Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Development and application of inhaled therapies in airway diseases

1. Summary of the impact

Research at the University of Manchester (UoM) has led a step-change in respiratory care for airway disease from oral to novel inhaled therapies targeted at asthma and chronic obstructive pulmonary disease (COPD) patients worldwide. UoM researchers carried out >250 studies, partnered industry to deliver >15 new inhaled drug formulations to market and were the first to test novel CFC-free inhalers. UoM led the development of global guidelines that influence better diagnosis and management of airways diseases. Through leadership within the Montreal Protocol since 1995, UoM researchers coordinated the safe global transition to CFC-free inhalers for ~200m patients with asthma and COPD, whilst protecting the ozone layer and climate.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Asthma and COPD together affect >10% of the world's population. COPD is the third commonest cause of death worldwide. The aim of the research at UoM since 1993 has been to provide better disease understanding, with a focus on safer and more effective treatments targeted to the right patients. This research has spanned the pre-clinical research essential to select effective drugs for clinical development, early phase clinical trials of these drugs in healthy subjects and patients and leadership of large clinical trials needed for drug registration.

Key UoM researchers:

- **Ashley Woodcock** (Professor, 1993-date)
- **Jorgen Vestbo** (Professor, 2003-date)
- **Dave Singh** (Senior Lecturer, 2003-2013; Professor, 2013-date)
- **Adnan Custovic** (Senior Clinical Research Fellow, 2000-2002; Professor, 2002-date)

Woodcock has conducted asthma clinical trials since 1993 that have formed the basis for the modern management of asthma, e.g. inhaled corticosteroids and long-acting beta$_2$-agonists, oral steroid tapering in acute asthma, and with **Custovic** allergen avoidance in allergic asthma (1, 2). **Woodcock** and **Custovic** established the Manchester Asthma and Allergy Cohort, which has explored the gene-environment interactions underlying allergic disease. **Woodcock** led the research for the safe phase-out of CFCs in inhalers. He developed new methods for assessing equivalence of HFC inhalers as safe alternatives to CFC inhalers (3, 4). He used his research experience as Co-chair of the Medical Technical Options Committee to the UNEP Montreal Protocol since 1995, leading negotiations on the reduction of CFC use in inhalers from 15,000 tonnes per year in 1996 towards complete phase-out in 2015.

Singh focuses on translating the basic pharmacological properties of known and novel drugs for treatment of asthma and COPD, using human tissue models, leading to the selection of candidate molecules that have entered early phase clinical trials. He tested novel and existing drugs by optimising methodologies which have led to effective and early decision-making on the clinical potential of these drugs (e.g. failed nitric oxide synthase inhibitor, successful development to market of novel antichoinergics) in rapid proof of concept studies (5, 6).

Vestbo has, since his appointment at UoM in 2003, led seminal trials in COPD that have ensured a step-change in treatment via the introduction of inhaled long-acting bronchodilators, inhaled corticosteroids and combination therapy. **Vestbo** has utilised large population-based cohorts to explore the natural history and risk factors for airways diseases as well as conducting work on biomarkers.

Vestbo and **Singh** have together led research into the definition of COPD subgroups that have a

different prognosis and/or response to therapy. They led one of the world's largest observational COPD studies (the ECLIPSE study, 2164 patients followed for 3 years), **Vestbo** as Chair of the Steering Committee and **Singh** as PI in blood and sputum biomarkers. This study documented the heterogeneity of COPD, the variable course of the disease, and for the first time identified a subgroup of COPD patients characterised by frequent exacerbations requiring a novel treatment strategy (6).

3. References to the research

1. O'Driscoll BR, Kalra S, Wilson M, Pickering CAC, **Woodcock A**. Double-blind trial of steroid tapering in acute asthma. *The Lancet*. 1993; 341:324-7. DOI: 10.1016/0140-6736(93)90134-3
2. **Woodcock A**, Forster L, Matthews E, Martin J, Letley L, Vickers M, Britton J, Strachan D, Howarth P, Altmann D, Frost C, **Custovic A**. Control of exposure to mite allergen by the use of allergen permeable bed covers for adults with asthma. *The New England Journal of Medicine*. 2003; 349:221-32. DOI: 10.1056/NEJMoa023175
3. **Singh SD**, Richards D, Knowles RG, Schwartz S, **Woodcock AA**, Langley SJ, O'Connor BJ. Selective inducible nitric oxide synthase inhibition has no effect on allergen challenge in asthma. *American Journal of Respiratory and Critical Care Medicine*. 2007:176; 988-93. DOI: 10.1164/rccm.200704-588OC
4. **Singh D**, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax*. 2008; 63; 592-8. DOI: 10.1136/thx.2007.087213
5. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, **Vestbo J**, on behalf of the TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *The New England Journal of Medicine.* 2007; 356:775-89. DOI: 10.1056/NEJMoa063070
6. Hurst JR, **Vestbo J**, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, MacNee W, Calverley P, Rennard S, Wouters EFM, Wedzicha JA. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. *The New England Journal of Medicine*. 2010; 363(12):1128-38. DOI: 10.1056/NEJMoa0909883

