Institution: University of Sussex

Unit of Assessment: UoA 4 Psychology

Title of case study: Serotonin 2C receptor agonists: a new drug treatment for obesity

1. Summary of the impact

In June 2013 Arena launched Belviq® (generic name: lorcaserin) as a novel drug treatment for obesity. Lorcaserin was approved by the Federal Drugs Administration (FDA – the USA drug regulatory body) on 26 June 2012 and scheduled by the Drug Enforcement Agency (DEA) in April 2013. The scientific rationale for the development programme for lorcaserin, which is a serotonin 2C receptor agonist, as a treatment for obesity rested, in significant part, on research carried out between 1997 and 2010 at the University of Sussex.

2. Underpinning research

Serotonin (5-HT) is a neurotransmitter that is widely distributed in the brain and elsewhere in mammals. It is implicated in the modulation of appetite and mood but also regulates many peripheral functions in gut, lung, heart and skin tissues. The serotonin releaser and reuptake inhibitor fenfluramine was widely used in the European and American markets as an obesity treatment during the 1980s. Studies in both rodents and humans established that the drug enhanced the feeling of satiety that arises after consuming food. In the early 1990s the more selective and potent *d* isomer of fenfluramine was introduced in both Europe and North America. It quickly became clear that the drug was associated with several unacceptable side effects, including heart valve regurgitation and pulmonary hypertension. Fenfluramine was withdrawn from both the American and European markets in September 1997. By 2010, following several further drug withdrawals, the only compound still available for the treatment of obesity in the European and US markets was the peripheral lipase inhibitor orlistat.

The effects of serotonin are mediated through at least 14 receptor subtypes and, following the withdrawal of fenfluramine, the scientific challenge was to establish the receptor subtype that mediated the effects of serotonin on satiety. Clifton's laboratory at Sussex had characterised the detailed behavioural effects of fenfluramine on feeding in rats and, in 1997, rapidly built a collaboration with Colin Dourish (Vernalis) and Larry Tecott (University of California, San Francisco) to exploit serotonin 2C ($5\text{-}HT_{2C}$) receptor null mutant mice in similar paradigms. The resulting study provided the first definitive evidence that the enhancement of satiety by fenfluramine depended on the presence of functional serotonin 2C receptors and provided the rationale for the development of serotonin 2C receptor agonists for the treatment of obesity [see Section 3, R1]. Two subsequent BBSRC-funded LINK grants (PI Clifton) between Sussex and Vernalis explored the behavioural effects of both serotonin 2C and 1B agonists in greater detail. Key findings included:

- that serotonin 2C agonists not only enhanced satiety but also reduced appetitive responding for food, most easily understood as an effect on 'hunger'; and
- that serotonin 1B receptor agonists, although they reduce food intake, can be discounted as a potential target for obesity treatment [R2–R6].

Clifton has been at Sussex throughout. Vickers was a PhD student and subsequently a post-doctoral RA at Sussex. He then moved to Vernalis and to RenaSci where he is now Vice President Pharmacology. Dourish left Vernalis and established P1Vital, initially based at Addenbrookes Hospital, Oxford. On a first BBSRC LINK grant, Lee was the post-doctoral RA, Somerville (Sussex School of Life Sciences) a Co-I, and Clifton PI. Subsequently, Lee moved to Swansea where she is

now a Senior Lecturer and Deputy Head of the Department of Psychology. Morris was the post-doc on a second grant, and is now taking a maternity break; Somerville was a Co-I and Clifton PI.

3. References to the research

R1 Vickers, S.P., Clifton, P.G., Dourish, C.T. and Tecott, L.H. (1999) 'Reduced satiating effect of d-fenfluramine in serotonin 5-HT(2C) receptor mutant mice', *Psychopharmacology*, 143(3): 309–314.

R2 Clifton, P.G., Lee, M.D. and Dourish, C.T. (2000) 'Similarities in the action of Ro 60-0175, a 5-HT2C receptor agonist and d-fenfluramine on feeding patterns in the rat', *Psychopharmacology*, 152(3): 256–267.

R3 Hewitt, K.N., Lee, M.D., Dourish, C.T. and Clifton, P.G. (2002) 'Serotonin 2C receptor agonists and the behavioural satiety sequence in mice', *Pharmacology, Biochemistry, and Behavior*, 71(4): 691–700.

