Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-18 Breathing New Life into the Treatment of Respiratory Illnesses

1. Summary of the impact

Ongoing research by the University of Southampton has led to significant advances in the understanding of respiratory diseases, for which the dearth of available treatments had health repercussions on a global scale for many years. The formation of a spin-out company, Synairgen, has enabled the discovery and development of new therapeutics, the filing of several major patents in the UK, the US and Asia and external collaborations with industry and government funders. These continuing developments are key to tackling conditions that affect millions of sufferers in the UK alone and which, according to some estimates, cost the NHS £2.6bn every year. The research has given rise to more than £16m in follow-on funding from the NIHR and the MRC for further studies into the treatment of respiratory illnesses.

2. Underpinning research

The British Thoracic Society reported in 2006 that respiratory disease kills one in four people in the UK and costs the National Heath Service £2.6bn each year. According to Asthma UK's *Living on a Knife Edge* report in 2010, 5.2m people in the UK – 1.1m of them children – receive treatment for asthma. Around 2.6m asthma sufferers live with symptoms classed as severe, and around 500,000 of these experience severe symptoms because treatments currently available are incapable of bringing the disease under control. In addition, acute chronic obstructive pulmonary disease (COPD) attacks are the most common cause of hospitalisation in the country.

Since 1993 research led by Stephen Holgate, Professor of Immunopharmacology (1987-present) at the University of Southampton's Faculty of Medicine, has sought to understand the underlying mechanisms of respiratory disease in order to develop new treatments to prevent – or minimise the severity of – acute asthma and COPD attacks that can cause hospitalisation or even death. The body of research revolves around a key area of biologics: the use of human tissues and cells to explore different therapeutics for viral diseases.

In 1993, in collaboration with Dr David Tyrrell, FRS Director of the Medical Research Council (MRC) Common Cold Unit in Salisbury, Holgate and clinical research fellow Dr Sebastian Johnston (left, 1999), developed the first comprehensive gene-based tests to detect respiratory viruses in secretions. The tests were applied in longitudinal asthma studies in children **[3.1, 3.2]** and adults **[3.3]** as well as airway biopsy studies in asthma patients **[3.4]**, which showed inflammation during exacerbations is the result of virus infection rather than allergy **[3.5]**. These pioneer studies in Southampton established unequivocally that viral infections – especially rhinoviruses (RV) – cause asthma attacks, thereby stimulating a wave of research into developing new approaches for treating such exacerbations.

Through controlled infection of human volunteers, research found the airway epithelium plays a pivotal role in acting as a "host" for common cold viruses and that RV infections of the lower respiratory tract are directly linked with asthma exacerbations **[3.4]**. This stimulated the discovery by Donna Davies (Professor of Respiratory Cell and Molecular Biology 1998-present) and her team (in collaboration with Johnston) of a deficiency in the production of anti-viral interferons by bronchial epithelial cells (BECs) grown from asthmatic donors **[3.6]**. Crucially, the cells could be protected against virus infection by adding exogenous interferon beta (IFN-β), a breakthrough in the search for therapy. Follow-up studies into COPD showed BECs from long-term smokers are highly susceptible to RV infection but, as in asthma, are protected by exogenous IFN-β, a drug already used systemically to treat multiple sclerosis.

These novel mechanistic findings were the subject of a patent filed by the University of Southampton for the use of inhaled IFN-β for treatment of virus-induced exacerbations of asthma and COPD. This was licensed to Synairgen, a spin-out company set up by the University in 2004 to turn research findings into potentially world-changing drugs.

3. References to the research

3.1 Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA and Holgate ST. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995; 310: 1225-1229.

3.2 Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, Cunningham A, Robinson BS, Myint SH, Ward ME, Tyrrell DA and Holgate ST. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med* 1996; 154: 654-660.

3.3 Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST and Johnston SL. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002; 359: 831-834.

3.4 Papadopoulos NG, Bates PJ, Bardin PG, Papi A, Leir SH, Fraenkel DJ, Meyer J, Lackie PM, Sanderson G, Holgate ST and Johnston SL. Rhinoviruses infect the lower airways. *J Infect Dis* 2000; 181: 1875-1884.

3.5 Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL and Holgate ST. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am J Respir Crit Care Med* 1995; 151: 879-886.

3.6 Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, Holgate ST and Davies DE. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005; 201: 937-947.

