Institution: **University of Sheffield**

Unit of Assessment**: 5 - Biological Sciences**

Title of case study: **A Treatment for Irritable Bowel Syndrome (IBS)**

1. Summary of the impact

Research at the University of Sheffield contributed to the development by GlaxoSmithKline (GSK) of a drug to treat Irritable Bowel Syndrome (IBS) that has transformed the lives of thousands of patients and generated significant revenue. The drug, alosetron, which blocks 5-HT3 receptors in the gastrointestinal tract, was approved by the Food and Drug Administration (US) (FDA) in 2000 and launched under the trade name Lotronex. It is currently the only drug on the market aimed specifically at the treatment of diarrheal IBS. Although GSK voluntarily withdrew the drug from the market following concerns over possible side effects, Lotronex was relaunched in 2004 following petition from IBS sufferers and user groups. The licence for Lotronex was sold in 2008 to Prometheus Laboratories, Inc. and annual sales of the drug now exceed $34 million. In 2011 Prometheus was bought by Nestle for an estimated $1.1billion. This case study has significant impact on commerce and health and welfare.

2. Underpinning research

Research in Professor David Grundy's laboratory at the University of Sheffield is focused on understanding the mechanisms underlying sensory signals generated from within the gastrointestinal tract and the potential to target these mechanisms using drugs to treat visceral pain. In the mid-1990s, Grundy initiated studies of the role of endogenous 5-hydroxytryptamine (5-HT, serotonin) in sensory signalling due to its abundance within specialized entero-endocrine cells in the mucosal epithelium in the gastrointestinal tract. Using electrophysiological techniques that he pioneered, he was able to record the impulse traffic in sensory fibres on route to the CNS from afferent fibres in mesenteric nerve bundles as they emanated from the bowel wall. Grundy characterised the sensitivity of different populations of afferent fibres to 5-HT ([**R1**]: Hillsley and Grundy, 1998) and pharmacologically separated these on the basis of direct effects of 5-HT on the afferent terminal and indirect activation secondary to evoked contraction of the smooth muscle in the gut wall ([**R2**]: Hillsley, Kirkup and Grundy, 1998). He determined that direct effects are mediated by a class of ligand-gated ion channel called the 5-HT3 receptor. During this period GlaxoWellcome (now GlaxoSmithKline) developed a drug programme around 5-HT3 receptors, initially to develop novel antiemetics, but subsequently focused on visceral analgesics to treat chronic pain in conditions such as Irritable Bowel Syndrome (IBS).

In 1994 GSK began to collaborate with Grundy to investigate the effect of a candidate 5-HT3 receptor antagonist (alosetron) on sensory signalling from the bowel. Catherine Kozlowski was seconded by GSK into Grundy's research group to carry out this work (and submitted her doctoral thesis to the University of Sheffield in 1999). Their collaborative research demonstrated that alosetron caused a dose-depending attenuation of pain behaviour and nociceptive signalling from the rat colon, which was published in Gut ([**R3**]: Kozlowski et al., 2000). These data provided the mechanistic understanding that was used in GSK's patent application for alosetron, in the FDA submissions and in the generation of marketing material prior to the US launch of Lotronex for the treatment of women with diarrhoea predominant IBS in 2000. At this time, GSK were predicting Lotronex sales of $2 billion over the first 5 years. However, within about 9 months, a severe adverse effect (ischemic colitis) was identified that had not been apparent in the earlier clinical trials. GSK voluntarily withdrew the drug from the US market and suspended attempts to licence in

Europe and elsewhere. In 2002 the FDA announced approval for a supplemental New Drug Application to allow restricted marketing of Lotronex, to treat only women with severe IBS. Lotronex therefore became the first drug returned to the US market after withdrawal for safety concerns.

Grundy was a member of the GSK Advisory Board (5 June 2005) convened to consider the preclinical and clinical mechanisms that might underlie the development of ischemic colitis. The board recommended further studies, which were overseen by Grundy while on sabbatical at GSK and published in 2007 ([**R4**]: Grundy, McClean and Stead, 2007). This study found that alosteron had no effect on baseline colonic blood flow in the anaesthetized rat; nor did it interfere with vascular control mechanisms activated during ischaemia and reactive hyperaemia. Grundy's data suggested that the rare and episodic nature of ischemic colitis in patients receiving Lotronex could not be predicted from a preclinical perspective and that other predisposing factors exist in some IBS patients. Since re-launch, Lotronex has gone on to be the only drug on the market aimed specifically at the treatment of diarrheal IBS and has gained annual sales during the REF period in excess of $34 million/annum.

