Institution: King's College London

Unit of Assessment: UoA5

Title of case study: Identification and validation of nerve growth factor as a peripheral pain mediator

1. Summary of the impact

There a great need to develop novel drugs to treat pain and in particular chronic pain. Scientists at King's College London (KCL) identified nerve growth factor (NGF) as an important mediator of persistent pain and validated it as a therapeutic target by demonstrating the beneficial effects of neutralising its activity using biological reagents in a number of animal models. The KCL team collaborated closely with the scientists at Genentech who went on to develop a neutralising antibody to NGF for the treatment of pain. This drug has been found to exhibit unprecedented efficacy in phase III trials in man and is currently being considered for registration. Their discovery has also led to several other major pharmaceutical companies initiating drug discovery programs in this area and has contributed to the subject area of pain management.

2. Underpinning research

Chronic pain remains a major unmet medical need affecting around 20% of Europeans with a considerable socio-economic burden due to both cost of therapy and loss of working hours. Pharmacological treatment of chronic pain is focussed around two major classes of drug – opiates and non-steroid anti-inflammatory agents – both of which have significant side effects and limited long-term efficacy. Research into new pain-relieving compounds has been led at King's College London (KCL) by Prof Steve McMahon (1984-present, Sherrington Professor of Physiology) supported by several colleagues including Dr Dave Bennett (2006-12, Wellcome Trust Fellow) and Dr John Priestley (at KCL until 1999).

Following early work on the influences of peripheral tissues on the properties of their sensory innervation, KCL scientists hypothesised that nerve growth factor (NGF), which at this point was largely viewed as a molecule with only beneficial properties, acted as a peripheral pain mediator in a number of chronic pain states. This ground-breaking hypothesis was rigorously tested by the KCL team with the key results published in a number of high impact papers.

Following development by the biotechnology company Genentech in 1994 of a NGF knockout mouse, KCL scientists demonstrated that these animals failed to respond to noxious mechanical stimuli. This provided the first clue that NGF might be a pain mediator (Crowley C, et al. Cell. 1994). This could have been interpreted as reflecting a role for NGF solely in the development of pain sensing neurons, especially as *in-utero* up to 80% of dorsal root ganglion (DRG) cells are dependent on NGF for their survival. However, a number of breakthrough studies by KCL showed that the high-affinity NGF receptor TrkA was expressed on pain sensing neurons in adult animals. For instance, in the rat, TrkA was found to be expressed by a very high percentage of visceral afferents of DRG neurons (McMahon S, et al. Neuron, 1994; Bennett, DL et al. Eur J Neurosci, 1996) and in cells in the dorsal horn of the spinal cord (Averil S, et al. Eur J Neurosci, 1995). This indicated an ongoing function for NGF as opposed to a role restricted to development.

The next major breakthrough came when KCL scientists showed that administration of NGF can induce pain. Studies with adult rats found that single intradermal injections of doses over 250 ng of human recombinant NGF into the hindpaw led to a prolonged thermal hyperalgesia to radiant heat, suggesting activation and sensitization of cutaneous nociceptors (Andreev N, et al. Eur J Neurosci, 1995). Together with collaborators at Genentech these observations led to seminal studies demonstrating that endogenous NGF could be neutralised by administration of a TrkA-IgG fusion molecule (a biological molecule that directly binds NGF and prevents its action). They also found that neutralisation of endogenous NGF reduced abnormal pain sensitivity in a variety of models of pain, particularly those associated with peripheral inflammation. For instance, in one study, administration of TrkA-IgG to cultured sensory neurons produced a sustained thermal and chemical hypoalgesia and led to a downregulation of the sensory neuropeptide calcitonin gene-related peptide. Acute administration of TrkA-IgG also blocked the hyperalgesia that normally develops with carrageenan-induced inflammation (McMahon S, et al. Nature Med, 1995). Another

study used an *in vitro* rat skin nerve preparation in which carrageenan administration produced a marked increase in the proportion of nociceptors displaying ongoing activity and spontaneously active fibres were sensitized to heat. Here, when TrkA-IgG was coadministered with carrageenan at the onset of inflammation, primary afferent nociceptors did not sensitize and displayed essentially normal response properties (Koltzenburg M, et al. Eur J Neurosci, 1999).