4. Details of the impact

See section 5 for corroborating sources S1-S10.

Context

In the 1980s, most asthma patients took short-acting beta agonists, but by the 1990s treatment of asthma with inhaled corticosteroids and bronchodilators was fairly well established. However, little was known about dosing of inhaled corticosteroids or combining inhaled corticosteroids with novel long-acting β_2-agonists. The impact of allergen avoidance on allergic diseases was poorly understood. In COPD, even less was known and no long-term intervention trials with inhaled therapy had been carried out.

UoM researchers have safely carried out >250 clinical studies. They have: played a key role in bringing 15 different inhaled formulations to the market; managed the switch to CFC-free inhalers for many millions of patients; and led guidelines that have been very influential for both physicians and patients (e.g. Global Initiative for Asthma website had 12,586,493 hits in 2012). The first Charity-owned 36-bed dedicated asthma/COPD clinical trial unit, the Medicines Evaluation Unit (MEU, Director **Singh**) (S1) is located in Manchester and employs over 80 people. Discussing the importance of the work carried out at UoM, the Chief Executive Officer of GlaxoSmithKline (GSK) comments: 'it is obvious that a significant contribution to human health has been delivered. Importantly this contribution has benefited patients in the UK and globally' (S2). The key impacts are detailed below.

Reach and significance of the impact

Treating asthma

There are an estimated 300m individuals with asthma worldwide. The trial work on inhaled therapies by **Woodcock** and **Singh**, as well as the work on allergen avoidance by **Woodcock**

(with **Custovic**), has had significant impact on both the latest revision of the asthma guidelines from the Global Initiative for Asthma (GINA), published in 2012 (S3) as well other national and international guidelines, including those of the British Thoracic Society, also published in 2012 (S4).

Woodcock leads the Salford Lung study, the world's first pragmatic double-blind randomised controlled trial (DBRCT) targeting ~7,000 asthma/COPD patients, to provide data on overall health benefits of inhaled therapy. **Woodcock** with **Custovic** led the only large DBRCT on house dust mite avoidance in asthma (2). This single study convincingly showed no benefit, and prevented patients and health services worldwide from wasting £billions on measures (covers ~£200/set; 2m mite-sensitive asthmatics; 25% uptake; estimated saving £100m/annum in UK alone, for last 10 years).

Understanding and treating COPD

WHO estimates that there are 210m individuals with COPD worldwide. The number is increasing as smoking rates rise in developing countries. Large pivotal trials in COPD, many of them led/co-authored by **Vestbo**, form the basis for modern management of COPD as reflected in the Global Initiative for Obstructive Lung Diseases (GOLD) Strategy Document, revised in 2011 (S5) and the current NICE guidelines for diagnosis and management of COPD, published in 2010 (S6).

The GOLD guidelines website had over 13m hits in 2012 alone. Traditional guidelines focussed on measurements of lung function but current documents, influenced by **Vestbo's** research, reflect today's view of COPD. **Vestbo** was appointed head of the Science Committee for the 2011 revision of the GOLD Strategy document. This document is changing the way COPD patients are managed worldwide with a focus on risk reduction, detection, symptom relief, and management of comorbidities. This document has inspired numerous national COPD guidelines worldwide with implications for millions of patients. The Executive Director of GOLD underlines the importance of **Vestbo**'**s** work for patient care: '[Vestbo's] work has stimulated research scientists and benefitted patients around the world, including many in the United States. It has been a privilege for me […] to be associated with Dr Vestbo in the GOLD program where I find his knowledge of airway biology to be outstanding but perhaps even more important his commitment to take findings from research to impact on improved care of patients with these chronic lung diseases sets an example for other clinical scientists.' (S7)