3. References to the research

R1 Hillsley K and Grundy D. (1998) Sensitivity to 5-hydroxytryptamine in different afferent subpopulations within mesenteric nerves supplying the rat jejunum. *J. Physiol*., 509, 717-727. doi: 10.1111/j.1469-7793.1998.717bm.x

R2 Hillsley K, Kirkup AJ and Grundy D. (1998) Direct and indirect actions of 5-HT on the discharge of mesenteric afferent fibres innervating the rat jejunum. *J. Physiol*., 506, 551-561. doi: 10.1111/j.1469-7793.1998.551bw.x

R3 Kozlowski CM, Green A, Grundy D, Boissonade FM and Bountra C. (2000) The 5-HT3 receptor agonist Alosetron inhibits the colorectal distension-induced depressor response and spinal c-fos expression in the anaesthetised rat. *Gut*, 46: 474-480. doi: 10.1136/gut.46.4.474

R4 Grundy D, McClean P and Stead RH (2007) Impact of 5-HT3 receptor blockade on colonic haemodynamic responses to ischaemia and reperfusion in the rat. *Neurogastroenterol Motil*., 19: 607-16. doi: 10.1111/j.1365-2982.2007.00938.x

4. Details of the impact

Research in Sheffield provided mechanistic understanding of the role of 5-HT in visceral pain and demonstrated that a specific receptor antagonist (alosteron) has visceral analgesic properties, effective in the treatment of diarrhoea-predominant IBS (D-IBS). The research undertaken in Sheffield was part of a substantial investment by GSK in the research and development of Lotronex for treatment of IBS [**S1,S2**]. The importance of Grundy's contributions is confirmed by the project leader at GSK, Dr Allen Mangel, currently vice-president at RTI Health Solutions. A letter from Dr Mangel explains how *"the pivotal work from Dr. Grundy's laboratory provided the basis to explain why 5-HT3 receptor antagonists, such as Lotronex, behave as visceral analgesic agents reducing debilitating abdominal pain in D-IBS. This information was provided both to the FDA Gastroenterology Reviewing Division and the GI Drug Advisory Committee that led to the ultimate approval of Lotronex in the United States for the treatment of female D-IBS patients"* [**S3**]. Sheffield research was an important early step towards the launch of Lotronex for the treatment of patients with irritable bowel syndrome. This is currently the only drug available to treat IBS and has resulted in considerable impacts on commerce and on health and welfare.

Commerce

The socioeconomic impact of functional gut disorders is significant, with direct and indirect healthcare costs estimated at £34 billion in the seven largest western economies.

In 2008, exclusive US rights to market Lotronex were acquired from GSK by Prometheus, a US company that specialises in diagnostics and therapeutics, for $80 million plus 714,285 shares of Prometheus Laboratories Inc. common stock [**S4**]. In order to reduce the potential for harmful side effects, Lotronex was subject to a special prescribing program designed to ensure that only doctors who had enrolled in the "Prescribing Program for Lotronex" could issue prescriptions [**S5**]. Recent data show that, of 29,072 patients who received 203,939 prescriptions for Lotronex, the incidence of serious outcomes has remained rare and cases are typically of short duration that resolve upon withdrawal of treatment [**S6**]. The Prometheus website describes Lotronex as one of two major gastrointestinal products (the other being Entocort) and therefore represents an important product in their portfolio. Sales figures show a steady increase from $25.2 million in 2008, $30.4 million in 2009 and in 2010 net sales of Lotronex were $34.8 million, an increase of approximately 14.5% on the previous year. In 2010, Prometheus employed approximately 125 sales representatives, sales managers and regional field trainers [**S7**].

In July 2011 Prometheus was bought by Nestle Health Science for an estimated $1.1billion [**S8**].

