Institution: University of Bath

Unit of Assessment: 3. Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Drug Discovery & Clinical Translation

1. Summary of the impact

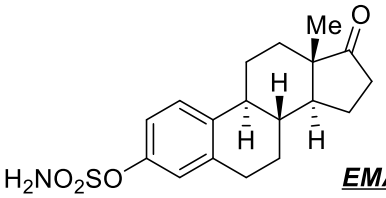
Cancer is a widespread deadly disease; annually, one million new breast cancers are diagnosed globally. Endometriosis is a poorly understood disorder, with 80 million patients worldwide. Current therapies for both are inadequate and discovery of new drugs is critical. The Bath group has pioneered identification of new targets and designed two "first-in-class" clinical drugs. The Bath/Imperial College spin-out company Sterix (subsequently acquired by a major pharmaceutical company) has translated them into patients and to the pharmaceutical industry. The steroid sulfatase inhibitors, *Irosustat* and *J995* have entered eighteen clinical trials worldwide in patients with these hormone-dependent diseases, with several ongoing since 2008. Disease was stabilised for cancer patients; the advanced clinical evaluation of both drugs is in progress.

2. Underpinning research

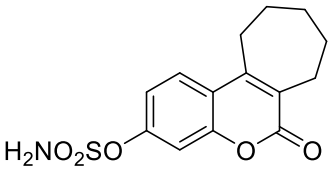
Basic Science. Many hormone-dependent tumours depend upon oestrogens for growth and development. One important source of tumour oestrogen is hydrolysis of oestrone 3-*O*-sulfate to oestrone by steroid sulfatase (STS) [1]. Collaborative research undertaken at the University of Bath (led by Professor Barry Potter (1990-date) with Dr LWL Woo (1996-date), and Dr NM Howarth (1991-4)) and Imperial College pioneered a novel therapeutic concept to treat postmenopausal, hormone-dependent breast cancer through inhibition of STS, and synthesis of the first highly potent inhibitors was reported in 1994 [2]. One of these compounds, *EMATE*, inhibits the target irreversibly at picomolar concentrations most probably through an electrophilic sulfonylamine generated specifically at the active site of STS. *EMATE*'s anticancer activity was demonstrated *in vivo* at Imperial College. The unprecedented aryl sulfamate pharmacophore achieved strong patent protection [3], providing a powerful competitive advantage and supporting active commercialisation. Oestrogen sulfamates bind to carbonic anhydrase in red blood cells and avoid first-pass metabolism in the liver. Thus, hepatic oestrogenicity is almost absent, avoiding the over-production of clotting factors and the associated risk of adverse events typically seen with hormone-replacement therapy (HRT) and oral contraception. The pharmacophore confers properties that are widely exploitable in drug discovery, therefore; specifically, excellent oral activity, bioavailability and pharmacokinetics.

Clinical Translation.

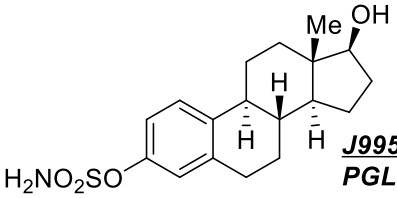
Cancer: Many hundreds of potent non-oestrogenic inhibitors of STS were also designed at Bath for applications in oncology [4], supported by Cancer Research UK. This research led to *Irosustat* (also known as *STX64*) an irreversible STS inhibitor [5] with excellent oral bioavailability and pharmacokinetics. CRUK selected *Irosustat* for the "first-in-class" Phase I/II clinical trial of an STS inhibitor in fourteen women with advanced breast cancer in London and Belfast (2003-2005); it was very well tolerated [6]. Median STS inhibition was 98% in biomarker leucocytes and 99% in target tumour tissue, showing the effectiveness of the drug, even at 5-20 mg. Strikingly, five of eight evaluable patients, whose cancer had been worsening on other therapies [including "third-generation" aromatase inhibitors], showed evidence of stable disease for up to 7 months (*British Medical Journal*; doi: 10.1136/bmj.39213.390243.801); consequently, some patients received further compassionate dosing.



EMATE



Irusostat, STX64, BN83495



J995, PGL2001

Formal academic-industry partnerships between Ipsen (a French pharmaceutical company), University of Bath and Imperial College were initiated and drug discovery efforts were greatly expanded, based upon our very substantial intellectual property. Joint research demonstrated the wider applicability of our approach to other hormone-

dependent cancers, e.g., prostate cancer [7] and endometrial cancer [8].

Other diseases: Compound *J995* (closely related to *EMATE*; also known as *PGL2001*) started HRT-related clinical trials in 1998. It has reached Phase II (six clinical trials to date) with over 170 post-menopausal women being dosed in Phase I and Phase II studies. The drug is safe and well-tolerated at all tested doses. Further research between Bath and Imperial College has also revealed that *Irosustat* has potential for treatment of endometriosis [9].