Grants:

2012-2017: Djukanovic R, Holgate ST, Grocott M, Arshad H, Davies D; NIHR. Life-course Approach to Respiratory Health; NIHR Respiratory Biomedical Research Unit **£7.3 million**

2009-2014: ST Holgate, DE Davies, PH Howarth, GC Roberts, H Arshad, P Thurner; MRC Programme Grant. A life course approach to investigating asthma pathogenesis and progression **£2.56 million**

2010-2011: DE Davies, J Cakebread; Asthma UK. The influence of co-infection on the innate immune response of asthmatic bronchial epithelial cells to respiratory viruses. **£49,500**

2008-2013: Djukanovic R, Holgate ST, Howarth PH, Roberts G; NIHR. Airways disease in children and adults**;** NIHR Respiratory Biomedical Research Unit **£6.5 million**

2006-2010: Davies DE, Holgate ST, Roberts G, Warner J; Medical Research Council. The molecular basis of impaired innate immunity to virus infection in asthma. **£650,000**

2006-2009: Davies DE, Holgate ST, Warner JO, Roberts GC; Asthma UK. Analysis of the innate immune response to virus infection of bronchial epithelial cells from asthmatic children. **£143,553**

2007-2010: Davies DE, Holloway JA, Morgan H, Holgate ST; National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). Modelling the human asthmatic airway by tissue engineering. **£299,875**

2003-2005: Davies D.E, Holgate ST; Asthma UK. Rhinovirus infection and activation of the epithelial-mesenchymal trophic unit in asthma. **£122,694**

4. Details of the impact

For decades the dearth in available treatments for exacerbations of asthma and COPD has had global health repercussions. Within the UK, asthma exacerbations have an estimated impact of £1.2bn in lost productivity, £850m in NHS provision and £161m in social security costs. COPD exacerbations are the major cause of morbidity, mortality and reduced health. They are the commonest cause of medical hospital admission in the UK, with an average length of stay of nine days accounting for just over one million bed days annually in England – at a cost to the NHS in excess of £253m/year **[5.1]**. Patients with frequent exacerbations exhibit accelerated disease

progression, increased hospital admission and greater mortality. Since 60-80% of exacerbations are virus-driven, they are much more common in autumn/winter, adding to seasonal pressures in the NHS.

Studies at Southampton have led to the discovery of a new drug under development by the spin-out company Synairgen Plc to address these previously unmet clinical needs. Findings from Southampton's original body of research are also shaping the development of novel treatments for other serious viral infections such as avian and swine flu, driving collaborations with the Public Health England (formerly Health Protection Agency) and the US Department of Defense.

Synairgen was founded in 2003 by Stephen Holgate, Donna Davies and Ratko Djukanovic (1988-present), with investment from IP2IPO Group plc (now IP Group). It was floated on the Alternative Investment Market (AIM) in 2004, raising £10.5m, and its market capitalisation on admission was £28m **[5.2]**. Since 2008 it has concentrated its effort on the clinical development of inhaled IFN-β1 for the treatment of exacerbations of asthma and COPD caused by respiratory viruses. In 2009 Synairgen completed Phase I trials of inhaled IFN-β1a in moderately asthmatic subjects and progressed to Phase II proof of concept studies. Underlining significant investor confidence, the company raised £6m (net) in 2009 to fund Phase II clinical trials in asthma and £2.5m (net) in 2011 to accelerate completion of asthma Phase II, conduct various in vitro experiments and fund avian flu research **[5.3]**.

During the Phase I and Phase II clinical trials Synairgen linked with researchers in NIHR Biomedical Research Units in Southampton and Nottingham, clinical trial units in Manchester, Leicester, Glasgow, Belfast, Newcastle, Oxford, Sheffield and Norwich and commercial trial sites in Liverpool, Cardiff, Birmingham, Leeds and Reading, as well as five sites in Australia **[5.4]**. These Phase I and Phase II clinical trials have been highly successful and have shown that IFN-β1a by inhalation is safe both in normal and asthmatic volunteers **[5.5]**. Evidence of anti-viral biological activity in asthma was demonstrated by showing treatment-related elevation of anti-viral lung biomarkers. In a further placebo-controlled RCT involving 134 asthma patients, efficacy of IFN-β1a in preventing viral exacerbation in moderate-severe asthma has been demonstrated on a range of patient-centred and objective asthma endpoints, as well as confirming enhanced local and systemic anti-viral activity as reflected in circulating and lung biomarkers **[5.6, 5.8, 5.9]**. Moderate-severe asthma, comprising ~10% of the asthma population, accounts for 50% of the total health costs of asthma of which the majority relate to exacerbations against which IFN-β1a is active **[5.1]**. Media coverage in the likes of the Daily Mail, Huffington Post and MSN News in April 2012 **[5.8]** reported Leanne Metcalf, Assistant Director of Research at Asthma UK, as saying: "This has the potential to be one of the biggest breakthroughs in asthma treatments in the past 20 years … This clinical trial demonstrates the potential of this anti-viral drug to prevent asthma attacks for thousands of people with severe asthma."

