Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-28 Transforming severe asthma therapy

1. Summary of the impact

Southampton research has been central to the development and international licensing of one of only two novel asthma therapies in the last 30 years, transforming asthma control and survival for severe allergic asthmatics.

Key studies by the Southampton Group have underpinned the development of immunoglobulin (Ig)-E as a key therapeutic target for controlling allergic asthma, with the Southampton-led first-in-man safety and efficacy trials critical to the registration of the anti-IgE therapy, omalizumab.

This contribution also generated significant inward investment in UK R&D and opened up wider investigation of anti-IgE therapy in a broad range of atopic and inflammatory indications.

2. Underpinning research

Studies by Holgate (Professor of Immunopharmacology), Howarth (Professor of Allergy and Respiratory Medicine), Djukanovic (Professor of Respiratory Medicine 2004-2011 and of Medicine to date) and their Respiratory Research Groups directly underpinned the elucidation of IgE roles in asthma, the continued investment in development of anti-IgE therapy by pharmaceutical companies, and the progression of the only licensed anti-IgE therapeutic into the clinic.

In 1994 two key Southampton studies expanded on the group's earlier identification of the mechanistic role of IgE-mediated mast cell activation in early-phase asthma responses, with the first demonstrations of prolonged inflammatory effects associated with late-phase cellular infiltration. An initial study by Bradding et al **[3.1]** comparing bronchial biopsies from normal and asthmatic subjects identified mast cells as the prevalent source of inflammatory cytokines pivotal to inflammatory cell infiltration of bronchial tissues. The influence on inflammatory cell infiltration was confirmed by a further comparison of bronchial biopsies five to six hours after localised allergen challenge, revealing significant, localised infiltration of neutrophils, eosinophils and $CD3^+$ lymphocytes **[3.2]**. Further bronchial biopsy studies over 1995-6 defined the involvement of IgE in allergen processing by bronchial dendritic cells **[3.3]**, underscoring the centrality of IgE in allergic asthma and its desirability as an upstream therapeutic target.

In 1996, the Southampton group was the first to demonstrate the safety and bioactivity of an anti-IgE therapeutic in man, using the CGP51901 chimeric human/mouse monoclonal antibody developed by CIBA-Giegy (later to become Novartis) **[3.4]**. Targeting a receptor-binding epitope in the constant chain of IgE, thus avoiding anaphylaxis through cross-linking of bound IgE-receptor complexes, the murine analogue of CGP51901 had previously been shown to be safe in mice. The Southampton study demonstrated good tolerance, accompanied by dose-dependent suppression of free serum IgE and dose-dependent time to recovery of baseline IgE levels over a significant period.

Having provided this basis for further development of anti-IgE therapy in humans, Holgate was Principal Investigator on one of five pivotal clinical trials demonstrating the safety and efficacy of the omalizumab humanised anti-IgE monoclonal antibody in severe allergic asthma **[3.5]**. This trial showed significant reductions in inhaled corticosteroid (fluticasone) dose, and associated reductions in rescue medicine requirements, improved asthma symptoms and greater quality of life scores over placebo. This trial, alongside four others as part of the omalizumab 011 International Study Group, provided the evidence base for registration of omalizumab in the USA and Europe. Holgate was selected as one of three experts by Novartis to advise on these in addition to leading the Southampton trial.

Further studies by Djukanovic and the Southampton Group demonstrated key anti-inflammatory

influences of omalizumab on greatly reducing IgE receptor expression and the eosinophilic inflammatory response **[3.6]**.

In 2006, Holgate led a *post-hoc* analysis of pooled trial data to identify definitive predictors of response to omalizumab treatment, to enable effective targeting **[3.7]**. The findings of this research indicated that assessment at 16 weeks after commencement of omalizumab treatment was the most robust measure of response, with 60% of patients responding. This measure, and response rate, now form the basis of product and clinical guidelines on the use of omalizumab in severe allergic asthma.

3. References to the research

3.1 Bradding P, Roberts JA, Britten KM, Montefort S, Djukanovic R, Mueller R, Heusser CH, Howarth PH, Holgate ST. Interleukin-4, -5, and -6 and tumor necrosis factor-alpha in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994;10: 471-80.