Recognition of underpinning research. To date, this project has generated more than one hundred publications in high profile medicinal chemistry and cancer journals. Potter has received several related major academic and industrial prizes. Academic and translational impact is underlined by *four* Royal Society of Chemistry (RSC) medals awarded since 2007 and the Glaxo-SmithKline (GSK) International Achievement Award for 2010, relating wholly or in part to this work. The citation for the RSC George & Christine Sosnovsky Award & Medal was *"for [Potter's] landmark contribution to the medicinal chemistry of breast cancer using a hormone-based approach and the development of the aryl sulfamate pharmacophore"*. The RSC Malcolm Campbell Memorial Prize and Medal, awarded jointly to the 4-scientist team from the Bath and Imperial College was for *"Discovery of the first steroid sulfatase inhibitors and translation into cancer patients"*. Importantly, industrial impact was recognised through the 2010 GSK International Achievement Award to Potter and Reed (IC), citing *"work that has demonstrated a substantial advancement in the application of scientific knowledge within the pharmaceutical sciences"*. Potter was denoted 2012 "Investigator of the Year" at the European Life Science Awards. He is co-inventor of *ca.* 770 patent filings worldwide derived from 46 distinct families. Of these, 430 have been formally granted, including 45 USPs, 25 EPs and 10 JPs. Illustrative examples include: US6653298, US6339079, US6676934 and US6239169.

3. References to the research

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3. Steroid Sulfatase Inhibitors. M J Reed and B V L Potter, *US Patent* 5,616,574 (1997). https://docs.google.com/viewer?url=patentimages.storage.googleapis.com/pdfs/US5616574.pdf
4. Structure-activity relationship for the first-in-class clinical steroid sulfatase inhibitor Irosustat (STX64, BN83495). L W L Woo, D Ganeshapillai, M P Thomas, O B Sutcliffe, B Malini, M F Mahon, A Purohit and B V L Potter, *ChemMedChem* (2011) **6,** 2109-2034 [*recognised as VIP paper with journal front cover feature*]. DOI: 10.1002/cmdc.201100288
5. Potent active site-directed inhibition of steroid sulphatase by tricyclic coumarin-based sulphamates. L W L Woo, A Purohit, B Malini, M J Reed and B V L Potter, *Chem. & Biol.* (2000) **7**, 773-791. DOI: 10.1016/S1074-5521(00)00023-5
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9. Inhibition of steroid sulphatase activity in endometriotic implants by 667 COUMATE: a potential new therapy. A Purohit, L Fusi, J Brosens, D Parish, M S Fernandes, L W L Woo, B V L Potter and M J Reed. *Human Reproduction* (2008) **23**, 290-297. DOI: 10.1093/humrep/dem308

4. Details of the impact

Economic underpinning that has enabled clinical impact since 2008: Initial clinical translation and £1.8M revenue was achieved through a licence to a major international pharmaceutical company for *EMATE* as a synthetic liver-sparing oestrogen, the first since ethinylestradiol (first marketed in 1938) suitable for oral dosing. This licence funded, in 1998, incorporation of the Bath-Imperial spin-out, Sterix. Intellectual property was vested with Sterix from which large development contracts to both universities [*ca.* £12M to Bath (1998-2010)] facilitated R&D activity that led to *Irosustat*. Sterix attracted £8M of venture capital in 2001 to support the initial clinical trial of this drug. Then, in 2004, Sterix was acquired by the French pharmaceutical company, Ipsen, which provided substantial research funding to both universities [£8.3M to Bath] and initiated wider clinical trials. Revenue for *J995* from initial licensing and milestones from 1998 through to 2003/4 in Europe amounted to £4.2M and a Japanese licence of £1.34M was also secured during 2002-2003 [Sterix Ltd, Annual Accounts, Companies House]. Sterix employed up to 40 research staff, directly or indirectly, and returned ~£28M to the UK university sector in direct research contracts.

Overview: Successful drug discovery in academia is a very rare event and clinical translation is even rarer. The validation of new drug targets, the synthesis of "first-in-class" drugs to address them, and their clinical translation into humans reflects extraordinary impact by any measure. Moreover, this success has been achieved twice, dosing hundreds of healthy women volunteers as well as cancer patients with drugs first designed at Bath. Overall, this research has had impact for industry, the economy, clinical practitioners and, most importantly, patients. There is also potential for further benefit deriving from ongoing clinical trials. The work has facilitated the design of compounds with highly desirable pharmaceutical properties and has defined novel therapies with indicative clinical proof of benefits to patients primarily in hormone-dependent cancers.

