Institution: University of Cambridge

Unit of Assessment: UoA5

Title of case study: Cambridge Biotechnology – developing drugs acting at adenosine and leptin receptors

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

Research led by Dr. Peter Richardson in the Department of Pharmacology led to the development of an A_{2A} adenosine receptor antagonist (istradefylline) for the treatment of Parkinson's disease. In 2001, Dr Richardson founded the spin-out company Cambridge Biotechnology (CBT) to develop these drugs. A pH-sensitive adenosine A_{2A} receptor agonist is now being developed for the treatment of neuropathic pain, with one product licensed for use in Japan in 2013 (Nouriast). Small-molecule leptin mimetics as potential anti-obesity drugs were also developed, initially by CBT and since 2009 by Astra Zeneca following acquisition of the research programme. CBT has undergone a number of high-value acquisitions, by Biovitrium, Proximagen, and most recently Upsher-Smith. It continues to operate as a wholly-owned subsidiary, employing 30-35 people from 2001 to the present.

2. Underpinning research (indicative maximum 500 words)

Dr Peter Richardson joined the Department of Pharmacology in 1989 (Lecturer then Senior Lecturer), where until 2006 he ran a research group devoted to understanding drug action at both the adenosine A_{2A} receptor and the leptin receptor.

A_{2A} receptors and Parkinson's disease

The group's early work (1993-94) revealed that the adenosine A_{2A} receptor interacted with other receptor systems, such as the cholinergic and GABAergic systems[1,2]. The interaction of the adenosine A_{2A} receptor with the cholinergic system in the striatum produced motor effects (specifically regulation of apomorphine induced turning in rats with unilateral dopamine denervation) in lesioned rats[1], suggesting a potential use of adenosine A_{2A} receptor antagonists in the treatment of Parkinson's disease (PD). As a consequence of this work, in 1994 Richardson became an advisor to the Kyowa Hakko Kogyo Company (now Kyowa Hakko Kirin) of Japan, with whom he undertook a programme of collaborative research on adenosine A_{2A} receptors. In 2002, the team demonstrated by patch-clamping that GABAergic synaptic transmission in the rat globus pallidus was enhanced by presynaptic adenosine A_{2A} receptors, via a cyclic AMP-dependent mechanism[3] (as opposed to acting collaterally on post-synaptic neurons). In 2003 they further demonstrated that the target neurons of A_{2A} receptor-mediated modulation were the striatopallidal medium spiny neurons[4]. At the same time, Richardson advised on the mechanism and early development of the company's adenosine A_{2A} receptor antagonist KW6002 (istradefylline) in PD.

A_{2A} receptors and pain

In 1994, the group demonstrated that a number of agonists for the adenosine A_{2A} receptor bound with higher affinity at pathophysiologically relevant reduced pH[5]. Follow-up research in 1995 revealed that the adenosine A_{2A} receptor-mediated dilatation of the rat mesenteric arterial bed is potentiated by a reduction in pH, similar to that seen in ischaemic conditions[6]. This work identified ways of screening novel molecules for the appropriate pH sensitive properties, and led to the granting of the following patents:

1. Use of spongosine (2-methoxyadenosine) for the treatment of pain, in particular hyperalgesia WO2004052377. (2004) Richardson, P.J.
2. Compounds for the treatment of pain. WO2004078183. (2004) Richardson, P.J., Lee, K. and Lione, L.
3. Use of adenosine receptor agonists in therapy. WO2004078184. (2004) Richardson, P.J.
4. Identification of therapeutic compounds. WO2004079329. (2004) Richardson, P.J.
5. Therapeutic compounds. WO2005/084653. Richardson, P.J.

This research programme was licensed from the University to CBT in 2001/2 (see below).

Leptin receptors

In a separate research project, Dr. Richardson's group studied the effect of the peptide leptin on the ability of insulin to stimulate fatty acid uptake in adipocytes[7]. Leptin plays an important role in obesity, mainly due to a resistance to leptin developed by obese subjects. Understanding how leptin acts is therefore crucial for the development of therapies destined to tackle metabolic disorders. Pathologically increased intracellular fatty acid concentrations have been linked to insulin desensitization, type 2 diabetes, obesity, and cardiovascular disease. All of these intracellular processes depend on fatty acids traversing the plasma membrane to enter the cell. The group's work revealed that in differentiated 3T3-L1 adipocytes, insulin had a concentration-dependent stimulatory effect on fatty acid uptake, whereas leptin did nothing. Leptin, when co-incubated with insulin, caused a concentration-dependent inhibition of the insulin-stimulated fatty acid uptake, suggesting that leptin has a direct inhibitory effect on the stimulation of fatty acid uptake by insulin[7]. This result led the group to search for a small-molecule leptin mimetic that might have a role as an anti-obesity drug (leptin is a 16 kDa protein, so a small molecule mimetic could be a lot more cost-effective).

