wood JN. Peripheral nervous system-specific genes identified by subtractive cDNA cloning. J Biol Chem. 1995 Sep 8;270(36):21264-70. http://doi.org/fjmkf8

[2] Akopian AN, Souslova V, England S, Okuse K, Ogata N, Ure J, Smith A, Kerr BJ, McMahon

SB, Boyce S, Hill R, Stanfa LC, Dickenson AH, Wood JN. The tetrodotoxin-resistant sodium channel SNS (Nav1.8) has a specialized function in pain pathways. Nat Neurosci. 1999 Jun;2(6):541-8. http://dx.doi.org/10.1038/9195

[3] Ekberg J, Jayamanne A, Vaughan CW, Aslan S, Thomas L, Mould J, Drinkwater R, Baker MD, Abrahamsen B, Wood JN, Adams DJ, Christie MJ, Lewis RJ. muO-conotoxin MrVIB selectively blocks Nav1.8 sensory neuron specific sodium channels and chronic pain behavior without motor deficits. Proc Natl Acad Sci USA. 2006 Nov 7;103(45):17030-5. http://doi.org/bhjt9v

[4] Nassar MA, Stirling LC, Forlani G, Baker MD, Matthews EA, Dickenson AH, Wood JN. Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. Proc Natl Acad Sci. 2004 Aug 24;101(34):12706-11. http://doi.org/cftnb5

[5] Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B, Ostman J, Klugbauer N, Wood JN, Gardiner RM, Rees M. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron. 2006 Dec 7;52(5):767-74. http://dx.doi.org/10.1016/j.neuron.2006.10.006

[6] Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, Karbani G, Jafri H, Mannan J, Raashid Y, Al-Gazali L, Hamamy H, Valente EM, Gorman S, Williams R, McHale DP, Wood JN, Gribble FM, Woods CG. An SCN9A channelopathy causes congenital inability to experience pain. Nature. 2006 Dec 14;444(7121):894-8. http://doi.org/d7psmm

[7] Minett MS, Nassar MA, Clark AK, Passmore G, Dickenson AH, Wang F, Malcangio M, Wood JN. Distinct Nav1.7-dependent pain sensations require different sets of sensory and sympathetic neurons. Nat Commun. 2012 Apr 24;3:791. http://dx.doi.org/10.1038/ncomms1795

Example major grant: MRC programme grant G9717869 Mechanisms of nociception 09/2004-04/2009 £1,340,503

4. Details of the impact

Clinical understanding and diagnosis of pain disorders.

Through our research, several human pain disorders have been linked to mutations in both Nav1.7 and Nav1.8, leading to an increase in the clinical understanding of these disorders and to their correct diagnosis. By identifying peripheral ion channel mutations linked to painful (and pain-free) conditions, we have increased the potential for better diagnosis in this patient population. The Department of Clinical Neurophysiology at the National Hospital for Neurology and Neurosurgery (NHNN) receives approximately 100 requests per year for the differential diagnostic assessment of small fibre neuropathies. This differential diagnostic approach increasingly uses sequencing for mutations in Nav1.7 and Nav1.8 in cases of idiopathic pain, thus starting a new line of diagnostic procedure which may help to define useful therapeutic approaches **[a]**.

Similar diagnostic work, using our findings, also takes place at other centres. For example, genetic testing in the Netherlands for mutations to Nav1.7 and Nav1.8 has revealed that, of patients with idiopathic painful neuropathy (which affects up to 5% of the general population), ~30% have a gain-of-function mutation in Nav1.7 **[b]** and ~10% have a gain-of-function mutation in Nav1.8 **[c]**. Researchers involved in this study, which built on the earlier UCL research, reported that: "*a lot of patients with small fiber neuropathy were sent to psychiatrists, or sent home, and told, 'You have pain, but we don't see anything, so there's nothing wrong with you... [The new findings offer] a recognition that they have a real disease, and that there is something causing the disease*" **[d]**.

This year, we showed that two patients with the more rare human pain disorder, primary erythromelalgia, also have gain-of-function variants of Nav1.7 **[e]**.

Impacts on the pharmaceutical industry

The neuropathic pain market is huge, with peak sales of prescribed drugs across the seven major markets expected to reach $4.1bn by 2019. The major challenge in the pain drug market is to reduce the side-effects associated with treatment, and our discovery of roles for Nav1.7 and Nav1.8 in peripheral pain has provided the pharmaceutical industry with ideal targets for the development of more specific analgesics **[f]**. Indeed, all major pharmaceutical companies now have programmes based on these targets, with Nav1.7 being the most appealing target because our research showed that its loss leads to a pain-free phenotype in man.

As a result of our work, more than 1,000 patents on new analgesic compounds targeting Nav1.7 and 1.8 are currently held by pharmaceutical companies (522 on Nav1.7 and 597 on Nav1.8 **[g]**), with many of these compounds now in clinical trials. For example, Convergence has developed a novel small molecule state-dependent Nav1.7 blocker, CNV1014802, which began Phase II trials for the treatment of trigeminal neuralgia in 2011 **[h]**. Similarly, Ralfinamide (Newron) and Eladur (Durect/King/Pfizer), both Nav1.7 blockers, are undergoing Phase II clinical trials for neuropathic lower back pain and post-herpetic neuralgia. Ralfinamide and Eladur are expected to go to market and reach peak year sales of $120m and $198m, respectively, by 2019 **[f – see table 47]**.

We have provided the pharmaceutical industry with the transgenic mouse lines developed in our lab, saving significant time and money in the industrial development of new analgesic compounds. Currently, six licences for our mice are held by pharmaceutical companies (including five of the major companies; names can be provided confidentially). These have a financial impact for UCL: with each mouse line worth £50,000, they bring in cumulative income in the six-figure range **[i]**.