Health and Welfare

IBS is estimated to affect between 8 and 15% of the population in the US and Europe and has an enormous impact on healthcare provision and quality of life, particularly in women. Functional gastrointestinal disorders including IBS represent one of the great unmet clinical needs and are estimated to account for 40% of all new referrals to gastroenterology clinics [**S5**]. The International Foundation for Functional Gastrointestinal Disorders (IFFGD) describes what life is like for patients with IBS. The main symptoms are pain or abdominal discomfort associated with either diarrhoea or constipation. It can have a devastating effect on quality of life because of unpredictable pain, urgency and incontinence. Patients complain about the impact it has on both their professional and personal life, with the misery of incontinence several times per day. As one IBS patient describes in an on-line forum, *"let me tell you what it feels like. You have now gone from being a productive, full-time working mother, a loving wife, likeable friend and positive contributor to society – to a highly anxious, depressed and housebound individual"*. Recent data describe an increased risk of suicide in patients with IBS [**S9**].

Lotronex is specifically used for the treatment of diarrhoeal IBS. Data from clinical trials documents the improvement in symptoms with adequate relief of pain and discomfort, as well as improvement of bowel symptoms, frequency, urgency and stool consistency when compared with placebo (Cremonni et al, Aliment Pharmacol Ther. 36:437-48, 2012). An indication of the extent to which symptoms improve can be gauged from the reaction of patients following withdrawal of the drug after a small number of patients developed potentially life-threatening ischemic colitis. A Lotronex Action Group was set up by patients who had benefited from treatment that was no longer available to them in order to lobby for an FDA review and reintroduction of the drug. The group gained support from prominent politicians, including members of Congress who petitioned on behalf of patients. The group was demanding the return of the drug that *"gave me my life back and my peace of mind"*. Their petition was successful when the FDA approved Lotonex for the second time in 2002 and to this day continues to provide adequate relief for large numbers of patients. The pressure created by sufferers for the return of Lotronex is clear evidence of the impact it has had on their lives, and it is well documented. Patient testimonies included in the Lotronex Action Group submission to the FDA are evidence of the impact that blocking 5-HT3 receptor-mediated sensory signalling can have on pain signalling from the bowel [**S10**].

5. Sources to corroborate the impact

S1 Evidence of financial support of Sheffield research by Glaxo Studentship to Catherine Kozlowski (nee Scott) 1995-1998. PhD thesis "The Neuropharmacology of Visceral Afferents Neurons"

S2 GSK European patent application relevant to Lotronex (Abstract: This invention relates to the use of 5-HT3 receptor antagonists in the treatment of nonconstipated female IBS patients.) This patent includes information published in the above thesis and Ref 3, and also cites Scott CM, **Grundy D**, Boissonade F, Bountra C. Gastroenterology 1997; 112:A822. http://www.google.com/patents/EP1021174A2?cl=en

S3 Letter from Dr Allen Mangel, Alosetron Project Leader for GlaxoSmithKline and currently Executive Vice President for RTI-Health Solutions US, confirms the impact of the Sheffield research on commercial drug development and regulatory approval. Letter is quoted from above and is available in full on request.

S4 GSK press release November 2007 "Prometheus to acquire Lotronex from GlaxoSmithKline" http://www.gsk.com/media/press-releases/2007/prometheus-to-acquire-lotronex-from-glaxosmithkline.html

S5 US Federal Drug Administration documentation on Lotronex, including transcript of GI drug Advisory Committee meeting http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110450.htm

S6 Research showing that serious side effects to Lotronex are rare (e.g. Chang *et al.* American Journal of Gastroenterology 105:866-75, 2010).

S7 Sales figures and market information for Lotronex available from http://www.faqs.org/sec-filings/110225/PROMETHEUS-LABORATORIES-INC_S-1.A/#b

and Prometheus Company Fact Sheet documenting the importance of Lotronex and IBS *http://www.nestlehealthscience.com/asset-library/documents/newsroom/Prometheus_Fact_Sheet_For%20External_Use.pdf*

S8 Reuters reports, May 2011 "*Prometheus Announces Agreement to be Acquired by Nestle Health Science*" http://www.reuters.com/article/2011/05/24/idUS44461+24-May-2011+PRN20110524 and "*Nestle might have paid over $1 bn for buy - analyst"* http://uk.reuters.com/article/2011/05/24/nestle-idUSLDE74N0G620110524

S9 Research showing increased suicide rate of IBS patients (e.g. Spiegel *et al.* Aliment Pharmacol Ther. 26:183-93, 2007).

S10 Evidence of the impact of Lotronex drug on IBS patient lives. Evidence and testimonials submitted by Lotronex Action Group to the Lotronex Public Advisory Committee meeting, available from: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3848OPH1_44_lotronex%20Action%20Group.pdf