Institution: University of Warwick

Unit of Assessment: A1 Clinical Medicine

Title of case study: Academia-Industry interfaces for the development of new therapeutic strategies for neurological disorders

Period when the underpinning research was undertaken: 2001 – 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
David Spanswick	Professor of Molecular Neurosciences	2000 - present

Period when the claimed impact occurred: 1 August 2013 – 1 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Abnormal electrical activity within the nervous system is the common feature of all neurological disorders. By developing technologies and models to monitor and manipulate such activity and through discoveries of mechanisms contributing to abnormal neural function, Warwick research has enabled new therapeutic approaches to treat disorders of the nervous system. Through the Warwick spin-out Neurosolutions, and its sister companies in North America and Australia, and their engagement with industry, fundamental research has driven the creation and development of biotechnology companies and new therapeutic strategies. Impacts include a new treatment for epilepsy generating health benefits for patients and revenue of more than GBP600,000,000.

2. Underpinning research (indicative maximum 500 words)

The research group is led by David Spanswick, Professor of Molecular Neuroscience, Warwick Medical School (WMS) 2000-present, and specializes in in vitro Central Nervous System single-cell molecular and electrophysiological approaches to understanding neural circuit function in health and disease. The group's common goal is the translation of fundamental research, skills and "know-how" into health and socio-economic impact.

By combining a unique suite of skills in electrophysiology with models of disease and behaviour, the researchers have addressed fundamental mechanisms contributing to neurological disorders. The group initially focussed on epilepsy, obesity and pain [3.1, 3.2, 3.3] with expertise in this area underpinning the Warwick spin-out Neurosolutions in 2001, a company designed to interface between academia and industry to facilitate new therapeutic approaches to treat these conditions. Through internal training programs and academic collaborations, the group expanded its capabilities to develop models of Alzheimer's disease and psychiatric conditions including anxiety, depression and schizophrenia [3.4] with Dawn Collins (WMS 2002-Present). Through international academic collaboration, the group introduced viral delivery-based optogenetic and chemogenetic technologies as new routes to target neurological disease [3.5].

The science underpinning the concept of the group is based on the fundamental notion that all neurological conditions have one common feature: nerve cells and their associated neural circuits are characterised by abnormal electrical activity and any treatment must correct this activity to yield positive outcomes and behaviour. To achieve this, the researchers employed electrophysiological approaches at the heart of all programs, being able to monitor electrical activity in vivo and in vitro with a resolution ranging from ion channel activity, through single cells to neural circuits in vitro, whole body animal studies in vivo and behaviour. This

multidisciplinary platform enables the researchers to address mechanisms underpinning abnormal electrical activity in preclinical models - to identify novel approaches, targets and mechanisms of action of therapeutic strategies; to re-profile existing therapeutics for new indications; and to facilitate and accelerate the development of new therapeutic strategies targeting neurological disorders.

To maximise the potential of the research via interaction with the biotechnology and biopharmaceutical industry and as a vehicle to commercialise research, Professor Spanswick founded the spin-out Neurosolutions in 2001, based at the University of Warwick. The development of the Neurosolutions portfolio into neurological indications beyond pain was supported by knowledge transfer partnerships (DTC, TSB and BBSRC-supported). Training and development of skilled staff has been driven through PhD programmes funded by Neurosolutions itself and MRC-DTI (MRC-industry-funded) funded PhD programs with Neurosolutions as the industry partner. In 2010, the group expanded its operations to North America, creating Cerebrasol as a partner to Neurosolutions. In 2013, Professor Spanswick recapitulated the Neurosolutions model at Monash University (Australia) creating PacificDiscoveryServices (PDS).

Key people: Fei-Yue Zhao (Visiting research Fellow, University of Warwick 2001-present; Andrew Whyment (Post-Doctoral Research Fellow, University of Warwick 2004-2005, Honorary Research Fellow, WMS 2005-2020); Haifeng Wei (Associate Fellow, WMS 2008-present); Ross Jeggo (visiting academic and honorary research Fellow, WMS, 2003-2015 and currently Head of Neuroscience Research, Directeur de Recherche Neuropsychiatrie at Servier).