3. References to the research

- Andreev N, Dimitrieva N, Koltzenburg M, McMahon SB. Peripheral administration of nerve growth factor in the adult rat produces a thermal hyperalgesia that requires the presence of sympathetic post-ganglionic neurones. Pain 1995;63:109-15. http://dx.doi.org/10.1016/0304-3959(95)00024-M (137 Scopus citations)
- Averill S, McMahon SB, Clary DO, Reichardt LF, Priestley JV. Immunocytochemical localization of trkA receptors in chemically identified subgroups of adult rat sensory neurons. Eur J Neurosci 1995;7:1484-94. Doi: 10.1111/j.1460-9568.1995.tb01143.x (422 Scopus citations)
- Bennett DL, Averill S, Clary DO, Priestley JV, McMahon SB. Postnatal changes in the expression of the trkA high-affinity NGF receptor in primary sensory neurons. Eur J Neurosci 1996;8:2204-8. Doi: 10.1111/j.1460-9568.1996.tb00742.x (106 Scopus citations)
- Crowley C, Spencer SD, Nishimura MC, Chen KS, Pitts-Meek S, Armanini MP, Ling LH, McMahon SB, Shelton DL, Levinson AD, et al. Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. Cell 1994; 76:1001-11. Doi: 10.1016/0092-8674(94)90378-6 (Scopus citations 614)
- Koltzenburg M, Bennett DL, Shelton DL, McMahon SB. Neutralization of endogenous NGF prevents the sensitization of nociceptors supplying inflamed skin. Eur J Neurosci 1999;11:1698-704. Doi: 10.1046/j.1460-9568.1999.00590.x (122 Scopus citations)
- McMahon SB, Armanini MP, Ling LH, Phillips HS. Expression and co-expression of Trk receptors in subpopulations of adult primary sensory neurons projecting to identified peripheral targets. Neuron 1994;12:1161-71. Doi: 10.1016/0896-6273(94)90323-9 (385 Scopus citations)
- McMahon SB, Bennett DL, Priestley JV, Shelton DL. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-IgG fusion molecule. Nature Med 1995;1:774-80. Doi: doi:10.1038/nm0895-774 (Scopus citations 285)

Grants supporting this work

- 1993-1998. PIs: SB McMahon, J Priestley, M Rattray. Neurotrophins and the maintenance and repair of sensory neurones: normal role and therapeutic implications. Medical Research Council, £728,500.
- 1999-2003. PIs: SB McMahon, M Malcangio. Trophic factor regulation of synaptic efficacy of primary sensory neurons' Wellcome Trust, £381,900
- 1999-2004. PIs: SB McMahon, J Priestley. Trophic regulation of pain signalling systems in the adult. Wellcome Trust Ref, £794,900
- 2001-2004. PI: SB McMahon. Mechanisms of neuropathic sensory disorders and their regulation by neurotrophic factors. Wellcome Trust, £79,300

4. Details of the impact (indicative maximum 750 words)

KCL research leads to the development of tanezumab

King's College London (KCL) scientists contributed to the identification and validation of nerve growth factor (NGF) as a peripheral pain mediator. Collaborative work with Genentech led to this San Francisco-based biotechnology company developing a neutralising antibody to NGF for the treatment of pain: tanezumab (RN-624). Genentech established as spinout company – Rinat – to take tanezumab forward and in 2006 the drug was acquired by the pharmaceutical company Pfizer. Pfizer have invested heavily in tanezumab and sponsored a large number of Phase II and III clinical trials involving over 10,000 patients for a variety of conditions including osteoarthritis (OA) pain, low back pain and visceral pain. The successful results of these trials have been published in a number of peer-reviewed journals. For example, Phase II and III trials using tanezumab to reduce joint pain and improve function in people with OA of the knee, involving 450 and 690 people respectively, have shown superior analgesic efficacy of tanezumab compared to a placebo. These studies also showed that tanezumab was well tolerated, something essential in pain management

therapy as current treatment options can be limited by their adverse event profiles (1a,b). Both of these papers draw on KCL research when discussing the background to the discovery of the role of NGF in causing or augmenting pain, including McMahon 1995 and a 1996 review of NGF by McMahon that includes the early studies detailed above (1c).

More recently tanezumab has been shown to be an effective treatment for OA hip pain in a trial involving over 600 patients that used McMahon's 2006 review to paint the background of tanezumab's development (1d). Other studies, involving over 1500 patients in total and citing Andreev 1995 when discussing how NGF administration results in hyperalgesia, have shown tanezumab to be safe and efficacious in the treatment of chronic low back pain (1e,f). The contribution of KCL work to the development of tanezumab is also reflected in the inclusion of this research in a number of patents. For instance, Crowley 1994 is one of the first references cited in two of Pfizer's patents for anti-NGF antibodies, published in 2009 (1g) and 2010 (1h). The second of these also cites Andreev 1995, McMahon 1995 and McMahon's 1996 review.

KCL research spurs development of other NGF-blocking compounds

Since the trials of tanezumab established the translatability of the preclinical work pioneered at KCL several other companies have invested heavily in clinical trials for compounds blocking NGF's actions. For instance, PG110 (ABT-110) a humanized mAb developed by the company PanGenetics, was acquired in 2009 by Abbott Labs for $190 million (2a). The patent for this product cites the majority of the above-discussed KCL studies as well as McMahon's 1996 review (2b). Other NGF products in development include fulranumab, a fully human mAb by Amgen for OA pain (2c); fasinumab, a fully human mAb by Regeneron/Sanofi-Aventis (2d) and MEDI-578, a monoclonal single chain variable fragment for OA of the knee by Medimmune/AstraZenica (2e). This reflects considerable investment by each company in the first important new class of drugs for general pain for around 100 years.