3.2 Montefort S, Gratziou C, Goulding D, Polosa R, Haskard DO, Howarth PH, Holgate ST, Carroll MP. Bronchial biopsy evidence for leukocyte infiltration and upregulation of leukocyte-endothelial cell adhesion molecules 6 hours after local allergen challenge of sensitized asthmatic airways. *J Clin Invest* 1994;93: 1411-21.

3.3 Tunon-De-Lara JM, Redington AE, Bradding P, Church MK, Hartley JA, Semper AE, Holgate ST. Dendritic cells in normal and asthmatic airways: expression of the alpha subunit of the high affinity immunoglobulin E receptor (Fc epsilon RI-alpha). *Clin Exp Allergy* 1996;26: 648-55.

3.4 Corne J, Djukanovic R, Thomas L, Warner J, Botta L, Grandordy B, Gygax D, Heusser C, Patalano F, Richardson W, Kilchherr E, Staehelin T, Davis F, Gordon W, Sun L, Liou R, Wang G, Chang TW, Holgate S. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. *J Clin Invest* 1997;99: 879-87.

3.5 Holgate ST, Chuchalin AG, Hébert J, Lötvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, Cioppa GD; Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34: 632-8.

3.6 Djukanović R, Wilson SJ, Kraft M, Jarjour NN, Steel M, K. Chung F, Bao W, Fowler-Taylor A, John Matthews, Busse WW, Holgate ST, and Fahy JV. Effects of Treatment with Anti-immunoglobulin E Antibody Omalizumab on Airway Inflammation in Allergic Asthma. *Am J Respir Crit Care Med* 2004;170(6): 583-593

3.7 Bousquet J, Rabe K, Humbert M, Chung KF, Berger W, Fox H, Ayre G, Chen H, Thomas K, Blogg M, Holgate S. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med* 2007; 101: 1483-92

Grants (selected)

- 1995-1998 S Holgate and PJ Watt. MRC Infrastructure Grant. Mucosal Immunology: a protein engineering laboratory for studies on vaccine design and asthma research. £453,000. Three years.
- 1995-1998 S Holgate. European Commission. European network for understanding mechanisms of severe asthma (ENFUMOSA). 300,000 ECU. Three years.
- 1996-1999 S Holgate. National Asthma Campaign. Analysis of allergen recognition sites in IgE antibodies from patients with asthma. £108,040. Three years.
- 1997-2001 S Holgate. MRC Programme Grant (G8604034). The Mechanisms of Asthma Chronicity and Disease Progression. £1,929,623. Four years.

4. Details of the impact

Southampton research has been central to the development and international licensing of the anti-Ig-E monoclonal antibody (mAb) omalizumab (Xolair), one of only two novel asthma therapies to emerge in the last 30 years. This body of work has transformed asthma control and survival prospects for severe allergic asthmatics, was critical to major inward investment in UK R&D and has stimulated wider development of anti-IgE therapeutics in a broad range of atopic indications.

Omalizumab provides an effective therapeutic option for those with severe, persistent allergic asthma, including those for whom standard therapy provides only limited control **[5.1, 5.2]**. This group are at the highest risk of mortality amongst the three to four million children and adults with allergic asthma in the UK and prior to licensing of omalizumab, therapeutic options for control of their condition were constrained: Conventional long-term, high dose regimens of inhaled corticosteroid (ICS) plus long-acting β_2-agonist (LABA) provided limited control, with impacts on bone mineralisation and growth, particularly in children; and anti-leukotrienes demonstrated only equivocal improvements in efficacy in a small subset of patients.

Omalizumab yields significantly reduced rescue medication and ICS usage, fewer hospitalisation events and days in hospital, improved lung function and increased quality of life measures **[5.3]**. Southampton has played an instrumental role in the progression of omalizumab to the clinic, through commercial research partnerships, leadership of key clinical trials and its central role in elucidating the mechanisms and implications of IgE involvement in asthma **[5.4]**.

