Institution: University of Bristol

Unit of Assessment: 4 – Psychology, Psychiatry and Neuroscience

Title of case study: Development of chemical probes leads to economic benefits for biochemical suppliers and industry investment in drug development

1. Summary of the impact

Research conducted at the University of Bristol since the late 1990s has pioneered the development of over 60 chemical probes that are selective for individual ionotropic and metabotropic glutamate receptors. The development of these probes has led to numerous commercial impacts, including: the establishment of two companies, which both sold during the assessment period for a combined value of £85 million, and sales revenue for global providers of biochemicals. This research has also stimulated considerable industry investment in drug development.

2. Underpinning research

Glutamate receptors play an important role in the central nervous system (CNS) and have been implicated in a wide range of neurological disorders. The University of Bristol has an international reputation in glutamate receptor research, underpinned by the work of Jeffrey Watkins, Professor of Pharmacology (1973-1999 (Emeritus)) and David Jane, Professor in Chemical Pharmacology (Lecturer 1999-2008; Professor 2008-current), who have developed chemical probes, which are used by the worldwide neuroscience community to understand the function of these receptors in health and disease.

Background

N-Methyl-D-aspartic acid (NMDA) receptors are a family of glutamate-gated ion channel receptors that play an important role in synaptic neurotransmission and controlling neuronal plasticity. Hypo- or hyperactivation of the NMDA receptors (NMDAR) is critically involved in conditions such as epilepsy, schizophrenia, pain, depression and neuronal loss following stroke. The receptors are composed of two subunits, GluN1 and GluN2, and it is the GluN2 subunit that contains the glutamate binding site and therefore the target of therapeutic applications. It is known that variation in the GluN2 subunits underlie differences in the physiological properties of NMDAR complexes. However, examination of these subunits has been hindered by the absence of highly selective antagonists – chemicals that bind to the receptor and block or inhibit its function – that can be used to help understand the respective roles of these subunits in brain function. Ultimately, such selective antagonists would also have advantages over previous generations of non-selective antagonists as they would target only the subunit subtype involved in the disorder being treated, leading to an improved side effect profile.

Development of NMDA receptor antagonists In the late 1990s Watkins and Jane started to develop leads for NMDAR antagonists that showed a preference for individual NMDAR subunits. From 2001 to 2005, with funding from the National Institutes of Health (NIH), Jane worked with Dr. Dan Monaghan (University of Nebraska) on a new class of NMDAR antagonist that showed a preference for GluN2C and GluN2D subunits versus GluN2A and GluN2B subunits; at the time, only NR2B-selective antagonists had been described. In 2008 this research was funded for a further four years by the NIH, which led to the synthesis of a series of selective GluN2C/GluN2D antagonists (e.g. UBP141, UBP145) [1]. In 2010, Jane and Monaghan identified a new class of pharmacological agents that indirectly modulate NMDARs (e.g. UBP608, UBP714 and UBP710), some of which displayed GluN2 subunit selectivity [2]. These allosteric modulators are thought to have relevance to the treatment of Alzheimer's disease and other neurodegenerative disorders as well as enhancement of cognitive function, schizophrenia, epilepsy and neuropathic pain. This work has recently been funded for a further five years by the NIH.

Development of metabotropic glutamate receptor ligands

Jane and Watkins were the first to develop and use selective antagonists for metabotropic glutamate receptors - a type of membrane receptor that acts through a secondary messenger - including the compound MCPG [3]. These antagonists were the subject of three patents filed between 1993 and 1995, and licensed to Eli Lilly, a global pharmaceutical company based in the US, in 1997. The license agreement was worth £100,000 and included sponsorship of 3 PhD students (Conway, Kennedy and Miller) as part of a four year collaboration. During this collaboration, Eli Lilly has evaluated around 70 Bristol compounds for activity at eight metabotropic glutamate receptor subtypes (mGlu1-8). One of these compounds, DCPG, was shown to be a mGlu8 selective agonist [4]. DCPG has recently been shown to potentially inhibit anxiety, which has established the principle that mGlu8 agonists/positive allosteric modulators may have clinical utility in the treatment of anxiety. In 2010, Eli Lilly funded an additional PhD project, supervised by Professor David Lodge, Visiting Fellow at Bristol, which used an mGlu8 antagonist developed by Jane to show that higher concentrations of DCPG may additionally activate mGlu2 receptors [5].

Development of AMPA/kainate receptor agonist and antagonists

Selective agonists and antagonists for AMPA and kainate receptors (AMPARs and KARs) – both ionotropic receptors that respond to glutamate - have been synthesised by Jane's group. These include antagonists that are selective for subtypes of KARs, such as UBP302, UBP304, UBP310 and ACET (reviewed in [6]). Some of these compounds have been shown to be antagonists of both GluK1 and GluK3 subunits [7]. Given that KAR antagonists may have therapeutic utility in a range of CNS disorders [6], scientists at Eli Lilly have collaborated with Jane to assist in the pharmacological characterisation of compounds synthesised at Bristol. To date ~50 Bristol compounds have been sent to Lilly for testing on cloned AMPA and kainate receptor subtypes. This collaboration has resulted in the publication of 6 papers with co-authors from Eli Lilly.