3. References to the research (indicative maximum of six references)

[3.1] Hopkins SC, **Zhao FY**, Bowen CA, Fang X, **Wei H**, Heffernan ML, Spear KL, **Spanswick D**, Varney MA, Large TH. (2013) Pharmacodynamic effects of a D-amino acid oxidase inhibitor indicate a spinal site of action in rat models of neuropathic pain. *J Pharmacol Exp Ther*, 345(3), 502-511. doi: 10.1124/jpet.113.204016. PubMed PMID: 23520265.

[3.2] Simonds SE, **Pryor JT**, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG Jr, Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, **Spanswick D**, Farooqi IS, Cowley MA. (2014) Leptin mediates the increase in blood pressure associated with obesity. *Cell*, 159(6), 1404-1416. doi: 10.1016/j.cell.2014.10.058. PubMed PMID: 25480301; PubMed Central PMCID: PMC4259491.

[3.3] Dodd GT, Michael NJ, Lee-Young RS, Mangiafico SP, **Pryor JT**, Munder AC, Simonds SE, Brüning JC, Zhang ZY, Cowley MA, Andrikopoulos S, Horvath TL, **Spanswick D**, Tiganis T. (2018) Insulin regulates POMC neuronal plasticity to control glucose metabolism. *Elife*, 7, e38704. doi: 10.7554/eLife.38704. PubMed PMID: 30230471; PubMed Central PMCID: PMC6170188.

[3.4] Rammes G, Gravius A, Ruitenberg M, Wegener N, Chambon C, Sroka-Saidi K, **Jeggo R**, Staniaszek L, **Spanswick D**, O'Hare E, Palmer P, Kim E-M; Bywalez W, Egger V, Parsons CG. (2015) MRZ-99030 – A novel modulator of Aβ aggregation: II – Reversal of Aβ oligomer-induced deficits in long-term potentiation (LTP) and cognitive performance in rats and mice. *Neuropharmacology*, 92, 170–182. doi: 10.1016/j.neuropharm.2014.12.037. PubMed PMID: 25637092.

[3.5] Milton LK, Mirabella PN, Greaves E, **Spanswick D** et al. (2020) Suppression of Corticostriatal Circuit Activity Improves Cognitive Flexibility and Prevents Body Weight Loss in Activity-Based Anorexia in Rats. *Biol Psychiatry*, S0006-3223(20), 31711-X. doi:10.1016/j.biopsych.2020.06.022. PubMed PMID: 32892984.

Patents

1. Patent Title: Thiazolopyrimidines for Use in Therapy. 2006
   Inventors: **Zhao**, **Fei-Yeu; Dixon, Alistair Kerr**; **Treherne**, **Jonathan Mark**; Koseki, **Chizuko**; **Lee**, **Kevin**; **Spanswick, David**.
   Patent number: US 20100216819.
   https://patentscope.wipo.int/search/en/detail.jsf?docId=US43341728&_cid=P20-KMG7U1-84548-1
2. Patent Title: Thiazolopyrimidines for use in treating pain. 2007
   Inventors: Lee, Kevin; Spanswick, David; Zhao, Fei-Yue; Treherne, Jonathan Mark; Dixon, Alistair Kerr; Koseki, Chizuko.
   Patent number: NZ 564170
   https://patentscope.wipo.int/search/en/detail.jsf?docId=NZ179081826&_cid=P20-KMG7UN-84736-1
3. Patent Title: Thiazolopyrimidines for Use in Therapy. 2006
   Inventors: **Lee, Kevin**; **Spanswick, David**; **Dixon, Alistair Kerr**; **Koseki, Chizuko**; **Zhao, Fei-Yue**; **Treherne, Jonathan Mark.**
   Patent number: ZA 200711062
   https://patents.google.com/patent/DE602006004735D1
4. Patent Title: Local Pharmaceutical compositions comprising an extract of spilanthes. 2009
   Inventors: Freedman, Francoise Barbira; **Lee, Kevin; Spanswick, David; Treherne, Jonathan Mark; Zhao, Fei-Yue;** Chessell, I.
   Patent number: WO 2010010394.
   https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2010010394&_cid=P20-KMG7YA-86184-1

The work has been funded via Knowledge Transfer Partnerships and studentships, for example: TSB/Neurosolutions sponsored KTP: The development, validation and commercialisation of a new package of models to investigate stress/anxiety and depressive behaviours, 2012 (2 years). D.R. Collins & D. Spanswick. **GBP128,000**.

