Institution: University of Warwick

Unit of Assessment: A1 – Clinical Medicine

Title of case study: Neurosolutions: a commercial partnership between academia and industry to develop novel drugs for neurological disorders

1. Summary of the impact

Based on electrophysiological research conducted at the University of Warwick from 2000, Neurosolutions was founded as a spin-out company in 2001. As well as developing its own novel compounds, Neurosolutions provides specialised translational biomedical research services to the biotechnology and pharmaceutical industries to facilitate preclinical drug development of novel strategies to treat neurological disorders. In 2005, Neurosolutions floated on the Australian Stock Exchange (ASX) as Neurodiscovery to support the clinical development in-house of two compounds (both are patent-protected): NSL-043 for neuropathic pain (which completed 2 phase I studies in 2008-2009) and NSL-101 for dental pain (which completed phase II trials in 2009-2010). In 2010, Neurosolutions expanded its operations to Montreal, Canada. Neurosolutions is a profit-making contract research organisation with 15 full-time staff based in the UK and in Montreal, has annual revenues averaging £1.4M per annum and has earned around £7.5M in contracts from the biotechnology and pharmaceutical industries since its launch.

2. Underpinning research

The science underpinning Neurosolutions was based on four key areas of research conducted at Warwick from 2000 to the present day by: Professor David Spanswick (Professor of Molecular Neurosciences, Warwick Medical School; 2000–present) and Professor Kevin Lee (Senior Lecturer, Department of Biological Sciences, University of Warwick 2001–2004; Honorary Professor Warwick Medical School; 2005-present; Currently CSO Rare disease research at Pfizer; 2010-present); Dr Fei-Yue Zhao, visiting academic, University of Warwick 2001-present); Dr Ross Jeggo (Senior Research Fellow, Warwick Medical School; 2007–2008, and a visiting academic, School of Life Sciences; 2003–present); Dr Tony Rush (Senior Research Fellow, Warwick Medical School; 2007–2008) and visiting academic, School of Life Sciences (2006-2009). This research is centred upon the following key areas:

1. Central neural control of bodyweight and obesity. Research on central control of energy balance at Warwick revealed hypothalamic orexigenic NPY/AgRP neurones to be a key site of action of these hormones[1, E, H] and described a broad role for ATP-sensitive potassium channels in energy-sensing neurones in the arcuate nucleus, including NPY/AgRP and anorexigenic POMC/CART neurones.[2] This work extended previous research conducted in Aberdeen showing leptin inhibits hypothalamic neurones by activation of ATP-sensitive potassium channels (*Nature* 1997; 390 (6659): 521-525 (587 citations)) and that insulin has a similar action via a phosphoinositide 3-kinase (PI3-kinase)-dependent mechanism (*Nature Neurosci*. 2000; 3(8): 757-758 (459 citations).
2. Our expertise in spinal cord slice electrophysiology and ability to probe the functional operation of neural circuits in normal and diseased states. Our group is one of few in the world to use dual whole-cell patch clamp recording techniques in isolated mammalian brain and spinal slice preparations to record electrical activity transmitted directly between coupled nerve cells.[3, A, B, F, G] It was this relatively rare technology and the ability to record from spinal cord tissue in vitro using dual recording techniques that led to academic collaborations with GlaxoSmithKline (GSK; see B), to identify the mechanism of action of a family of novel anticonvulsants with utility for pain, and Pfizer on novel targets for treating neuropathic pain. [B, C] Lee was a pioneer in the use of electrophysiological recording techniques combined with single-cell molecular biology techniques to identify gene expression profiles in single identified neurones in normal and diseased states. This technology is exploited in all aspects of the research at UoW. [1, 2, 3; D-H] Rush's research also focussed on electrophysiological recording techniques to probe properties of ion channels at the single-cell level. This improved understanding of the action of novel agents targeting ion channels, in particular those channels involved in transmitting pain signals in peripheral nerves.[4]
3. Zhao's research focussed on pain, in particular novel peripheral and spinal targets for treating pain. Electrophysiological recording and behavioural research techniques were used to explore mechanisms underlying pain and the site, mode and mechanism of action

and therapeutic potential of novel analgesics.[5] Similar research techniques were employed by Jeggo focussed on Alzheimer's Disease and neurodegeneration.[6]