Following reports that a small number of OA patients in these trials needed early joint replacement, the FDA recently halted all trials of NGF blockers and reviewed the data to assess potential side effects of the treatments. Subsequently their Arthritis Drugs Advisory Committee voted 21-0 that anti-NGF agents should continue to be developed to treat OA pain. The panel also voted 20-1 that anti-NGFs should be studied in indications for which there are no products with demonstrated analgesic efficacy, such as interstitial cystitis or chronic pancreatitis. The green light was given based on the fact that this is an entirely new and very effective treatment for pain and many studies have resumed (2f).

KCL studies impact knowledge of pain therapy

NGF blocking agents have been heralded as the 'next big thing' in pain management in several recent reviews that cite KCL research when discussing the background to their development (e.g. 3a,b). Research from KCL is also highly cited in the book 'The Senses: A Comprehensive Reference' in chapters about 'Pharmacological Modulation of Pain' (citing Andreev 1995) and 'Neurotrophins and Pain' (citing the majority of studies discussed above), among others (3c) and in 'The Human Nervous System,' the standard reference book for the anatomy of the central and peripheral nervous system, in the chapter on 'Pain Systems' (citing Averill 1995, Bennett 1996, McMahon 1994) (3d).

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

1. **KCL research leads to the development of tanezumab**
   a. Lane NE, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med 2010:363:1521-531. Doi: 10.1056/NEJMoa0901510
   b. Brown MT, et al. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. J Pain 2012;13(8):790-98. Doi: 10.1016/j.jpain.2012.05.006
   c. McMahon SB. NGF as a mediator of inflammatory pain. Philos Trans R Soc Lond B Biol Sci 1996;351:431-40: http://rstb.royalsocietypublishing.org/content/351/1338/431.long
   d. Brown MT, et al. Tanezumab reduces osteoarthritic hip pain: results of a randomized, double-blind, placebo-controlled phase III trial. Arthritis Rheum 2013; 7:1795-1803. Doi:

10.1002/art.37950
e. Kivitz AJ, et al. Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain. Pain 2013;154:1009-21. Doi. 10.1016/j.pain.2013.03.006
f. Katz N, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. Pain 2011; 152:2248-2258. Doi. 10.1016/j.pain.2011.05.003
g. Patent: Anti-NGF antibodies and methods using same. US 7569364 B2. Original Assignee: Pfizer Inc. Publication date: 4.8.2009: http://www.google.com/patents/US7569364
h. Patent: Anti-NGF antibodies and methods using same US 7655232 B2. Original Assignee: Pfizer Inc. Publication date: 2.2.2010: https://www.google.com/patents/US7655232

2. KCL research spurs development of other NGF-blocking compounds

a. ABT-110: http://www.streetinsider.com/Corporate+News/Abbott+Labs+(ABT)+PanGenetics+BVs+PG110+Fully+Humanized+Antibody+for+$170M+Plus+Milestones/5100451.html
b. Patent. Method for the treatment of pain with humanized anti-nerve growth factor antibodies. US 8257710 B2. Original Assignee: Abbot Research B.B. Publication date: 4.9.2012: https://www.google.com/patents/US8257710?dq=US08257710&hl=en&sa=X&ei=MJdzUpqTBtGqhQfnzoHYBQ&ved=0CDkQ6AEwAA
c. Fulranumab: Sanga P, et al. Efficacy, safety, and tolerability of fulranumab, an anti-nerve growth factor antibody, in the treatment of patients with moderate to severe osteoarthritis pain. Pain 2013;154(10):1910-9. Epub 2013 Jun 5. Doi: 10.1016/j.pain.2013.05.051.
d. Fasinumab: http://www.regeneron.com/regn475
e. MEDI-578: http://www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/D2460C00001_C
f. FDA decision: http://www.painresearchforum.org/news/14439-fda-gives-green-light-restart-ngf-antibody-trials

3. **KCL studies impact knowledge of pain therapy**

a. Kumar V, Mahal BA. NGF - the TrkA to successful pain treatment. J Pain Res 2012;5:279-87. Doi: 10.2147/JPR.S33408.
b. Chessell IP, et al. Biologics: the next generation of analgesic drugs? Drug Discov Today 2012;17(15-16):875-9. Doi: 10.1016/j.drudis.2012.03.005
c. The Senses: A Comprehensive Reference, Six-Volume Set. Bushnell CM, et al (Eds).
   - Dray A. Pharmacological Modulation of Pain. Volume 5;2010;795-819. Doi: 10.1016/B978-012370880-9.00196-1
   - Mendell LM. Neurotrophins and Pain. Volume 5;2010;259-278. 10.1016/B978-012370880-9.00161-4
d. The Human Nervous System. Third edition. Mai JK, Paxinos G (Eds). Chpt 32. Westlund KN, Willis WD. Pain System. Academic Press. (November 28, 2011) ISBN-10: 0123742366