Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Development of Novel Therapies to Treat Severe Airway Disease

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

Research undertaken within Imperial College showed that corticosteroid resistance in inflammatory diseases, such as chronic obstructive pulmonary disease (COPD) and severe asthma, is explained by reduced histone deacetylase-2 and that reversal of this resistance is possible with theophylline (in low clinical doses) and PI3Kδ inhibitors, which restore HDAC2 function. This led to the founding of a spin-out company RespiVert to develop potent inhaled inhibitors of PI3Kδ. The company has been very successful in finding such new molecules, which have proven to be safe in Phase I studies. RespiVert was acquired by Johnson & Johnson in 2010 and Phase II studies are now in progress in COPD and severe asthma.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Peter Barnes, Margaret Turner Warwick Chair (1985-present)
Dr Kazuhiro Ito, Reader (2002-2007), Honorary Senior Research Fellow (2007-present)
Professor Ian Adcock, Professor of Respiratory Cell and Molecular Biology (1990-present)

Corticosteroids are the most effective and widely used anti-inflammatory treatments in the world and are invaluable in the management of asthma and other inflammatory and immune diseases. However, some inflammatory diseases are poorly controlled even by high doses of corticosteroids. This corticosteroid resistance is a major barrier to the effective treatment of many important chronic inflammatory diseases, including COPD, severe asthma and cystic fibrosis.

In the late 1990s, a research team of Imperial College, led by Professor Barnes FRS, Dr Ito and Professor Adcock identified a key molecular mechanism by which corticosteroids suppress inflammation through the recruitment of a nuclear enzyme histone deacetylase-2 (HDAC2) (1). In patients with COPD or severe asthma and asthmatics who smoke, HDAC2 is markedly reduced so that corticosteroids are unable to suppress activated inflammatory genes resulting in amplification of inflammation and steroid resistance (2, 3).

The Imperial team have shown that oxidative stress and cigarette smoke inactivate HDAC2 by activating the enzyme phopshoinosiotide-3-kinase-δ (PI3Kδ) (4). They discovered that low concentrations of theophylline (a drug commonly used to treat asthma) restore HDAC2, reduced by oxidative stress, to normal and thus reverse corticosteroid resistance *in vitro*, *in vivo* in smoke-exposed mice and in COPD patients in a pilot clinical study (4, 5, 6). They have shown that theophylline restores HDAC2 by selectively inhibiting PI3Kδ (4) and this effect is mimicked by the use of a selective PI3Kδ inhibitor (IC87114) and by switching off the PI3Kδ gene in mice. These effects are also mimicked by: i) the antidepressant, nortriptyline, which they found also selectively inhibits PI3Kδ; ii) the antioxidant, sulforaphane, which counteracts the oxidative stress driving corticosteroid resistance and; iii) a group of drugs known as macrolides, which also increase HDAC2 gene expression (so may be synergistic with theophylline).

These studies led to the setting up of a spinout company in 2006 at Imperial College called RespiVert. The founders were Professor Barnes, Dr Ito from Imperial College, together with Dr Rapeport and Dr Strong previously working in respiratory research at GlaxoSmithKline (GSK). Venture capital funding was obtained amounting to £13 million, together with a contribution of £2m from Imperial Innovations. The remit of this company was to focus on highly potent inhaled anti-inflammatory treatments that would be effective in corticosteroid-resistant inflammation and based on the previous Imperial research on mechanisms of corticosteroid resistance.

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

(1) Ito, K., Barnes, P.J., Adcock, I.M. (2000). Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits IL-1β-induced histone H4 acetylation on lysines 8 and 12. *Mol Cell Biol*, 20 (18), 6891-903. DOI. Times cited: 381 (as at 4th November 2013 from ISI Web of Science). Journal Impact Factor: 5.37

(2) Ito, K., Ito, M., Elliott, W.M., Cosio, B., Caramori, G., Kon, O.M., Barczyk, A., Hayashi, S., Adcock, I.M., Hogg, J.C., Barnes, P.J. (2005). Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *New Engl J Med,* 352 (19), 1967-76. DOI. Times cited: 368 (as at 4th November 2013 from ISI Web of Science). Journal Impact Factor: 51.65

(3) Ito, K., Yamamura, S., Essilfie-Quaye, S., Cosio, B., Ito, M., Barnes, P.J., Adcock, I.M. (2006). Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF-κB suppression*. J Exp Med,* 203 (1), 7-13. DOI. Times cited: 228 (as at 4th November 2013 from ISI Web of Science). Journal Impact Factor: 13.21

(4) To, Y., Ito, K., Kizawa, Y., Failla, M., Ito, M., Kusama, T., Elliott, W.M., Hogg, J.C., Adcock, I.M., Barnes, P.J. (2010). Targeting phosphoinositide-3-kinase-δ with theophylline reverses corticosteroid insensitivity in COPD. *Am J Resp Crit Care Med,* 182 (7), 897-904.DOI. Times cited: 58 (as at 4th November 2013 from ISI Web of Science). Journal Impact Factor: 11.04