In 2001, Dr. Richardson founded Cambridge Biotechnology (CBT), to take forward work on A_{2A} agonists for the treatment of inflammation and pain, and on novel small-molecule leptin mimetics. The company was initially based within the Department of Pharmacology.

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

1. Vellucci, S.V., Sirinathsinghji, D.J.S. and Richardson, P.J. (1993) Adenosine A2 receptor regulation of apomorphine induced turning in rats with unilateral dopamine denervation. Psychopharmacol. 111, 383-388. Doi: 10.1007/BF02244956
2. Kirk, I.P. and Richardson, P.J. (1994) Adenosine A_{2A} receptor mediated modulation of striatal [^{3}H]-GABA and [^{3}H]-ACh release. J. Neurochem. 62, 960-966. DOI: 10.1046/j.1471-4159.1994.62030960.x
3. Shindou, T., Nonaka, H., Richardson, P.J., Mori, A., Kase, H. and Ichimura, M. (2002) Presynaptic adenosine A_{2A} receptors enhance GABAergic synaptic transmission via a cyclic AMP dependent mechanism in the rat globus pallidus. Br J Pharmacol. 136, 296-302 DOI: 10.1038/sj.bjp.0704702
4. Shindou, T., Richardson, P.J., Mori, A., Kase, H. and Ichimura, M. (2003) Adenosine modulates the striatal GABAergic inputs to the globus pallidus via adenosine A_{2A} receptors in rats. Neurosci Lett. 352, 167-70 DOI: 10.1016/j.neulet.2003.08.059
5. Askalan, R., Richardson, P.J. (1994) Role of histidine residues in the adenosine A_{2A} receptor ligand binding site. J. Neurochem. 63, 1477-1484. DOI: 10.1046/j.1471-4159.1994.63041477.x
6. Hiley, C.R., Bottrill, F.E., Warnock, J. and Richardson, P.J. (1995) Effects of pH on responses to adenosine, CGS 21680, carbachol and nitroprusside in the isolated perfused superior mesenteric arterial bed of the rat. Br. J. Pharmacol. 116, 2641-2646. DOI: 10.1111/j.1476-5381.1995.tb17220.x
7. Ho, M., Foxall, S., Higginbottom, M., Donofrio, DM., Liao, J., Richardson, P.J. and Maneuf, YP. (2006) Leptin-mediated inhibition of the insulin-stimulated increase in fatty acid uptake in differentiated 3T3-L1 adipocytes. Metabolism, 55, 8-12. Doi: 10.1016/j.metabol.2005.06.013

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

The research detailed above has had a number of impacts, primarily on health and welfare, and on commerce.

Impacts on commerce: industry has invested in research and development, the performance of an existing business has been improved, jobs have been protected

CBT raised £6.3 million in 2001/2 and a further £4 million in 2005. It was acquired by Biovitrium for £27 million later in 2005, and at this point moved from the Department to a purpose-built research facility south of Cambridge (at Babraham). By 2008, CBT, as a wholly-owned subsidiary of Biovitrium, employed 30 research staff and two administrative staff, and was primarily focused on

the discovery and development of novel small molecule therapeutics in the areas of pain, inflammation and obesity. The company also continued to work on small molecule leptin mimetics, following out-licensing of the technology from the Richardson group in 2001. In 2009, Biovitrium's (pre-clinical) leptin mimetic project was sold in its entirety to AstraZeneca for €186 million[7].

In October 2009, CBT was sold by Biovitrium to Proximagen plc[8] (value undisclosed), a company focusing on the development and commercialization of novel therapeutics for diseases of the central nervous system (CNS). As part of the deal, Proximagen acquired certain CBT programmes (see below under 'Impacts on health and welfare'); CBT continued to exist as a wholly-owned subsidiary of Proximagen, serving as its drug discovery and development arm, and with CBT employees serving as the scientific core of Proximagen. In addition to progressing the various research programmes, CBT assisted Proximagen in fund raising (£50M in 2009 and £10M in 2011), and in preparing the company for its subsequent acquisition by Upsher-Smith.

