Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Development of Long-Acting Anticholinergics (e.g. tiotropium bromide) for the Treatment of Chronic Obstructive Pulmonary Disease

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

Imperial College preclinical studies guided the desired selectivity profile for long-acting muscarinic receptor antagonists (LAMA). Binding, functional and clinical studies from Imperial laboratories were the first to demonstrate the long duration of tiotropium bromide (Spiriva®) in human tissue, and confirmed its long duration of action in patients and established it as the first-line treatment for chronic obstructive pulmonary disease (COPD). Tiotropium has had a beneficial impact on the management of COPD and is incorporated into the major international treatment guidelines. It improves symptoms, reduces exacerbations and mortality, and provides a cost-effective therapy. Imperial have also produced the first pre-clinical and clinical data for the next LAMA in development (glycopyrrolate, Seebri®), which has recently been marketed. Our profiling of tiotropium has also led to the development of several novel LAMA.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Peter Barnes, Margaret Turner-Warwick Chair (1985-present)
Professor Maria Belvisi, Professor of Respiratory Pharmacology (1997-present)
Dr Hema Patel, Research Fellow (1992-2007)
Dr Brian O'Connor, Senior Clinical Lecturer (1992-1997)
Dr Trevor Hansel, Reader in Respiratory Clinical Pharmacology (1997-present)

Between 1993-1995, research in Imperial laboratories described for the first time the presence of auto-inhibitory, muscarinic receptors of the M_2 subtype on parasympathetic, cholinergic nerve terminals in human airways (1). The group demonstrated that blocking this receptor with the then existing non-selective anticholinergic drugs (e.g. ipratropium) increased acetylcholine release at the nerve ending potentially limiting the effectiveness of these drugs as bronchodilators (through blockade of M_3-receptors on airway smooth muscle) and thus their utility in the treatment of COPD. This selectivity and kinetic profile (increasing selectivity of compounds for M_3 over the M_2 receptor) developed by the Imperial team has been incorporated into the design of all subsequent LAMA.

Cholinergic tone appears to be the only reversible component of COPD. With the discovery of different muscarinic receptor subtypes (1), the development of more selective anticholinergics became possible. A limitation of the then existing drugs was their short duration of action. In collaboration with Boehringer Ingelheim from 1993, Imperial provided key, ground-breaking data sets demonstrating the kinetic selectivity of tiotropium bromide for M_3-receptors as well as a duration of action of >24 hours in human lung binding and functional and clinical studies (2-3). These were the first publications of the pharmacology of tiotropium in human airways.

Professor Barnes and colleagues demonstrated the long duration of action of tiotropium in human and guinea-pig airways using electrical stimulation to stimulate cholinergic nerves in a robust assay subsequently used to confirm long duration of other LAMA. In one of the first human proof-of-concept studies using LAMA's they confirmed the attributes of tiotropium to the collaborative partners Boehringer Ingelheim who were uncertain about its value. This work formed the basis of the clinical development programme for tiotropium which would not have proceeded without this contribution (4). The prolonged bronchodilator response and protection against methacholine challenge suggested that tiotropium would be useful for the treatment of COPD and nocturnal asthma and that once-daily dosing may be sufficient (4). It is now accepted that once-daily administration of tiotropium is well tolerated and has shown significant advantages over ipratropium bromide given four times daily, in the management of COPD.

Imperial studies, conducted between 1995-1999, evaluated the pharmacological profile of an old muscarinic antagonist, glycopyrrolate (previously used by injection in anaesthesia to dry salivary secretions). In guinea-pig and human airways the group were the first to demonstrate that glycopyrrolate had both high affinity for and slow dissociation from M_3-receptors in a similar manner to tiotropium, predicting that it could also be a once daily bronchodilator in COPD patients (5). We then showed that inhaled glycopyrrolate had a prolonged bronchodilator response and protection against methacholine-induced bronchoconstriction that was superior to ipratropium bromide and similar to tiotropium (6). Following this publication, glycopyrrolate (now off patent) was developed in an inhaled formulation by Vectura who subsequently sold it to Novartis for large scale clinical development. Several other LAMA and also combination inhalers of LAMA with long acting β_2-adrenoceptor agonists (LABA) are also in advanced clinical development (see below).

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

(1) Patel, H.J., Barnes, P.J., Takahashi, T., Tadjkarimi, S., Yacoub, M.H., Belvisi, M.G. (1995). Evidence for prejunctional muscarinic autoreceptors in human and guinea-pig trachea. *Am. Journal Respir. Crit. Care Med.*, 152 (3), 872 - 878. DOI. Times cited: 70 (as at 6th November 2013 from ISI Web of Science). Journal Impact Factor: 11.04.

