Institution: University of Aberdeen

Unit of Assessment: 5 - Biological Sciences

Title of case study: Discovery and commercialisation of new drug for rheumatoid arthritis and related conditions

1. Summary of the impact

The University of Aberdeen's discovery of a novel drug for the treatment of rheumatoid arthritis and related inflammatory/autoimmune disorders has brought substantial industrial investment in research and development. The new drug is expected to enter clinical trials shortly and has the potential to transform the way rheumatoid arthritis is currently treated, as few patients currently have access to the expensive biological agents which dominate existing therapy. Aberdeen has commercialised its research into a university spin-out company and subsequently licensed the programme to a UK drug-development company, Modern Biosciences plc. The research has created and protected UK expertise and jobs.

The specific impacts on commerce have been: substantial industrial investment in research and development, job creation and protection within UK industry, commercialisation of a new product via a licencing deal, and academic consultancy in industry.

2. Underpinning research

Rheumatoid Arthritis (RA) is a chronic, progressive and disabling condition affecting 165 million people worldwide. Along with other common immune disorders such as psoriasis and inflammatory bowel disease, RA has proved difficult to treat because of the high cost of available therapies, to which more than 80 per cent of patients are not given access.

Research carried out at the University of Aberdeen has provided evidence that small-molecule drugs may be just as effective as expensive biological agents in treating autoimmune disease. The research grew out of work begun in 1999, sponsored by the company Nicox on their drug HCT1026 (a nitric oxide-generating derivative of an anti-inflammatory drug related to ibuprofen) developed to treat pain associated with osteoarthritis, without causing stomach ulcers. This was a natural area for Aberdeen to explore as it is a recognized world-leader in bone and musculoskeletal research. Observations suggested that the drug in question also prevented bone loss. Dr Iain Greig, Senior Research Fellow at Aberdeen's Institute of Medical Sciences and now Head of Operations at the Kosterlitz Centre for Therapeutics there, joined the University in 1998 and became involved in this research in 2000 when it was clear there was substantial crossover with Aberdeen's bone research. The medicinal chemistry Greig provided helped lead to the discovery of a number of highly potent novel compounds that had therapeutic potential for the prevention of bone loss [1 to 3] and [b].

As part of a project team that also included Professor Stuart Ralston and Dr Rob van't Hof - both of whom moved to Edinburgh University in 2005 - Greig embarked on a drug development programme aimed at taking these compounds into the clinic for the treatment of osteoporosis. Fundamental studies on the mode of action of these compounds led to the discovery that the drugs acted at a point shared between the pathways involved in activating the cells that cause bone loss and the activation of the immune system found in rheumatoid arthritis. The team then re-focused their efforts in this direction, generating compounds, biphenylketones [4, 5] and [c, e, i] and biphenylsulfonamides [3] and [d], which act by a novel mechanism, targeting a previously unexplored factor in the signalling pathway that regulates immune cells [4]. Precise details have not been revealed because of commercial sensitivities surrounding what would be a first-in-class drug. A further series of compounds, triarylsulfonamides [6] [f], were developed which met the stringent requirements of the pharmaceutical industry prior to licensing.

Greig and the University of Aberdeen created the spin-out company OsteoRx Ltd and licensed these compounds to Modern Biosciences, which embarked on a development programme in 2008. Under this licence agreement, Greig initially continued to provide medicinal chemistry support at Aberdeen. Utilizing the expertise and insight he had built up during many years of working on the

project, he discovered two further compound classes whilst trying to resolve a potential toxicological liability and a metabolic liability. Both liabilities were successfully replaced with other chemical moieties. The medicinal chemistry was then transferred to a number of providers, mostly conducted by a UK company, Peakdale Molecular, with guidance from Greig.

3. References to the research

[1] van 't Hof RJ, Idris AI, Ridge SA, Dunford J, Greig IR and Ralston SH (2004). Identification of biphenylcarboxylic acid derivatives as a novel class of bone resorption inhibitors. *J. Bone Miner. Res.*, 19, 1651-1660. *Paper detailing the discovery of an entirely new class of therapeutic agents against a novel biological target, and demonstration of anti-resorptive properties in a model for post-menopausal bone loss.*

[2] Idris AI, van 't Hof RJ, Greig IR, Ridge SA, Ross RA, Ralston SH. (2005). Regulation of bone mass, bone loss and osteoclast activity by the cannabinoid CB1 receptor. *Nat. Med.*, 11, 774-779. *Highly cited paper (146 citations) showing the first evidence of a role for the cannabinoid system in regulation of bone metabolism, and potential for targeting this in the treatment of osteoporosis.*