In addition, fundamental science underpinning the development of the Australian arm of the company (PacificDiscoveryServices) and expansion of Neurosolutions was extensively funded by peer-reviewed Australia National Health & Medical Research Council Grants, 2012 – 2021 totalling **AUD5,398,598** and Australian Research Council grants, 2012 – 2018 totalling **AUD1,062,450**. [5.1]

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

After the success of Neurosolutions, the Warwick spin-out founded in 2001, the research group expanded operations to North America (Cerebrasol; 2010), to meet increasing demand for services from US-based pharmaceutical/biotechnology companies, and Australia (PacificDiscoveryServices; PDS) in 2013, after Spanswick's joint appointment at Monash. Over the REF assessment period, the group of companies has employed 21 full-time staff based on three sites globally, and 5 PhD students wholly or partly funded by Neurosolutions.

Revenue from contracts in the period 2014 to 2020 exceeded £7M (GBP7,000,000) with a global clientele spanning small academic groups and start-ups through to small-medium enterprise biotechs and major pharmaceutical companies. The group has engaged over 65 companies globally between 2014 to present [5.1]. The research has delivered economic impact through the development of intellectual property and creation of new companies, benefited existing companies by driving or supporting their drug and technology development programmes and enabling the development of new therapeutics. Some indicative examples include:

Development of Eslicarbazepine as a treatment for epilepsy
In 2007 to 2008, Neurosolutions and Cerebrasol conducted preclinical studies of Eslicarbazepine (BIA-2-093) with Portuguese pharmaceutical company Bial, identifying its mechanism of action, utility as an anticonvulsant and its suitability for the treatment of neuropathic pain when compared to the established therapeutics carbamazepine, and oxcarbazepine [5.2]. Multiple phase I, II and III clinical trials were subsequently undertaken with Eslicarbazepine, with the drug completing trials successfully. In early 2009, Bial sold the rights in Europe to the Japanese company Eisai, marketed under the tradename Zebinix. In the US, it is marketed by Sunovion under the tradename Aptiom, receiving approval from the FDA in November 2013 for adults and in 2017 for children. [5.3] In the US, the total revenue generated by sales of Aptiom across the period April 30 2014 to June 30 2020 was 81.3 billion yen equivalent to approximately GBP600,000,000. [5.4] Revenue figures for sales of Zebinix in Europe are not publicly available but are generally estimated to be a multi-million pound sum.

Epilepsy is the fourth most common neurological condition and manifests as unprovoked seizures, which are caused by abnormal firing of impulses from nerve cells in the brain. Partial-onset seizures, one type of seizure and the most common, are characterized by bursts of electrical activity that are initially focused in specific areas of the brain and may become more widespread, with symptoms varying according to the affected areas. The unpredictable nature of seizures can have a significant impact on those with epilepsy. Reducing the frequency of seizures can greatly lessen the burden of the condition. A recent clinical trial - an open-label extension study conducted in adults completing a phase 3, randomized, double-blind, non-inferiority trial - found that more than 80% of patients using Eslicarbazepine as a monotherapy remained seizure-free throughout the 2-year study period. [5.5]. The consultancy work conducted by Cerebrasol with BIAL – Portela & Ca S. A. at Warwick Medical School during the period 2007-2008, played a critical role in the clinical development of Eslicarbazepine Acetate, its subsequent approval by regulatory authorities from 2011 onwards (EMA, FDA, SwissMedic) and the availability for adult and pediatric patients afflicted with epilepsy under the trade names of Zebinix and Aptiom. See statement by Bial board member. [5.6].

Novel targets, therapeutics, strategies and technologies for chronic pain.
Extensive research undertaken by Neurosolutions and Cerebrasol in collaboration with Wex Pharmaceuticals has focussed on the use of Halneuron® (TTX) for **chemotherapy-induced neuropathic pain.** Collaborating together since 2011, Neurosolutions/Cerebrasol were involved in the design and delivery of proof-of-concept studies for a chronic dosing regimen to treat persistent pain and inform phase II and III clinical trials – and Phase II trials for chemotherapy induced neuropathic pain (TTX-CINP-201) have been undertaken in the assessment period. This was a randomized, double-blind, placebo controlled, Phase II multicenter study of Tetrodotoxin in the treatment of chemotherapy induced neuropathic pain. The study determined that TTX is well tolerated, with promising efficacy. An unforeseen benefit for patients was prolonged pain relief and alleviation of spasticity associated with chemotherapy-induced neuropathy. Neurosolutions/Cerebrasol are currently engaged in identifying the mechanism of action underlying clinical benefits of this treatment, and Phase III trials have commenced. Wex Chief Operating Officer writes: “Cerebrasol has played an important role in helping Wex Pharmaceuticals advance the underlying science with Halneuron® and the support necessary to help advance our clinical programs.’’ [5.7]