In 2012 Upsher-Smith, a US-based pharmaceutical company, acquired Proximagen (including CBT) for £223 million in the first instance (and potentially up to £356.8 million, depending on milestones)[9]. Although Upsher-Smith's existing strengths were in women's health, dermatology and cardiology, it was expanding its CNS drug discovery work, where it already had one treatment in Phase III trials. Of the 15 drug candidates taken on from Proximagen, nine originated from CBT, including the most advanced of these, PRX00933 (see below under 'Impacts on health and welfare'). This was Upsher-Smith's first and only acquisition outside of the US. The President and Chief Executive Officer of Upsher-Smith has stated that "*The acquisition of Proximagen adds significantly to our scientific capabilities and supports the acceleration of our vision of becoming a leader in the CNS category…..the combination of Upsher-Smith's clinical development and commercialization expertise with Proximagen's research and development platform provides the opportunity to further enhance our ability to bring new therapies to market to benefit patients*"[10]

CBT continues to operate as a wholly-owned subsidiary of Upsher-Smith, and remains drug discovery- and early development-focused (i.e. up to Phase II). CBT currently employs 34 scientists and 3 support staff at Babraham.

Impacts on health and welfare: a new clinical intervention has been developed, trialled and definitive outcome demonstrated

Research undertaken by Kyowa Hakko Kogyo Company (now Kyowa Hakko Kirin) with advisory input from Richardson found that in rodent and primate models, KW-6002 provided symptomatic relief from Parkinsonian motor deficits without provoking dyskinesia. Experiments with dopamine D_2Sh and D_2Lh receptor knockout mice showed that the anti-PD activities of A_{2A} antagonists are independent of the dopaminergic system[11]. Clinical studies of KW-6002 in patients with advanced PD with L-DOPA-related motor complications (conducted by the KW-6002 US-001 Study Group) also yielded promising results with regard to motor symptom relief without motor side effects[11]. Clinical trials carried out by Kyowa Hakko Kogyo in Japan (Phase 3 2009-2012, NCT00957203) demonstrated sufficient beneficial effects for the product to receive marketing authorisation as an antiparkinsonian agent (as Nouriast) in Japan in March 2013[12]. A repeat Phase III clinical trial in the US is being arranged (NCT not yet known) in order to obtain approval for marketing from the FDA (the original Phase III trial in the US failed because of issues with patient selection, NCT00199407).

When Proximagen acquired CBT in 2009, CBT's drug development programmes included a Phase IIB-ready anti-obesity drug (PRX00933, a 5HT2c agonist)[13], a Phase I-ready anti-inflammatory programme for rheumatoid arthritis and psoriasis (PRX167700), two programmes ready for toxicity testing (one now in preclinical development), and two discovery programmes. Proximagen took PRX00933 through Phase IIB trials for obesity, where it showed a dose-dependent and statistically significant decrease in body weight within FDA guidelines for this condition[14]. PRX167700 completed Phase I trials for rheumatoid arthritis and psoriasis in late 2012[15]; outcomes were successful, namely the drug was well tolerated and biomarker measurements confirmed biological activity. A phase II is currently being planned. PRX167700 is also currently undergoing Phase II trials in the UK for knee osteoarthritis (NCT01945346)[16].

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

7. AstraZeneca acquisition of Biovitrium: http://www.reuters.com/article/2009/12/21/idUS157279+21-Dec-2009+MW20091221
8. www.proximagen.com/docs/RNS30-10-09.pdf
9. Upsher-Smith acquisition of Proximagen: http://www.cabume.co.uk/medtech/cambridge-biotechnology-proves-worth-with-p3568m-acquisition.html
10. Statement from representative of Upsher-Smith available here: http://www.businesswire.com/news/home/20120814005877/en/Upsher-Smith-Completes-Acquisition-Proximagen-Group-plc
11. Kase, H. (2003) Progress in pursuit of therapeutic A_{2A} antagonists; the adenosine A_{2A} receptor selective antagonist KW6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease. Neurology 61, S97-100. doi: 10.1212/01.WNL.0000095219.22086.31
12. http://www.kyowa-kirin.com/news_releases/2013/e20130325_04.html
13. http://www.proximagen.com/docs/RNS23-11-11.pdf
14. http://www.proximagen.com/docs/RNS11-05-12.pdf
15. http://www.bionity.com/en/news/136767/proximagen-initiates-phase-i-clinical-trial-of-prx167700.html
16. http://clinicaltrials.gov/show/NCT01945346