[3] Greig IR, Idris AI, Ralston SH and van 't Hof RJ. (2006). Development and characterization of biphenyl sulfonamides as novel inhibitors of bone resorption. *J. Med. Chem.*, 49, 6487-7492. *Paper showing the development, quantitative structure activity relationship (SAR: a highly-accurate mathematical model for predicting potency) and anti-resorptive properties of the first highly potent and metabolically-stable compounds against the target described in ref 1.*

[4] Idris AI, Greig IR, Bassonga-Landao E, Ralston SH and van 't Hof RJ. (2009). Identification of novel biphenyl carboxylic acid derivatives as novel antiresorptive agents which do not impair PTH induced bone formation. *Endocrinology*, 150, 5-13. *Paper demonstrating that these compounds not only prevented bone loss, but that the effect was additive with agents encouraging bone gain, giving additional increases in bone density over that possible with existing agents.*

[5] Greig IR, Coste E, Ralston SH and van 't Hof RJ. (2010). Discovery of biphenylketones as dual modulators of inflammation and bone loss. *Bioorg. Med. Chem. Lett.*, 20, 5548-5551. *Paper showing the development, SAR, anti-inflammatory and anti-resorptive properties (in models for rheumatoid arthritis and post-menopausal bone loss) of the first small molecule compounds with the potential to treat both rheumatoid arthritis and associated bone loss.*

[6] Greig IR, Coste E, Ralston SH and van 't Hof RJ (2013). Development of triarylsulfonamides as novel anti-inflammatory agents. *Bioorg. Med. Chem. Lett.*, 23, 816–820. *Paper showing the development, structure activity relationship (SAR) and anti-inflammatory properties (in a model for rheumatoid arthritis) of the compounds which facilitated commercialisation and were taken forward into pre-clinical development.*

Key grant funding associated with the research

- *Technology Strategy Board, Biomedical Catalyst* (2012-2015), Modern Biosciences, £1,562,595, matched with approximately £1,200,000 from IP Group plc [a]
- *Modern Biosciences: Novel Anti-inflammatory agents*, Greig IR, (2007-2011), direct income £54,130, total investment in project to date >£2 million, (outsourced in vivo studies, pharmacokinetics, synthetic chemistry and patent fees; not including other costs such as company overhead costs of £500k pa, a major proportion of which can be attributed to this programme)
- *NESTech (Scottish Universities Challenge Fund)*: Novel Bone Resorption Inhibitors; Greig IR and E. Rattray, (2006-2008), £198,768
- *Arthritis Research Campaign*: Small molecule inhibitors of TNF signalling as novel anti-

rheumatic agents; van 't Hof RJ, Ralston SH, Greig IR and Idris AI, (2005-2007), £98,48

- *Scottish Enterprise, Proof of Concept,RSE Enterprise Fellowship (Greig) and Proof of Concept Follow on*: Novel Bone Resorption Inhibitors, Greig IR, van 't Hof RJ, Ralston SH and E. Rattray, (2002-2006), £285,869

4. Details of the impact

The research at the University of Aberdeen has given the pharmaceutical industry a new paradigm for the treatment of rheumatoid arthritis and other inflammatory / autoimmune disorders. The research identified a completely novel mechanism of action and biological target for the treatment of RA, which is now being translated into the next generation of drugs for fighting the disease. Compounds being taken forward to clinical trials were designed and synthesised at Aberdeen, which has received commercial investment in further research and development via a spin-out company and a licensing deal. UK jobs have been created and protected, and academics with the relevant expertise have taken on new consultative roles in industry.

A licensing and co-development deal was reached in 2007 with Modern Biosciences [a], a drug development company which sources late-stage discovery projects from academia and start-up companies, conducts early proof-of-principle clinical studies and out-licenses the resulting programmes to the pharmaceutical and biotechnology industries. The deal has brought potential investment into the research of nearly £5 million, which will take the programme to a point of filing an Investigational New Drug application, after which additional funds will be sought to take a candidate drug into Phase 1 and 2a studies, designed to prove safety and preliminary efficacy. These trials are expected to begin within a year, but tangible patient benefits may still be several years away. Precedent deal values for products at a similar stage of development (Phase 2a) have reached as much as $600 million and the market worth for this product is estimated at over £5 billion [a]. Of course, the uncertainty of the market for new pharmaceutical products means that it is difficult to make precise predictions about either the financial returns or the likely timescale of commercial exploitation.