Chemogenetic approaches for trigeminal neuralgia has been a focus of research and development undertaken since 2018 with Redpin Therapeutics, a venture capital-backed, preclinical-stage gene therapy company. Chemogenetics is a ground-breaking approach to selectively control cell function, including abnormal electrical activity in nerves, by using viruses to install engineered receptors sensitive to a chemical designed to target the receptor. By combining Neurosolutions technologies with Redpin’s ion channel based chemogenetic platform of designer targeted cell therapies, extensive pre-clinical proof-of-concept data for an FDA pre-submission supporting utility of this new technology for

trigeminal neuralgia has been submitted. Initial studies are focused on trigeminal neuralgia but feasibility studies on epilepsy and Parkinson's are advancing. Redpin Chief Scientific Officer writes: “As a result of our collaboration we have been able to attract additional Series A investments and our positive interactions with regulatory bodies have been greatly facilitated by the contributions of NeuroSolutions to our research and development programs.’’ [5.8]

New therapeutics and novel molecular targets for neuropathic pain. Neurosolutions with PacificDiscoveryServices re-profiled a compound, originally indicated for obesity. Using the platform technologies, researchers identified a novel mechanism of action and proof-of-concept for a potential treatment specifically for **neuropathic pain,** currently in Phase II clinical trials. This work underpinned the development of a new privately-owned Australian biotech, Lateral Pharma, in 2015. In collaboration with Evotec, a global drug discovery and development company, the researchers identified a **novel molecular target** of this compound, lacking the side-effects seen with other pain killers and opioids. Based on the signal transduction pathway identified, the compound is now being assessed for anti-viral properties and a potential treatment for COVID 19 [5.9]

New treatments for schizophrenia
The researchers have been engaged in identifying the mechanism of action of SEP363856 with Sunovion pharmaceuticals. SEP363856 has a unique mechanism of action compared to current antipsychotic medications and was successful in Phase II. The U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation (BTD) for SEP-363856 in May 2019 and the DIAMOND (Developing Innovative Approaches for Mental Disorders) Phase 3 trials for SEP-363856, a novel agent for the treatment of adults and adolescents with schizophrenia in September 2019. Executive Director of Translational Medicine at Sunovion writes: “This important collaboration enabled us to further delineate the mechanism of action that may underlie the pharmacological activities of novel compounds within Sunovion's drug discovery portfolio. The studies performed by Neurosolutions were instrumental in demonstrating that SEP-363856 inhibits dorsal raphe nucleus and ventral tegmental area neuronal firing via 5-HTlA and TAARl receptors. This was an extremely valuable contribution considering that SEP-363856 may represent a new class of psychotropic agent with a non-D2-receptor-binding mechanism of action for the treatment of psychosis in schizophrenia.’’ [5.10]

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

[5.1] Statement by Chief Operating Officer for the Neurosolutions/Cerbrasol/PDS) Group for the period 2014-2020. List of peer reviewed grants and publications from Australia underpinning the creation of PDS.
[5.2] Neurosolutions confidential reports 70 and 77.
[5.3] Press articles on sale of licence to Eisai**,** FDA approval for Aptiom for adults (2013) & children (2017)
[5.4] Financial reports for Sumitomo Dainippon Pharma Co., Ltd 2014-2020 demonstrating revenue for Aptiom
[5.5] Long-term efficacy and safety of eslicarbazepine acetate (ESL) monotherapy: results from BIA-2093-311/EXT study –the 2-year open-label extension of the ESL study (BIA-2093-311) (4165) https://n.neurology.org/content/94/15_Supplement/4165#%20
[5.6] Statement by Bial board member
[5.7] Statement by Chief Operating Officer Wex Pharmaceuticals.
[5.8] Statement by CSO Redpin Therapeutics.
[5.9] Statement by CEO Lateral Pharma.
[5.10] Statement by Executive Director Translational Medicine Sunovion Pharmaceutical Inc.