UoM studies exploring and characterising airways diseases have impacted on current management of COPD. Early work from **Singh** and **Vestbo** led a stratified medicine approach to 'phenotyping' COPD in 2009-11. This change from a 'one size fits all' strategy has changed the way the pharmaceutical industry designs randomised clinical trials in COPD. For example, they defined an 'exacerbator' phenotype, leading to targeted preventive strategies with macrolides and novel anti-inflammatories. Recent COPD guidelines reflect this stratified approach, with treatments tailored to the patient's clinical phenotype. In this growing disease area, these changes are impacting the treatment of millions of patients.

Drug development

Singh's work has directly influenced the drug discovery processes of many pharmaceutical companies. For example, his work on p38 MAPK inhibitors in 2009-12 (S8), in collaboration with industrial partners, has been pivotal in refocusing the development of these drugs on COPD rather than other inflammatory diseases; these drugs have progressed to phase 3 studies. This basic science research, coupled with scientific and leadership skills in early and late phase clinical trials, has increased the number of clinical trials performed by the spin-out Medicines Evaluation Unit (S1), with annual turnover increased from <£2m in 2007 to >£7m in 2012 and staff employment rising from 35 to >80 in 2013. Notable successes include conduct of the first ever study of inhaled glycopyrrolate as a bronchodilator (for a UK biotech company) in 2005, with close involvement in subsequent full development by a major pharma (2009-2012). Senior representatives of the pharmaceutical company Almirall comment that: 'the Medicines Evaluation Unit has rapidly become a centre of reference for early studies with new compounds and mechanisms, and is highly regarded for its focus on timely delivery and doing good science.' (S9)

Singh has also been pivotally involved as an investigator and advisor regarding clinical development and regulatory issues for the bronchodilator aclidinium in 2007-12. Both of these medicines are being licensed worldwide for COPD, and are already impacting on the lives of many millions of patients. UoM research and leadership has led to 15 different inhaled drug formulations getting to market; these treatments are used by most of the >500m asthma and COPD patients worldwide.

Ensuring safe inhaled medications and protecting the environment

Woodcock's leadership of the Medical Technical Options Committee to the UNEP Montreal Protocol since 1995 has had a huge impact globally, with 2015 projected to be the last year of CFC use in inhalers worldwide. With a final global ban on CFCs, ozone recovery will occur by 2060 and the worst effects of this chemical on the climate will be prevented. For these efforts, **Woodcock**, as a member of the International Panel for Climate Change (IPCC), shared the Nobel Peace Prize in 2007. The Executive Secretary of the Ozone Secretariat at the United Nations Environment Programme underlines the importance of this work: '[**Woodcock**] has helped the efforts of the international community to promoting effective cooperation between science, politics, environment and human health. Prof Woodcock's contributions to such cooperation has [*sic*] also helped the Vienna Convention for the Protection of the Ozone Layer and the Montreal Protocol on Substances that Deplete the Ozone Layer, to promote sustainable development and protect the global environment. These contributions have indeed salient benefits for the present and future generations.' (S10)

This major step in environmental protection and recovery has taken place without any harm to the users of inhaled medications. Indeed, as a result of the underlying research, ~200m patients with chronic airway disease have been safely transferred to CFC-free inhalers and can receive even better inhaled therapy today.

5. Sources to corroborate the impact

S1. Medicines Evaluation Unit: http://www.meu.org.uk/
S2. Letter from Chief Executive Officer, GSK.
S3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf
S4. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma: A National Clinical Guideline. 2008, revised 2012. http://www.brit-thoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%20Jan%202012.pdf
S5. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2013. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf (see p. 51; p. 56; p. 61; pp. 73-74; p. 76)
S6. NICE. CG101 Chronic Obstructive Pulmonary Disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2004, updated 2010. http://guidance.nice.org.uk/CG101/Guidance/pdf/English (see p. 167)
S7. Letter from Executive Director, GOLD.
S8. Letter from VP, Clinical Discovery, GSK.
S9. Letter from Senior Director, Discovery and Chief Scientific Officer & Executive Director of R&D, Almirall, Spain.
S10. Letter from Executive Secretary, Secretariat for the Vienna Convention and its Montreal Protocol – The Ozone Secretariat, United Nations Environment Programme.