This multidisciplinary academic expertise spanning the single-cell, molecular and genetic (Lee, Rush), spinal cord and brain signalling in neural circuits in isolated slice preparations (Spanswick, Lee) and whole animal electrophysiology and behaviour (Zhao, Jeggo), provided a suite of preclinical platform technologies designed to accelerate and facilitate translation of basic neuroscience to clinical trials. To interface and promote interaction with the pharmaceutical industry and provide the vehicle to commercialise our research, we founded the Warwick spin-out, Neurosolutions. We focused initially on pain and obesity and subsequently through Knowledge Transfer partnerships (DTC, TSB and BBSRC-supported; [I, J]) we expanded into other neurological indications including Alzheimer's disease and psychiatric disorders.

3. References to the research

1. van den Top, M. *et al*. Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. *Nature Neurosci*. 2004; 7(5): 493-494. **doi:10.1038/nn1226**

2. van den Top, M. *et al*. Pharmacological and molecular characterization of ATP-sensitive K^+ conductances in CART and NPY/AgRP expressing neurons of the hypothalamic arcuate nucleus. *Neuroscience* 2007; 144 (3): 815-824. **doi:10.1016/j.neuroscience.2006.09.0.**

3. van den Top, M. *et al*. Orexins induce increased excitability and synchronisation of rat sympathetic preganglionic neurones. *J. Physiol*. 2003; 549: 809-821. **doi:10.1113/jphysiol.2002.033290.**

4. Hudmon A, Choi JS, Tyrrell L, Black JA, Rush AM, Waxman SG, Dib-Hajj SD. Phosphorylation of sodium channel Na(v)1.8 by p38 mitogen-activated protein kinase increases current density in dorsal root ganglion neurons. J Neurosci. 2008; 28(12): 3190-201. doi: 10.1523/JNEUROSCI.4403-07.2008.

5. Zhao, F. Y. *et al*. GW406381, a novel COX-2 inhibitor, attenuates spontaneous ectopic discharge in sural nerves of rats following chronic constriction injury. *Pain* 2007; 128(1-2): 78-87. **doi:10.1016/j.pain.2006.08.032**

6. Scopes, D. I. *et al*. Aβ oligomer toxicity inhibitor protects memory in models of synaptic toxicity. *Br. J. Pharmacol*. 2012; 167(2): 383-392. **doi:10.1111/j.1476-5381.2012.01973.x**

Peer-reviewed and industrial grants

A. Epilepsy Research Foundation. Modulation of gap-junction function in *in vitro* models of epilepsy. £99,810. Oct 1998-Sep 2002. **PIs: D. Spanswick & S. Davies**.
B. GlaxoSmithKline. Modulation of electrical synapses by novel anticonvulsants. £50,000. Sep 2001-Aug 2002. **PI: D. Spanswick**.
C. Pfizer. Electrophysiological and pharmacological characterisation of spinal dorsal horn neurones. £81,000. Mar 2001-Sep 2003. **PI: D. Spanswick**.
D. Biotechnology & Biological Sciences Research Council (BBSRC). Characterization of lamina I neurons in the adult spinal cord in vitro, £179,867 (2001-2004). **PI: K. Lee**.
E. BBSRC. Integration of neurohormonal signalling mechanisms regulating energy balance in the arcuate nucleus *in vitro*. £258,124. Apr 2002-Mar 2005. **PI: D.Spanswick**.
F. BBSRC. Molecular and physiological properties of electrical synapses in mammalian central neurones. £217,256. Oct 2002-Sept 2005. **Applicants: K. Lee & D. Spanswick**.
G. The Wellcome Trust (073934/Z/03/Z): Modulation of neuronal activity patterning by electrotonic coupling in the amygdala. £172,256. Mar 2004-Feb 2007. **PI: D. Collins**.
H. BBSRC (BB/C001125/1). Integration of signalling mechanisms in neuropeptide Y/Agouti related protein (NPY/AgRP) pacemaker neurones in the arcuate nucleus of the hypothalamus. £310,996. **PI: D. Spanswick**.
I. BBSRC/Department of Trade Industry (DTI)-supported Knowledge Transfer Partnership (KTP). Design, development and implementation of isolated tissue and behavioural models of learning/memory disorders. Awarded in 2008 for 2.5 years. £156,523. Applicants: D. Spanswick, E. O'Hare (Queens University Belfast, N. Ireland) & Neurosolutions. **PI: D Spanswick**.
J. Technology Strategy Board (TSB)/Neurosolutions-sponsored Knowledge Transfer Partnership. The development, validation and commercialisation of a new package of models to investigate stress/anxiety and depressive behaviours. Awarded in 2012 for 2