(2) Takahashi, T., Belvisi, M.G., Patel, H.J., Ward, J.K., Tadjkarimi, S., Yacoub, M.H., Barnes, P.J. (1994). Effect of Ba679 BR, a novel long-acting anticholinergic agent, on cholinergic neurotransmission in guinea-pig and human airways. *Am. J. Respir. Crit. Care Med*., 150 (6), 1640-1645. DOI. Times cited: 60 (as at 6th November 2013 from ISI Web of Science). Journal Impact Factor: 11.04.

(3) Haddad, E.B., Mak, J.C., Barnes P.J. (1994). Characterization of [^{3}H]Ba 679 BR, a slowly dissociating muscarinic antagonist, in human lung: radioligand binding and autoradiographic mapping. *Mol Pharmacol,* 45 (5), 899-907. DOI. Times cited: 63 (as at 6th November 2013 from ISI Web of Science). Journal Impact Factor: 4.41.

(4) O'Connor, B.J., Towse, L.J., Barnes, P.J. (1996). Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. *Am J Respir Crit Care Med*, 154 (4), 876-880. DOI. Times cited: 69 (as at 6th November 2013 from ISI Web of Science). Journal Impact Factor: 11.04.

(5) Haddad, E.B., Patel, H.J., Keeling, J.E., Yacoub, M.H., Barnes, P.J., Belvisi, M.G. (1999). Pharmacological characterisation of the muscarinic receptor antagonist, glycopyrrolate, in human and guinea-pig airways. *Br. J. Pharmacol*.; 127 (2), 413 - 420. DOI. Times cited: 28 (as at 6th November 2013 from ISI Web of Science). Journal Impact Factor: 5.06.

(6) Hansel, T.T., Neighbour, H., Erin, E.M., Tan, A.J., Tennant, R., Maus, J.G., Barnes, P.J. (2005) Glycopyrrolate causes prolonged bronchoprotection and bronchodilatation in patients with asthma. *Chest*; 128 (4), 1974-1979. DOI. Times cited: 25 (as at 6th November 2013 from ISI Web of Science). Journal Impact Factor: 5.85.

Key funding:

- National Asthma Campaign (NAC; 1991-1994; £91,478), Principal Investigator (PI) M. Belvisi, Modulation of neurotransmitter release in human and guinea-pig airways.
- NAC (1993-1996; £91,836), PI M. Belvisi, Modulation of neurotransmitter release from cholinergic and excitatory non-adrenergic non-cholinergic nerves in human and guinea-pig airways by second messengers.
- Medical Research Council (MRC; 1993-1996; £186,000), PI P. Barnes, Muscarinic receptor subtypes in human airways.
- Boehringer Ingelheim (1994-1995; £120,000), PI P. Barnes, Duration of action of Ba679BR in patients using methacholine challenge.
- Muro Pharmaceuticals (1995-1996; £52,894), PI M. Belvisi, Investigate that selectivity and potency of the muscarinic receptor antagonist glycopyrrolate.
- Muro Pharmaceuticals (2003-2004; £110,000), PI P. Barnes, Duration of action of nebulised glycopyrrolate in human volunteers.

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

Impacts include: health and welfare, public policy and services, practitioners and services, commercial
Main beneficiaries include: patients, industry, NICE, Global Initiative for Chronic Obstructive Lung Disease (GOLD)

The research described played a major and critical role in the early development of tiotropium by Boehringer Ingelheim and is now the first-line therapy for COPD [1]. Tiotropium is the preferred initial treatment for patients with COPD, as recommended in the major guidelines for COPD management, including the most widely used global evidence-based guidelines (GOLD 2013)[2], and the NICE UK guidelines (2010) [3].

The NICE guidelines specify that tiotropium is the only once daily long-acting muscarinic antagonist (LAMA) available [3; page 108] and that this should be offered in preference to four-times-daily short-acting muscarinic antagonists [3; page 206]. Direct healthcare costs of COPD annually are estimated to be over £800 million (NICE COPD Costing Report 2011) and COPD is the second largest cause of emergency admission in the UK. It is estimated that as a result of implementing the NICE guidelines in relation to prescribing the number of hospital episodes will decrease by 5%, saving an estimated £15.5 million [4].

Tiotropium once daily has also proven to improve lung function, reduce exacerbations, and improve quality of life and mortality as reported in the UPLIFT study (the largest clinical trial ever reported in COPD)[5]. Tiotropium has had a beneficial impact on the current management of COPD, improving symptoms, reducing exacerbations and mortality and provides a cost-effective therapy [6].