The funding the research has attracted includes over £2 million from Modern Biosciences for the programme itself, with a further £1.6 million from the government-backed Biomedical Catalyst award [a], which was launched in 2011 with the aim of boosting growth in the UK life sciences sector. This award is to be matched by IP Group plc, a UK intellectual property company which aims to develop technology innovations in partnership with university research departments and which is MBS' lead investor. Separately, the research brought in direct grant funding of £600,000 to Aberdeen University, enabling further drug discovery projects.

In terms of jobs created, this has meant six full-time posts, and a further four expected over the next two years, at a UK medicinal chemistry contract research organisation, Peakdale Molecular [a]. It is particularly encouraging that such expertise has been protected from the general trend towards outsourcing work to lower cost overseas organisations. Greig was taken on as an intellectual property consultant by Modern Biosciences, a role which involved writing patents. He has continued to write [g - i] and manage a portfolio of 8 published patents [b - i], of which all have been granted, and two further recent filings. Greig was also taken on as a medicinal chemistry consultant by Modern Biosciences, initially providing hands-on synthesis at Aberdeen (most of [g] and much of [h]) and then more recently advising on drug design, with synthesis conducted by contract research organizations [a].

Commercial sensitivities on the part of Aberdeen's industry partners have precluded media or other public engagement about the potential patient benefits of the research.

Claimed impact as defined by REF: Industry has invested in research and development; a new product has been commercialised by the University of Aberdeen, via spin-out and a licensing deal; UK jobs have been created and protected; skilled people have taken up a specialist role (via academic consultancy) in industry; and a new process (in terms of a new paradigm for the treatment of rheumatoid arthritis) has been taken up by industry.

5. Sources to corroborate the impact

[a] Testimonial from Chief Executive Officer at Modern Biosciences. This describes the importance of research performed at Aberdeen for project development, investment and number of jobs created.

Details of the TSB Grant can be found at the following site, searching under "101365": https://www.innovateuk.org/projects;jsessionid=3402EEAAC60707FC2AA606D42132AD19.1

[b] Ralston SH, Greig IR, van 't Hof RJ and Armour KJ. Alkane diol derivatives as therapeutic agents for the treatment of bone conditions. Patent: WO03/037321 (2001). Granted US 29-06-10. Covers compounds shown in [1].

[c] Ralston SH, Greig IR, Mohamed AI and van 't Hof RJ. Ketones and reduced ketones as therapeutic agents for the treatment of bone conditions. Patent: WO2004/098582 (2003). Granted US 11-08-09. Covers compounds shown in [4 and 5].

[d] Ralston SH, Greig IR, Mohamed AI and van 't Hof RJ. Alkyl aryl sulfonamides as therapeutic agents for the treatment of bone conditions. Patent: WO2005118528 (2004). Granted US 21-06-09. Covers the compounds described in [3].

[e] Greig IR, Ralston SH and van 't Hof RJ. 2',4'-Dichloro-biphenyl-4-yl-hydroxy-ketones and related compounds and their use as therapeutic agents. Patent US2008221220 (2007). Granted 14-07-09. Covers a small subset of compounds shown in [5]

[f] Greig IR, Ralston SH and van 't Hof RJ. Biphenyl-4-yl-sulfonic acid arylamides and their use as therapeutic agents. Patent WO2008/114022 (2007). Granted US 03-09-13. Covers compounds shown in [6].

[g] Greig IR, Clase JA, Fisher R, Sheridan RM, Smith A, Tozer MJ and Tuffnell AR and van 't Hof RJ. Aryl-phenyl-sulfonamide-cycloalkyl compounds and their use, Patent: WO2010/032009 (2008). Granted 07-05-13. Covers compounds being taken forward into clinical trials.

[h] Greig IR, Clase JA, Fisher R, Sheridan RM, Smith A, Tozer MJ, Tuffnell AR and van 't Hof RJ. Aryl-phenyl-sulfonamide-phenylene compounds and their use. Patent: WO2010/032010 (2008). Granted 26-06-12. Covers compounds currently being developed as backups.

[i] Ralston SH, Greig IR, Mohamed AI and van 't Hof RJ. Ketones and reduced ketones as therapeutic agents for the treatment of bone conditions. US Divisional: US7598289 (2009). Granted 06-10-09. Covers the use of compounds shown in [5].

The above patent references are given to corroborate the impact. For simplicity, only dates of US grants are given as examples. Details of other territories in which these are being prosecuted, including European States and Japan, can be found on the European Patent Office website (http://worldwide.espacenet.com/). The costs associated with filing and prosecuting patent applications can only be borne where there is substantial value in the project; to have a portfolio of 8 international patents is a very significant financial commitment. All of the patent applications have been granted or allowed, demonstrating that the research had novelty, utility and inventive step.