This work was synergistically linked to Holgate's consultancy role with CIBA-Giegy, focused on development of an anti-IgE mAb asthma therapy for asthma. The Southampton-led safety study with CIBA-Giegy played a critical role in triggering US company Genentech's decision to further pursue development (latterly in partnership with Novartis) of its humanised anti-IgE mab, omalizumab, which had drawn on Southampton's mechanistic studies in earlier development **[5.4]** and led directly to its registration in the USA in 2003 and in Europe in 2009 **[5.5]**. Omalizumab's high unit cost and variations in patient therapeutic responses mean that effective targeting is required to ensure best care for the patient and cost management for healthcare providers. The Holgate-led definition of a 16 week post-treatment assessment of response status was the basis of a standardised and robust assessment framework developed in 2007 **[5.6, 5.7]** and which is now included in current product and healthcare guidance that enables clinicians to make informed treatment decisions. Omalizumab has now been included in the 2012 Global Initiative for Asthma (GINA) **[5.2]** and British Thoracic Society SIGN **[5.1]** Guidelines for the treatment of severe allergic asthma, following a detailed cost-benefit analysis, have recently (March 2013) been approved for use in the UK by NICE for adults and children who need frequent treatment with oral corticosteroids **[5.3]**.

The successful registration of omalizumab, combined with data from the mechanistic studies of IgE roles in allergenic inflammation led by Southampton, is having impacts beyond asthma therapy. Its clinical safety and the commonality of IgE as a therapeutic target has stimulated research into omalizumab use in a wide range of atopic and inflammatory indications, including urticaria, angioedemia, atopic dermatitis, allergic rhinitis, nasal polyposis and severe ocular allergies **[5.8]**. There are also early indications of positive influences on common allergic asthma co-morbidities such as allergic rhinitis, and a role for omalizumab in prophylactic control of anaphylaxis in specific allergen immunotherapy.

Southampton's IgE research and the concentration of expertise established through it, were critical factors in Novartis' decision to locate their respiratory biomedical research unit in the UK at Horsham. As only one of Novartis' eleven global research units based in the UK, it represents significant inward investment and commitment to the UK as a focus for respiratory therapy development **[5.9]**. Collaboration with Novartis continues, with Holgate providing consultancy input on the successor to omalizumab (QGE031) **[5.10]**, which has demonstrated 15-fold higher efficacy

in its first trials, indicating significant further potential cost and treatment benefits of anti-IgE mAb for severe allergic asthma and allied disorders.

5. Sources to corroborate the impact

5.1 British Guideline on the Management of Asthma : A national clinical guideline. May 2008, Revised January 2012
http://www.britthoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%20Jan%202012.pdf

5.2 Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention. Updated 2012
http ://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

5.3 NICE says yes to treatment for asthma in final draft guidance: March 2013
http://www.nice.org.uk/newsroom/pressreleases/OmalizumabForAsthmaFAD.jsp

5.4 Pelaia G, Gallelli L,Renda T,Romeo P, Busceti MT, Grembiale RD, Maselli R, Marsico SA, and Vatrella A. Update on optimal use of omalizumab in management of asthma. *J Asthma Allergy* 2011;4: 49–59.

5.5 European registration of Omalizumab, November 2009
http://ec.europa.eu/health/documents/community-register/html/h319.htm

5.6 Need for overall clinical assessment at 16 weeks to continue omalizumab treatment.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf

5.7 US FDA prescribing information: Genentech Inc. Xolair (Omalizumab) for subcutaneous injection. Full Prescribing Information (US), July 2007.
http://www.pharma.us.novartis.com/product/pi/pdf/Xolair.pdf

5.8 New indications: Ben-Shoshan M. Omalizumab for asthma: indications, off-label uses and future directions. *Recent Pat Inflamm Allergy Drug Discov* 2010;4: 183-92.

5.9 Corroborative statement from: Former Global Head of Respiratory Diseases, Novartis and former Head of NIBR UK, Novartis.

5.10 The 2013 Novartis International Respiratory Advisory Board (Holgate as Chair) – corroborative statement from: Director Medical Advocacy and Professional Relations, Novartis Pharma AG, Basel.