R4 Lee, M.D., Somerville, E.M., Kennett, G.A., Douris, C.T. and Clifton, P.G. (2004) 'Tonic regulation of satiety by 5-HT1B receptors in the mouse: converging evidence from behavioural and c-fos immunoreactivity studies', *European Journal of Neuroscience*, 19(11): 3017–3025.

R5 Somerville, E.M., Horwood, J.M., Lee, M.D., Kennett, G.A. and Clifton, P.G. (2007) '5-HT(2C) receptor activation inhibits appetitive and consummatory components of feeding and increases brain c-fos immunoreactivity in mice', *European Journal of Neuroscience*, 25(10): 3115–3124.

R6 Zhou, L., Sutton, G.M., Rochford, J.J., Semple, R.K., Lam, D.D., Oksanen, L.J., Thornton-Jones, Z.D., Clifton, P.G., Yueh, C.Y., Evans, M.L., McCrimmon, R.J., Elmquist, J.K., Butler, A.A. and Heisler, L.K. (2007) 'Serotonin 2C receptor agonists improve type 2 diabetes via melanocortin-4 receptor signaling pathways', *Cell Metabolism*, 6(5): 398–405.

R1 is the critical reference for this impact case study (Scopus citations = 192). It was a key support to the establishment of the joint project between Vernalis and Roche to develop serotonin 2C receptor agonists for the treatment of obesity. It also acted as a stimulus for the development programmes of a number of other companies, including Arena, who brought lorcaserin through to recent FDA approval. R2, R3 and R5 further characterised the effects of serotonin 2C agonists on feeding, R4 ruled out serotonin 1B receptor agonists as potential obesity treatments and R6 showed that serotonin 2C receptor agonists might have additional beneficial effects in Type 2 diabetes, which is almost invariably the consequence of severe obesity.

Outputs can be supplied by the University on request.

Two LINK grants from BBSRC supported this research (85/LKD12007, £172k; BB/C505291/1, £295k).

4. Details of the impact

The need for effective treatments of obesity is substantial; the incidence of obesity has increased rapidly in the last two decades and, worldwide, one in every nine adults was obese in 2008 [see Section 5, C1]. The disease burden associated with obesity and overweight now accounts for £5 billion of NHS spending a year [C2]. Reversal of these trends and their impact on both quality of life and health-care budgets will require substantial lifestyle alteration involving both voluntary activity

and diet, although medical treatment of severe and morbid obesity, including the use of anti-obesity drugs and bariatric surgery, will remain important.

The research described above had several material impacts on the development and subsequent introduction of serotonin 2C receptor agonists for the treatment of obesity. The primary impact was the launch of lorcaserin as 'first in class' serotonin 2C receptor agonist treatment for obesity in June 2013.

The research described in R1 was first published in Abstract form in June 1998. It indirectly supported a round of fundraising by Vernalis[1] which allowed the initiation of the collaborative programme of research between Vernalis and Roche for the development of serotonin 2C agonists. The work attracted considerable interest and it soon became clear that a number of other companies had initiated drug development programmes in this area after our work was published and Vernalis had announced the Roche collaboration. Phase 1 studies of selected compounds were initiated by Vernalis in 2001. Positive Phase 1 and 2 results on lorcaserin were reported during the early 2000s. Vernalis and Roche decided that the range of compounds that they had developed was not sufficiently selective, especially in relation to the serotonin 2A vs serotonin 2C receptor, and discontinued the project. This coincided with a broader strategic decision by Roche, and subsequently by Vernalis, to focus towards cancer, and away from psychiatric and other neuroscience-related areas, including obesity.

The development of lorcaserin by Arena started in the early 2000s, after the publication of R1, and the key description of the drug was provided by Thomsen *et al*. 2008 [C3] which cites R1 above. The Chief Scientific Officer of Arena has confirmed the importance of this reference in providing the scientific rationale for the drug development programme [C4]. His statement reads:

> The development of 5-HT_{2C} agonists for weight management was largely based upon the clinical efficacy of fenfluramine, and in particular the understanding that the efficacy of dexfenfluramine could be explained by activity at the 5-HT_{2C} receptor: A key piece of evidence in this regard was the finding by Vickers *et al.* (1999) that the effects of dexfenfluramine are absent in 5-HT_{2C} knockout mice.