Breast cancer: The first clinical trial (2003-05) of *Irosustat* demonstrated encouragingly positive effects in breast cancer patients and, after the acquisition of Sterix, Ipsen continued development of both *Irosustat* [*STX64*, *BN83495*] and *J995* [*PGL2001*] in concert with the two universities. Ipsen refined the pre-clinical package for *Irosustat* to full industrial standard. New international clinical trials have commenced since 2008 for *Irosustat* in breast cancer [1], prostate cancer and endometrial cancer [2], initiated by Ipsen. Concomitantly, Ipsen published in late 2009 [1] the clinical observation of stable disease in a new cohort of thirty-five oestrogen receptor-positive metastatic breast cancer patients, after dose optimisation [3]. Importantly, in this trial, the disease of one patient was stable for thirteen months, one for eight months, one for seven months and three for *ca*. six months. Biopsy-validated erythematous skin infiltration in one patient was no longer visible after one month of treatment. Nearly complete inhibition of the target enzyme was observed at all doses. Significantly, the Director of the Imperial CRUK Cancer Centre, the clinician who led the study, said of the effects on patients: *"To date, four of the patients who received Irosustat [BN83495] had tumours that remained stable for at least 6 months. One of these had cutaneous metastases that improved after one month of treatment. This is very encouraging, as these women are patients who are reaching the end of their hormonal treatment options. Importantly, Irosustat [BN83495] was well tolerated at the selected dose."* He added: *"I am confident that Irosustat [BN83495] will become a new hormonal option in the treatment of post-menopausal women with oestrogen receptor-positive metastatic breast cancer"* [3].

Further impact is illustrated by the formal use of this work (published in *The Oncologist,* a journal for practising clinical oncologists,) in a Continuing Medical Education (CME) programme for "physicians who wish to advance their current knowledge of clinical cancer medicine in breast cancer and are involved in providing patient care in a cancer care environment" [4]. Finally, overseen and substantially funded by CRUK, two further clinical trials with *Irosustat* were initiated in 2012; these trials aim to explore the benefit of combination dosing with an aromatase inhibitor and also to examine the effects of *Irosustat* in breast cancer patients using PET scanning [5,6].

Other cancers: Drug discovery research at Bath has also provided the stimulus for active clinical trials against other cancers: androgen-dependent prostate cancer and endometrial cancer *inter alia*. Prostate cancer represents a large unmet medical need and a Phase I/II clinical study [17 patients] of *Irosustat* commenced in 2008 at three centres in the USA (Johns Hopkins, Duke and Wisconsin), evaluating the pharmacodynamics and safety of the drug in metastatic prostate cancer patients [7]. A Phase II clinical programme comparing *Irosustat* and megestrol acetate in recurrent or metastatic advanced post-menopausal endometrial cancer patients at 44 separate centres

worldwide started in 2009. Results to-date have shown *inter alia* significant stable disease (47%) and an advantageous safety profile for *Irosustat* [8].

Endometriosis: Since 2008, clinical trials have also taken place in endometriosis through PregLem (Switzerland) and Gedeon Richter (Hungary). Ipsen spun out PregLem in 2007 with one of its two main clinical assets being *J995* [*PGL2001*], licensed outside oncological indications. Endometriosis is a benign gynaecological disease characterised by the presence of endometrial tissue outside the uterus, leading to chronic pelvic pain and infertility. In addition to production of oestrogens in the ovaries, there is compelling evidence that local synthesis of oestrogens in endometriotic lesions promotes progression of the disease and resistance to endocrine therapy. With an estimated 80M patients worldwide, the disease is still poorly understood, most treatments have unpleasant side-effects and current therapies are grossly inadequate. *J995* [*PGL2001*], is *en route* to be the first of a new class of treatment for endometriosis and other benign gynaecological conditions, and entered clinical trials in Germany in 2008 in healthy pre-menopausal women [9] to advance this compound towards a novel, once-a-week, oral medication. *J995* [*PGL2001*] was part of the clinical assets of PregLem, acquired by the Hungarian drug company Gedeon Richter in 2010 in a deal valued at *ca*. €337M [10]. The drug continues in clinical trials against endometriosis and multicentre Phase IIa studies to investigate its efficacy, safety, pharmacokinetics and pharmacodynamics started in Hungary, Poland and Romania in 2012 [11].

5. Sources to corroborate the impact

1. Ipsen clinical trial results published at the AACR San Antonio Breast Cancer Conference 2009: A Phase I Dose Escalation Study of Steroid Sulfatase Inhibitor BN83495/STX64 in Postmenopausal Women with ER Positive Breast Cancer: R Coombes, *et al.*, Cancer Res. 2009, 69 (suppl. 24), 4097. http://cancerres.aacrjournals.org/cgi/content/abstract/69/24_MeetingAbstracts/4097
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3. Ipsen establishes optimal biological dose for BN83495 steroid sulphatase (STS) inhibitor in oestrogen receptor-positive metastatic breast cancer. http://www.ipsen.com/wp-content/uploads/2013/03/PR-BN83495-Breast-cancer-Phase-I-EN-FINAL.pdf
4. Work used for Continuing Medical Education (CME) programme during 2008 in major clinical translational oncology journal: Steroid sulfatase: a new target for the endocrine therapy of breast cancer. SJ Stanway, *et al.*, The Oncologist (2007) 12, 370-374. http://theoncologist.alphamedpress.org/content/12/4/370.full.pdf+html
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6. The IPET trial, in which the effects of Irosustat on breast cancer will be evaluated by Positron Emission Tomography scanning: http://clinicaltrials.gov/show/NCT01662726
7. BN83495 in Prostate Cancer (STX64PC): http://clinicaltrials.gov/show/NCT00790374
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