Synairgen has filed three patents **[5.7]**. The patent for the use of inhaled IFN-β1a for treatment of virus-induced exacerbations of asthma and COPD was granted in the United States in 2009, Europe in 2010 and Japan in 2011. Based upon these positive trial outcomes in asthma, discussions are at an advanced stage with two large pharmaceutical companies to take forward clinical development of inhaled IFN-β1a in asthma and COPD. Following the announcement of these talks in September 2012, Synairgen's stock value rose 6%, giving it a total market value of £33.1m **[5.9]**.

An additional key focus is the elderly population, where RV infection has been linked with the increased use (and cost) of healthcare resources in long-term care institutions and unexpectedly high mortality. Ongoing research throughout the impact period shows increasing age is associated with a decrease in epithelial innate responses to RV. A US patent application for use of IFN-β1a to treat RV infection in the elderly was given Notice of Allowance in 2010.

Further work undertaken by Synairgen internally and in collaboration with the Public Health England has shown IFN-β has utility against established influenza (swine flu - H1N1, avian flu - H5N1 and seasonal flu) infection. In 2010 this resulted in the filing of a patent for the use of inhaled IFN-β1a against influenza, attracting the US Department of Defense's interest in its applicability for

combating bioterrorism.

Synairgen's proprietary technology has been endorsed by external research collaborations with companies including Centocor, Merck and Cambridge Antibody Technology (now AZ/Medimmune) **[5.7]**. The research impact also extends to Synairgen's employment of highly skilled staff: the company currently has around 25 employees and has aided the career development of 15 scientists, five clinical fellows, 12 nurses and four clinical trial management staff with specialist knowledge of drug development.

Thanks to reputation and expertise developed via the underpinning research, Holgate, Davies and Djukanovic have been invited to advise the pharmaceutical industry and government committees on measures to tackle complex respiratory disease **[5.10]**. The NIHR and MRC has awarded Southampton a total of £16.5m in follow-on funding during the REF impact period to further develop new treatments for respiratory illnesses (see list of grants in section 3).

5. Sources to corroborate the impact

5.1 British Thoracic Society – Burden of lung disease
http://www.brit-thoracic.org.uk/Portals/0/Library/BTS%20Publications/burden_of_lung_disease.pdf

5.2 Synairgen's fund raising in 2009 and 2011:
http://www.synairgen.com/documents/SNG-FundraisingAnnouncement2705.pdf
http://www.synairgen.com/documents/SynairgenFundraising27May2011.pdf

5.3 Antiviral activity of IFN-β against seasonal flu and swine flu:
http://www.synairgen.com/documents/Synairgen-Positiveinfluenzadata1705.pdf
http://www.synairgen.com/documents/PressreleaseH5N1final.pdf
http://www.dailyecho.co.uk/news/8171066.A_new_weapon_in_war_of_flu_virus/?ref=rss

5.4 Links with other clinical trials centres:
The Medicines Evaluation Unit, Manchester http://www.synairgen.com/documents/SNG-Phase1Study121109.pdf

5.5 Completion of phase 1 trials, proof of mechanism data and commencement of Phase II trials
http://www.synairgen.com/downloads/Phase%20I%20completion%20final.pdf [see repository]
http://www.synairgen.com/documents/SNG-Phase1Study121109.pdf

5.6 Completion of phase II clinical trial in asthma viral exacerbations:
http://www.synairgen.com/media/1536/19%20april%202012%20Phase%20II%20press%20release%20final.pdf

5.7 Synairgen's Annual Reports and Finances 2004-2012:
http://www.synairgen.com/investors/financial-information.aspx
http://www.synairgen.com/media/8878/15812_sy_annualreport_2012_web.pdf

5.8 Press/charity coverage of drug trial:
Daily Mail, April 19th 2012: 'Asthma drug protects sufferers from life-threatening symptoms caused by common cold'.
http://www.dailymail.co.uk/health/article-2132106/Asthma-drug-protects-sufferers-life-threatening-symptoms-caused-common-cold.html#ixzz2W6T9CP41

5.9 Synairgen in drug partnership talks after study results.
http://www.bloomberg.com/news/2012-09-02/synairgen-in-drug-partnership-talks-after-asthma-study-results.html

5.10 Heffner JE, Holgate ST, Chung KF, Niederman MS, Daley CL, Jett JR, Stradling JR, Wells AU, Light RW, Tapson VF, Hansell DM, Provonost PJ, Lee YC. Road ahead to respiratory health: experts chart future research directions. *Respirology* 2009; 14: 625-636.