Public engagement and media appearances

Our work on the genetic basis of pain has been featured on various TV programmes (e.g. The One Show, BBC, 2012; The Human Body, Discovery Channel, 2012) including most notably in BBC Horizon's *The Secret World of Pain*, 2011. This went out to an audience of 1.96m, and the Television and Radio Index for Learning and Teaching (TRILT) listed the documentary as number four in its weekly record of requested programmes **[j]**.

Increasing public awareness of the many possible physiological origins of pain is extremely important because patients with chronic pain are often faced with the additional trauma of their pain being dismissed as "psychological" (by friends and relatives if not doctors) when its physiological basis is unclear. The BBC internet forum Ouch! Disability Message Board also included contributions from people featured in the documentary, including Rebecca Key who explained that the documentary had sparked enough public interest for a seminar to be organised by the charity Neurosupport, held in Liverpool on 15 June 2011 **[k]**.

Similarly, it is an important revelation to many that pain is beneficial and to live without it can lead to serious physical injury. The documentary has had use in clinical practices at the Children's Hospital: Dr Konrad Jacobs, Psychologist on the Paediatric Rheumatology Team, Oxford University Hospitals, noted, "*There is a scene in it that I have started using clinically with children with chronic pain. In this scene (around 4:18) two children explain the consequences of not being able to feel any pain. This scene can be used to explain that pain can fulfil a useful function (but unfortunately not in their case)*" **[l]**.

Newspaper coverage also noted the impact of the documentary in changing the public's understanding of pain. The Metro newspaper noted, "*as ever, it's in the genes and there's one tricky customer that controls our experience of pain. Research into that is helping treatment of it and our understanding of how it works*." A review in the Daily Express highlighted, "*All this mind-body stuff is interesting but what makes it important and therefore good TV is the way scientists are turning it into useful treatments*" **[m]**.

5. Sources to corroborate the impact

[a] Impacts can be verified by Department of Clinical Neurophysiology, The National Hospital for Neurology and Neurosurgery Queen Square, London WC1N 3BG. Contact details provided.

[b] Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, Estacion M, Lauria G, Vanhoutte EK, Gerrits MM, Dib-Hajj S, Drenth JP, Waxman SG, Merkies IS. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol. 2012 Jan;71(1):26-39. http://dx.doi.org/10.1002/ana.22485

[c] Faber CG, Lauria G, Merkies IS, Cheng X, Han C, Ahn HS, Persson AK, Hoeijmakers JG, Gerrits MM, Pierro T, Lombardi R, Kapetis D, Dib-Hajj SD, Waxman SG. Gain-of-function Nav1.8 mutations in painful neuropathy. Proc Natl Acad Sci U S A. 2012 Nov 20;109(47):19444-9. http://dx.doi.org/10.1073/pnas.1216080109

[d] http://www.painresearchforum.org/news/7360-nav17-mutations-move-mainstream

[e] Cregg R, Laguda B, Werdehausen R, Cox JJ, Linley JE, Ramirez JD, Bodi I, Markiewicz M, Howell KJ, Chen YC, Agnew K, Houlden H, Lunn MP, Bennett DL, Wood JN, Kinali M. (2013) Novel mutations mapping to the fourth sodium channel domain of Nav1.7 result in variable clinical manifestations of primary erythromelalgia. Neuromolecular Med. 15(2):265-78. http://dx.doi.org/10.1007/s12017-012-8216-8

[f] Datamonitor report (2011): "Pipeline and Commercial Insight: Neuropathic Pain". p.150-1: "*While sodium channels have been targeted in the treatment of neuropathic pain for many years, treatments are not subtype-specific and are associated with serious side effects. As a result, a number of Big Pharma companies, including Pfizer and AstraZeneca, are actively researching the possibilities surrounding selective sodium channels for the development of novel pain therapies*."
Table 47, "*Key products in late-stage R&D pipeline for ion channel modulators, 2*010". Available on request.

[g] **Number of patents for compounds targeting sodium channels:** Wipo patent database searches in Any Field reveal 522 hits for "Nav1.7" and 597 hits for "Nav1.8".

[h] **Example of Nav1.7-targeted compound in clinical trials:** CNV1014802 at Convergence Pharmaceuticals http://www.convergencepharma.com/index.asp?page_id=14.
The website directly references our work in this area. Details available from Chief Scientific Officer at Convergence, Cambridge, CB22 3AT.

[i] **Supply of transgenic mice through UCL Business:** http://www.uclb.com/technology-finder/technology/voltage-gated-sodium-channel-knockout-mice-tools-for-developing-therapeutics-for-the-treatment-of-pain. Details available from UCLB. Letter to verify transgenic mouse licenses and MTAs available on request. Contact details provided.

[j] Viewing figures from www.barb.co.uk. Weekly Top 5 TV & Radio programme requests', British Universities Film & Video Council, 8 February 2011, http://bufvc.ac.uk/2011/02/08/weekly-top-5-tv-radio-programme-requests-10

[k] Ouch! Disability Message Board, 7 June 2011. http://www.bbc.co.uk/ouch/messageboards/NF2322273?thread=8035395&skip=50

[l] Konrad Jacobs, 'The secret world of pain', Paediatric Psychology Network, 2 February 2011, http://www.ppnuk.org/blog/ppn/the-secret-world-of-pain
http://www.noc.nhs.uk/oxparc/team/clinical-psychologist.aspx

[m] Matt Baylis, *Daily Express*, 1 February 2011, http://www.broadcastnow.co.uk/comment/critics/1-feb-11/5023071.article. 'Horizon: The Secret World Of Pain made you wince in wonder', *The Metro*, 31 January 2011. http://metro.co.uk/2011/01/31/horizon-the-secret-world-of-pain-tv-review-634862/