(5) Ito, K., Lim, S., Caramori, G., Cosio, B., Chung, K.F., Adcock, I.M., Barnes, P.J. (2002). A molecular mechanism of action of theophylline: Induction of histone deacetylase activity to decrease inflammatory gene expression. *PNAS*, 99 (13), 8921-6. DOI. Times cited: 210 (as at 4th November 2013 from ISI Web of Science). Journal Impact Factor: 9.73

(6) Cosio, B.G., Tsaprouni, L., Ito, K., Jazrawi, E., Adcock, I.M., Barnes, P.J. (2004). Theophylline restores histone deacetylase activity and steroid responses in COPD macrophages. *J Exp Med*, 200 (5), 689-95. DOI. Times cited: 185 (as at 4th November 2013 from ISI Web of Science). Journal Impact Factor: 13.21

Key funding:

- Wellcome Trust (2005-2010; £796,000), Principal Investigator (PI) P. Barnes, Role of histone deacetylase-2 in the regulation of inflammation and corticosteroid sensitivity in chronic obstructive pulmonary disease.
- Medical Research Council (MRC; 2005-2008; £284,000), PI P. Barnes, Glucocorticoid receptor acetylation and steroid resistance in COPD.
- Asthma UK (2004-2007; £120,000), PI P. Barnes, Inactivation of histone deacetylase-2: a mechanism of steroid resistance in smoking asthmatics.
- MRC (2006-2009; £494,000), PI P. Barnes, Reversal of corticosteroid insensitivity by theophylline.

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

Impacts include: commercial
Main beneficiaries include: industry

RespiVert has identified a range of novel small molecule inhibitors of the key signal transduction pathways responsible for progressive airways inflammation. The initial work from Imperial was expanded by RespiVert from 2007-2010 which resulted in the identification of a completely new class of treatments for severe lung diseases called Narrow Spectrum Kinase (NSKI) inhibitors. RespiVert provided over 10 posts for highly skilled scientists during this time.

Acquisition of RespiVert by Johnson & Johnson
In June 2010, RespiVert was acquired by Centocor Ortho Biotech (now Janssen Biotech), a wholly owned subsidiary of Johnson & Johnson for approximately $110 million. Imperial Innovations held 13.4% of RespiVert and the return of £9.5 million gross cash represented a 4.7x return on its three-year investment. After revenue-sharing payments of £0.2 million to Imperial, the disposal generated a profit of £7.2 million [1].

RespiVert has developed a number of Narrow Spectrum Kinase (NSKI) and PI3 kinase (PI3K) γδ inhibitors as first in class new treatments for COPD and severe asthma using inhaled delivery. The lead compound RV568 has been tested in four clinical studies and early evidence in a COPD biomarker study has delivered extremely promising data [2]. RV568 has now entered a Phase II multinational clinical trial for COPD. RespiVert filed several patents for compounds in its NSKI programme that describe newly identified modes of action for the treatment of COPD and steroid intensive inflammation during 2010-2012 [3-4].

RespiVert have also developed PI3 kinase compounds which are a new set of γ/δ isoform inhibitors for inhaled delivery that were derived from research on theophylline and PI3δ carried out by Professor Barnes and Dr Ito at Imperial [5]. This has led to the development of RV1729, a unique, first in class, inhaled dual isoform inhibitor that offers distinct options for the treatment of steroid refractory asthma and COPD. This compound has undergone single and multiple dose Phase I testing in normal volunteers in 2013 and has now entered Phase II testing in severe asthma and COPD patients.

The NSKI inhibitors developed by RespiVert have now been licenced to another start-up company, TopiVert in 2012 by Drs Rapeport and Ito, with a successful funding round of £8 million to develop topical medicines for inflammatory diseases of the eye and gut [6].

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

[1] Acquisition of RespiVert by Johnson and Johnson Centocor:
http://www.imperialinnovations.co.uk/ventures/exited/respivert (archived on 26th November 2013)
http://www.imperialinnovations.co.uk/news-centre/news/innovations-realises-95m-cash-sale-portfolio-compa/ (archived on 26th November 2013). This can also be corroborated by the Global Head of the Therapeutic Area Immunology for Centocor Research and Development Co, a division of Johnson & Johnson Pharmaceutical Research and Development LLC.

[2] Details of clinical trials involving RV568. Archived on 26th November 2013.

[3] US Patents: P38 MAP Kinase inhibitors (8,299,074 - archived), (8,299,073 - archived), (8,293,771 - archived), (8,293,748 - archived). All archived on 26th November 2013.

[4] WIPO Patents: WO/2011/158042 (archived), WO/2011/158039 (archived), WO/2011/121366 (archived). All archived on 26th November 2013.

[5] PI3K inhibitor compound patent: WO/2011/048111. Archived on 26th November 2013.

[6] Topivert successful funding press release:
http://www.imperialinnovations.co.uk/news-centre/news/8-million-funding-new-start-topivert/. Archived on 26th November 2013.