3. References to the research

[1] Costa, B.M., Feng, B., Tsintsadze, T.S., Morley, R.M., Irvine, M.W., Tsintsadze, V.P., Lozovaya, N.A., Jane, D.E. &Monaghan, D.T. (2009) 'NMDA receptor NR2 subunit selectivity of a series of novel piperazine-2,3-dicarboxylate derivatives; preferential blockade of extrasynaptic NMDA receptors in the rat hippocampal CA3-CA1 synapse', *Journal of Pharmacology and Experimental Therapeutics,* 331 (2): 618-626. DOI: 10.1124/jpet.109.156752

[2] Costa, B.M., Irvine, M.W., Fang, G., Eaves, R.J., Mayo-Martin, M.B., Skifter, D.A., Jane, D.E. & Monaghan, D.T. (2010) 'A novel family of negative and positive allosteric modulators of NMDA receptors', *Journal of Pharmacology and Experimental Therapeutics,* 335 (3): 614-621. DOI: 10.1124/jpet.110.174144

[3] Bashir, Z.I., Bortolotto, Z.A., Davies, C.H., Berretta, N., Irving, A.J., Seal, A.J., Henley, J.M., Jane, D.E., Watkins, J.C. & Collingridge, G.L. (1993) 'Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors', *Nature,* 363: 347-350. DOI:10.1038/363347a0

[4] Thomas, N.K., Wright, R.A., Howson, P.A., Kingston, A.E., Schoepp, D.D. & Jane, D.E. (2001) '(*S*)-3, 4-DCPG a potent and selective mGlu8a receptor agonist activates metabotropic glutamate receptors on primary afferent terminals in the neonatal rat spinal cord', *Neuropharmacology,* 40 (3): 311-318. DOI: 10.1016/S0028-3908(00)00169-6

[5] Mercier, M., Lodge, D., Fang, G., Nicolas, C., Collett, V., Jane, D.E., Collingridge, G.L. & Bortolotto, Z. (2013) 'Characterisation of an mGlu8 receptor-selective agonist and antagonist in the lateral and medial perforant path inputs to the dentate gyrus', *Neuropharmacology,*67: 294-303. DOI: 10.1016/j.neuropharm.2012.11.020

[6] Jane, D.E., Lodge, D.L. & Collingridge, G.L. (2009) 'Kainate receptors: pharmacology, function and therapeutic indications', *Neuropharmacology,* 56: 90-113. DOI:10.1016/j.neuropharm.2008.08.023

[7] Perrais, D., Pinheiro, P.S., Jane, D.E. & Mulle, C. (2009) 'Antagonism of recombinant and native GluK3-containing kainate receptors', *Neuropharmacology,* 56: 131-140. DOI: 10.1016/j.neuropharm.2008.08.002

4. Details of the impact

Compounds developed by Watkins and Jane are in high demand from academic and industrial scientists worldwide, to use as tools to probe the function of glutamate receptors in health and disease. A number of companies that provide neurochemicals sell compounds developed at Bristol and in recent years, compounds from Bristol have been given a UBP code to show that they originate from the **U**niversity of **B**ristol **P**harmacology department.

Commercial impact through the creation of viable spinout companies

In 1989, Watkins founded the company, Tocris Neuramin, to sell compounds he developed to the scientific community. In 2005, the Tocris Bioscience brand was launched and in 2006 the company was sold for £14 million [a], at which point Watkins retired as director. The company is a leading supplier of high performance life science reagents and peptides, with customers in virtually all of the world's major pharmaceutical companies, universities and research institutes. Their reputation as a source of state of the art compounds for scientific research was based in large part on their access to novel glutamate receptor ligands, developed in Bristol; 42% of the glutamate receptor chemical probes in the Tocris Bioscience catalogue in 2008 came from Bristol. Three postdoctoral researchers from Bristol have been employed by Tocris and the company has sponsored the work of two PhD students (Helen Troop and Nigel Dolman) through industrial CASE awards from the MRC and BBSRC. They currently have 32 Bristol glutamate receptor compounds in their catalogue. Tocris Bioscience has a strong track record of profitability, with revenues in 2010 of approximately £11.7 million [b]. In 2011, Tocris Bioscience was acquired by Techne Corporation for £75 million [b].