years. £128K. **Applicants: D. Spanswick, Dawn Collins (UoW) & Neurosolutions**.

Patents:

- NZ564170, Thiazolopyrimidines for Use in Therapy (2005).
- WO2010010394, Local Pharmaceutical Compositions (2008).

4. Details of the impact

The impact from research conducted at the UoW and Neurosolutions can be classified as:

1. Patents, intellectual property (IP) and research publications by Neurosolutions staff with academic and industrial partners, which have ultimately led to Neurosolutions generating annual revenues averaging £1.4M per annum.
2. Development of two novel compounds for treating pain. The first compound NSL-043 for treating neuropathic pain was developed in partnership with Sosei (Japan). The second, NSL-101 for treating dental pain, was developed in partnership with Ampika (Cambridge).
3. The creation of new biotechnology companies by providing "proof-of-concept" data to support financing/fund-raising of these new companies (e.g. Cambridge Biotechnology, Numedicus, Cerebrasol).
4. Facilitation of novel strategies and therapies for neurological disorders through research contracts with industrial clients, earning around £7.5M in revenue from the biotechnology and pharmaceutical industry since 2001.

In addition, D. Spanswick was nominated by industry for the BBSRC Entrepreneur of the Year Award in 2011. Further details of each impact are provided below.

By combining the biomedical research skills of Spanswick (neural networks in isolated mammalian central neural preparations), Lee and Rush (single-cell, molecular biology and electrophysiology) and Zhao and Jeggo (*in vivo* electrophysiology in whole organisms and behaviour) to address the site, mode and mechanism of action of novel compounds, Neurosolutions was founded as a commercial enterprise at the interface between academia and industry. Its aim was to provide services to the pharmaceutical and biotechnology industries, to facilitate the development of novel drugs for neurological disorders; and to commercialise academic research.

Intellectual Property: Research conducted at Neurosolutions led to the creation of intellectual property and two patents were granted (see Section 3). Neurosolutions undertook all preclinical development of compounds before taking public investment from Australia (£1.5M approx) and floating on the ASX in 2005 to support clinical development of NSL-043 for neuropathic pain (successfully completed 2 Phase I studies in 2008-2009 and may possibly enter Phase II trials with a local partner in China) and NSL-101 (which completed Phase II trials in 2009-2010 and is currently under formulation as a topical cream treatment).

Contract Research: Neurosolutions is a profit-making contract research organisation (a). With a growing reputation and increased demand for services from North America (see below for details), Neurosolutions expanded its operations with the creation of Cerebrasol (in Montreal) as a sister company in 2010 (b, c). Fifteen full-time staff are currently based in the UK and Montreal. Neurosolutions has provided expert translational neuroscience services to over 100 industrial clients worldwide since its foundation. Clients include major pharmaceutical companies - Merck (US), Eli-Lilly (US and UK); GSK, Pfizer, Organon, Schering-Plough (both now Merck); Johnson & Johnson; Astra Zeneca (Canada and Sweden); Merz, Evotech (Germany); Bial (Portugal); Sepracor and Sunovion (US); Lundbeck (Sweden); Upsher-Smith (US); Takeda (UK, US, Japan); UCB - and small to medium-sized companies - Neurotherapeutics, Envoy Therapeutics, Elan (US), Senexis, Xention, (UK); Pangenetics (Netherlands), Syngene (Australia). Owing to the confidential nature of much of the work undertaken with these companies we are unable to outline all aspects of the research in which Neurosolutions has added value/impact to companies. However, some examples are given below.