Block-buster global sales
Spiriva® achieved world-wide sales of $4.5 billion in 2012 [7]. It is widely used as the first-line therapy for COPD in the UK. Spiriva is also close to obtaining approval for use as an add-on bronchodilator in severe asthma (as predicted by our study [research reference 4] showing that tiotropium causes prolonged bronchodilatation in asthma patients) and this will further swell sales.

Identification of a second long-acting anticholinergic
Our demonstration that glycopyrrolate had a similar pharmacological profile to tiotropium, with a slow offset from M_3-receptors in human lung, led to the first demonstration that inhaled glycopyrrolate was suitable as a once daily bronchodilator. This was then co-developed by Sosei and Vectura, who formulated glycopyrrolate as a dry powder inhaler and sold it to Novartis who marketed the drug as Seebri® in 2012 [8]. Glycopyrrolate is also being developed as a metered dose inhaler (Pearl, Prosonix) and a nebuliser solution (Elevation Pharma/Sunovion)[9].

Development of novel LAMA
Imperial research has led to the development of novel LAMA, using the paradigm Imperial established for the discovery of the long-acting effects of tiotropium and glycopyrrolate. For example, umeclidinium bromide (GSK Phase 3 studies), aclidinium bromide (Almirall approved in Europe and USA 2012) and CHF5407 (Chiesi Phase 2 studies). For example, in 2010 CHF5407 uses our approach with binding and suppression of cholinergic neural bronchoconstriction in guinea-pig airways to profile CHF5407, citing our key early references [10]. In addition, several combination inhalers containing a LAMA and a LABA, which have additive effects are also in advanced clinical development, including glycopyrrolate/indacaterol (QVA149, Novartis), tiotropium/olodaterol (Boehringer Ingelheim), umeclidinium/vilanterol (GSK/Theravance), aclidinium/formoterol (Almirall) and it is likely that these combination inhalers will become the most effective bronchodilators for COPD patients in the future. In addition, highly skilled scientists, trained by the key researchers, are employed as a result of the pharma programmes developed on the basis of this work (e.g. Dr El-bdaoui Haddad and Dr Jonathan Ward, co-authors of research references 2, 3, and 5).

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

[1] Letter from the Head of Respiratory Research/Early Development at Boehringer Ingelheim supporting the claim that the work above was key to the development of tiotropium.

[2] COPD Guidelines indicate tiotropium as first-line therapy for COPD:
- GOLD: global COPD. A pocket guide to COPD. Diagnosis, Management and Prevention. February 2013. http://www.goldcopd.org/uploads/users/files/GOLD_Pocket_2013Feb13.pdf (refer to page 12; Bronchodilators: Medications central to the management of COPD). Archived on 6th November 2013.

[3] NICE guidelines: CG101 COPD (update): Full Guidelines. http://guidance.nice.org.uk/CG101/Guidance/pdf/English (refer to pages108 and 206). Archived on 6th November 2013.

[4] NICE COPD Costing Report: Implementing NICE guidance (2011). http://www.nice.org.uk/nicemedia/live/13029/53292/53292.pdf. Archived on 6th November 2013.

[5] Tashkin, D.P., Celli, B., Senn, S., Burkhart, D., Kesten, S., Menjoge, S. et al. (2008). A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*, 359 (15), 1543-1554. DOI.

[6] Cost-benefit analysis of tiotropium in COPD with better health care outcomes.
Mauskopf, J.A., Baker, C.L., Monz, B.U., Juniper, M.D. (2010). Cost effectiveness of tiotropium for chronic obstructive pulmonary disease: a systematic review of the evidence. *J Med.Econ.,* 13 (3), 403-417. DOI.

[7] World-wide sales of tiotropium (Spiriva®): $4.49 billion in 2012.
http://www.fiercepharma.com/special-reports/spiriva. Archived on 6th November 2013.

[8] European approval of glycopyrrolate (Seebri®). http://www.novartis.com/newsroom/media-releases/en/2012/1645116.shtml. Archived on 6th November 2013.

[9] Development of glycopyrrolate:
http://www.genengnews.com/gen-news-highlights/prosonix-imperial-ally-on-development-of-copd-drugs/81247001/ (archived on 6th November 2013)
http://www.sunovion.com/aboutSunovion/our-products.html (archived on 6th November 2013)

[10] Villetti, G., Pastore, F., Bergamaschi, M., Bassani, F., Bolzoni, P.T., Battipaglia, L. *et al*. (2010). Bronchodilator activity of (3R)-3-[[[(3-fluorophenyl)[(3,4,5-trifluorophenyl)methyl]amino] carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azoniabicyclo[2.2.2]octane bromide (CHF5407), a potent, long-acting, and selective muscarinic M_3 receptor antagonist. *J Pharmacol Exp Ther*, 335(3), 622-635. DOI. Novel LAMA profiled according to our experimental approach.