The Chief Scientific Officer, InterVivo Solutions, who has been responsible for several serotonin 2C receptor agonist development programmes, confirmed this point, stating:

> I can assure you that the Vickers paper has made a significant contribution to the development of 5-HT_{2C} agonists as treatments for obesity. In 1999, as I recall the d-fen/5-HT antagonist studies were pretty inconsistent with respect to 2C involvement and the Vickers paper probably gave the most direct support that d-fen effects were at least partially 5-HT_{2C} mediated [C5].

Phase 3 studies for lorcaserin were published in C6 and, as noted above, lorcaserin received approval for general introduction in June 2012 but was also referred to the Drug Enforcement Agency for consideration of abuse liability. This was rated low in April 2013, allowing marketing of the drug to commence shortly thereafter. It is the first obesity treatment to have been approved by the FDA since their approval of the lipase inhibitor Orlistat in 1999. As noted above, scheduling of lorcaserin by the DEA was completed in April 2013 and the drug became available for prescription in the United States in June 2013. Sales by Eisai (Arena's marketing partner) in the first three months totalled $9M (C7) and the most recent independent estimates suggest likely sales of $500 million in 2015 [C8].

Other companies are also continuing to develop novel serotonin 2C agonists for the treatment of obesity. An example is Bristol-Myers Squib whose publication [C9] cites R1 and R6 above, as well as several others publications from Clifton's laboratory. These papers are also cited in the patent applications for this series of compounds.

[1]'Vernalis' is used to identify the partner firm throughout. However, the corporate history is that

Vernalis is the current name of the firm that merged with Vanguard in 2003, and Vanguard acquired Cerebrus in 1999. It was Cerebrus who was the original partner – the collaboration continued with both Vanguard and Vernalis.

5. Sources to corroborate the impact

C1 Stevens, G.A., Singh, G.M., Lu, Y., Danaei, G., Lin, J.K., Finucane, M.M., Bahalim, A.N., McIntire, R.K., Gutierrez, H.R., Cowan, M., Paciorek, C.J., Farzadfar, F., Riley, L., Ezzati, M. and the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (2012) 'National, regional, and global trends in adult overweight and obesity prevalences', *Population Health Metrics*, 10(1): 22.

C2 UK Government estimate at https://www.gov.uk/government/policies/reducing-obesity-and-improving-diet, accessed 30 August 2013.

C3 Thomsen, W.J., Grottick, A.J., Menzaghi, F., Reyes-Saldana, H., Espitia, S., Yuskin, D., Whelan, K., Martin, M., Morgan, M., Chen, W., Al-Shamma, H., Smith, B., Chalmers, D. and Behan, D. (2008) 'Lorcaserin, a novel selective human 5-Hydroxytryptamine 2C agonist: in vitro and in vivo pharmacological characterization', *Journal of Pharmacology and Experimental Therapeutics*, 325(2): 577–587.

C4 Statement from Chief Scientific Officer, Arena Pharmaceuticals – quoted verbatim in Section 4. Personal communication to Professor Clifton.

C5 Statement from Chief Scientific Officer, Intervivo – a biopharma company involved in the development and characterisation of 5-HT_{2C} agonists.

C6 Smith, S.R., Weissman, N.J., Anderson, C.M., Sanchez, M., Chuang, E., Stubbe, S., Bays, H., Shanahan, W.R. and the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group (2010) 'Multicenter, placebo-controlled trial of lorcaserin for weight management', *The New England Journal of Medicine*, 363(3): 245–256.

C7 Eisai 2013.9 Reference Data, at http://www.eisai.com/pdf/eir/erepo/e2014Q2_52.pdf, accessed 11 November 2013

C8 Estimates from Piper Jaffray and Credit Suisse.

C9 Ahmad, S., Ngu, ., Miller, K.J., Wu, G., Hung, C.-P., Malmstrom,S., Zhang, G., O'Tanyi, E., Keim, W.J., Cullen, M.J., Rohrbach, K.W., Thomas, M., Ung, T., Qu, Q., Gan, J., Narayanan, R., Pelleymounter, M.A. and Robl, J.A. (2010) **'**Tricyclic dihydroquinazolinones as novel 5-HT_{2C} selective and orally efficacious anti-obesity agents', *Bioorganic and Medicinal Chemistry Letters*, 20(3): 1128–1133.