In 2005, ex-employees of Tocris Bioscience, including Jane's ex-PhD student Heong Wai Tse, founded Ascent Scientific. Ascent rapidly made its reputation by selling pharmacological tools for glutamate receptors developed in Bristol. They currently sell 20 glutamate receptor compounds. Ascent was acquired by Abcam to form Abcam Biochemicals for £10M in September 2011 [c].Three postdoctoral researchers from Bristol have been employed by Ascent/Abcam. Jane acts as a consultant for Ascent/Abcam (2008-present). Iain Sanderson, Head of Chemistry at Abcam Biochemicals and founder member of Ascent Scientific, has stated that Jane made an important contribution to the development of the company: "Prof. David Jane has been an invaluable source of knowledge and resource for Ascent Scientific both before and after acquisition and subsequent rebranding to Abcam Biochemicals. During the early stages of Ascent Scientific. Prof. Jane's guidance and advice was a contributory factor in enabling Ascent Scientific to grow quickly, particularly with its range of glutamate products. Many of these were originally developed in Prof. Jane's group…"[d]

Chemical suppliers benefit from sale of compounds developed at Bristol The compounds developed at Bristol [1-7] are sold through at least 7 chemical suppliers (Sigma-Aldrich, Glixx Laboratories, Santa Cruz Biotechnologies, Biotrend, Fluorochem, Abcam and Tocris). Sigma-Aldrich, for example, carries 8 compounds in their catalogue that were developed at Bristol. Although the financial value of these compounds can't be teased out of overall sales revenues, the research chemicals segment of Sigma-Aldrich's sales portfolio is "its biggest top-line contributor" [d] with the company reporting revenues of $675 million in the 1st quarter of 2013 [e].

Collaborations with industry lead to significant investment in research of drug development

An estimated 110 Bristol compounds have been sourced to Eli Lilly (UK) through collaborative agreements. Some have been found to be potent compounds which Eli Lilly have taken on to pursue for their own research.

2012-present: Development of group III metabotropic glutamate receptor agonists and antagonists. In an on-going collaboration, six compounds synthesised at Bristol have been sent to Eli Lilly for evaluation on mGlu1-8 as part of a project to develop mGlu8 selective agonists and antagonists [material transfer agreement available upon request]. A derivative of the mGlu2 receptor agonist, LY354740, which was developed by Eli Lilly under the Bristol patent license, went to Phase III trials. Though the trial was ended in 2012, the estimated investment by industry to bring a drug from Phase I to Phase III clinical trials is around US$215-220 million (in 2011 USD) [f] .

2008-2011: Development of GluN2A selective competitive NMDAR antagonists. In collaboration with the Eli Lilly Centre for Cognitive Neuroscience (CCN) (of which Jane has been a member since 2007) GluN2A selective competitive NMDAR antagonists have been developed. Eli Lilly has invested £30,000 in this project to support a postdoctoral researcher [g]. Jane's input into the CCN was to provide expertise in NMDAR medicinal chemistry and computer-aided design, to jointly supervise a postdoctoral chemist working under the direction of a chemist at Lilly and to supervise the pharmacological characterisation of new compounds on NMDAR subtypes.

2008-2010: Development of kainate receptor (KAR) antagonists
Twenty compounds designed and synthesised by the Bristol group were sent to Eli Lilly for evaluation on GluK1 and GluK3 containing KARs to aid in structure-activity relationship studies for the development of selective antagonists for these receptor subtypes.

2008: Industry invests in Bristol expertise
As Jane has expertise in the medicinal chemistry and computer-aided drug design of KAR antagonists he acted as a consultant for Eli Lilly in their drug discovery programme centred on developing GluK1 selective KAR antagonists [h]. KAR antagonists are in development for the treatment of chronic pain and migraine.

5. Sources to corroborate the impact

[a] Momentum Corporate Finance LLP (2011) "Momentum advises on £75 million sale of Tocris Bioscience to US-based Techne Corporation" URL: http://www.momentumcf.com/assets/files/downloads/Tocris%2075%20million%20sale.pdf
[b] Red Orbit (3 May 2011) "Techne Corporation Releases Unaudited Third Quarter Results for Fiscal Year 2011" URL: http://www.redorbit.com/news/health/2039642/techne_corporation_releases_unaudited_third_quarter_results_for_fiscal_year_2/
[c] Reuters (10 Sep 2013) "Acquisitions boost Abcam full-year profit" URL: http://www.reuters.com/article/2013/09/10/us-abcam-results-idUSBRE9890BD20130910
[d] Iain Sanderson, Head of Chemistry, Abcam Biochemicals – Letter of support can be made available on request.
[e] Jones, K. (25 Apr 2013) "Sigma-Aldrich 1st-Quarter Net Up 4.3% on Applied Chemical Sales" URL: http://online.wsj.com/article/BT-CO-20130425-710659.html
[f] Mestre-Ferrandiz, J., Sussex, J. and Towse, A. (2012) *The R&D Cost of a New Medicine,* Office of Health Economics, London. <http://ohematerials.org/NMECost/index.html#/0> Supports financial figures estimating industry investment in this research.
[g] Development of GluN2A antagonists grant from Eli Lilly CCN – University of Bristol grant code: RM8179. Evidence of industry investment in the research.
[h] Full economic costing reference for Eli Lilly consultancy: 72072. Can be made available upon request.