Commercial Impact: Promoting Development of new Biotechnology Companies: Neurosolutions has supported the development of 5 new biotechnology companies. For example, proof-of-concept studies on leptin mimetics for obesity and compounds for pain were undertaken for Cambridge Biotechnology, which was founded in 2001. Cambridge Biotechnology subsequently raised £10M from venture capitalists (Merlin Biosciences) and was subsequently acquired by

Boivitrum (2005), Proximagen (2009) and Upsher-Smith in 2012 for £356.8M (d). Similarly, Neurosolutions provided proof-of-concept data enabling the development of Numedicus. Neurosolutions undertook extensive preclinical proof-of-concept data on anti-Nerve Growth Factor antibodies and their utility for pain for the Dutch/UK company Pangenetics, which was subsequently acquired by Abbott for US$170M in November 2009 (e).

Scientific impact: design of novel strategies and identification of targets and mechanisms of action for therapeutic interventions. Neurosolutions has provided consultancy and research services to Neurotherapeutics (NTP; US), facilitating development of a research plan to identify the mechanism of action of a novel NTP compound and providing a preclinical data pack to support clinical development (f). A novel mechanism of action of a series of GSK anticonvulsant compounds (Carabersat, Tonabersat) was identified by Spanswick, initially academically and subsequently by Neurosolutions. One of these compounds (Tonabersat) was acquired by Proximagen with Upsher-Smith (US), and is undergoing further mechanism of action work with Neurosolutions (2012-2013). Tonabersat has already been subject to clinical trials for migraine and is currently being re-profiled for epilepsy (g). Such has been the success of the translational neuroscience research approach adopted by us that Neurosolutions has extended the research capability to psychiatry and neurodegeneration with a focus on cognitive deficits in Parkinson's disease. In-house technologies have already been used successfully to support development of novel compounds/treatment strategies for Alzheimer's disease with models of memory loss (Senexis, Merz, Elan), with one of the Senexis compounds recently (2012) acquired by BTG for clinical development (h).

Future Impact: Neurosolutions and Cerebrasol in partnership with TransPharmation and Monash University are extending operations into Australia (2013). This major collaborative project will form a new Australian company (Pacific Discovery Services) as part of a consortium focused on translational research and development of novel strategies and treatments for neurological disorders. The initial focus is pain and obesity, but will expand into other conditions as the company evolves.

5. Sources to corroborate the impact

a. See http://www.neurodiscoveryltd.com/default.htm
b. See http://www.cerebrasol.com/contact.html
c. Supporting statement from CEO, Neurosolutions Ltd. and Cerebrasol. (Identifier 1)
d. Supporting statement from Former Founder, MD and Chief Scientific Officer, Cambridge Biotechnology (former Head of Discovery at Biovitrium AB and Consultant to Proximagen): Provides a summary of the contributions of Neurosolutions to Cambridge Biotechnology Ltd, Biovitrium AB, Proximagen Group and Upsher Smith Laboratories. (Identifier 2).
e. See http://www.news-medical.net/news/20091113/Abbott-to-acquire-the-global-rights-to-PanGenetics-new-therapeutic-for-treatment-of-chronic-pain.aspx; Neurosolutions reports NSLR-103 and NSLR-110 illustrating some of the work done, and supporting statement from former Vice President Preclinical Development, Pangenetics (currently Chief Scientific Officer of SweetSpot Therapeutics Ltd.): Confirms the value of the work undertaken by Neurosolutions to Pangenetics. (Identifier 3).
f. See Neurosolutions reports NSLR-190, NSLR-199, NSLR-200, NSLR-201, NSLR-203, NSLR-206, NSLR-207, NSLR-208a, NSLR-208b, NSLR-209 (Restricted access – available on request only), highlighting the mechanism of action and preclinical proof-of-concept data delivered for NTP and research strategy developed for this client.
g. Supporting statement from Head of Discovery, Proximagen (Upsher Smith Laboratories): Provides a summary of contributions of Neurosolutions to the development of Tonabersat and Carabersat by Proximagen and Upsher Smith Laboratories. (Identifier 4).
h. Supporting statement from Director and Former CEO, Senexis Limited: Confirms Senexis has benefitted considerably from Neurosolutions research and that Neurosolutions' biomedical research has added value to Senexis' drug discovery programmes. (Identifier 5).