

## Impact case study (REF3b)

<b>Institution:</b> Imperial College London
<b>Unit of Assessment:</b> 01 Clinical Medicine
<b>Title of case study:</b> Sublingual Allergen Immunotherapy in the Treatment of Hayfever
<b>1. Summary of the impact</b> (indicative maximum 100 words)
<p>Subcutaneous allergen immunotherapy is highly effective in hayfever sufferers who fail to respond to anti-allergic drugs, but carries the risk of severe allergic side-effects. Professor Durham's group at Imperial College have defined the mechanisms and shown that sublingual tablet immunotherapy is an effective, safer alternative that induces long-term disease remission. The tablet approach is now widespread in Europe and is being successfully extended to other allergies (housedust mite) and internationally (ragweed allergy in USA and Japanese Cedar pollen allergy). The work is quoted in guidelines internationally and regulatory bodies now recognise the disease-modifying potential of immunotherapy and its ability to induce long-term remission.</p>
<b>2. Underpinning research</b> (indicative maximum 500 words)
<p>Key Imperial College London researchers: Professor Stephen Durham, Professor of Allergy and Respiratory Medicine (1988-present) Dr Kayhan Nouri-Aria, Research Lecturer (1996-2010) Dr Stephen Till, Health Foundation Clinical Research Fellow (1993 -2011) Dr Moises Calderon, Consultant Allergist and Research Fellow (2003-present) Dr Mohamed Shamji, Post-doctoral Research Fellow (2004-present) Dr Guy Scadding, Wellcome Clinical Research Fellow (2010-present)</p> <p>Allergen immunotherapy involves the repeated administration of allergen extracts to IgE-sensitised allergic subjects. Professor Durham's group at Imperial showed that allergen injection immunotherapy was highly effective in severe seasonal allergic rhinitis (hayfever) with/without seasonal asthma and that in contrast to anti-allergic drugs, immunotherapy was able to induce long-term clinical and immunological tolerance. The Imperial group defined the underlying mechanisms and showed that immunotherapy could also be administered effectively, safely and conveniently via the sublingual route (under the tongue) whilst retaining disease-modifying properties.</p> <p>Prior to 1993, allergen immunotherapy was practiced rarely. In 1986, the Committee on Safety of Medicines (CSM) reported a series of fatalities in the UK, questioned the safety of the treatment particularly in asthmatics, and consequently mandated a 2 hour observation period following injections. In 1993, Imperial's group initiated a series of prospective long-term, double-blind, placebo-controlled clinical trials of immunotherapy (1). A parallel initiative in 1996, also at Imperial, was the development of novel techniques of immuno-histochemistry and <i>in situ</i> hybridisation in the nasal mucosa, peripheral T cell assays and functional assays of serum 'blocking' IgG antibodies (2). This enabled a detailed and unbiased evaluation of the underlying mechanisms of immunotherapy that could be related directly to the clinical response to treatment.</p> <p>Imperial researchers showed that subcutaneous immunotherapy suppressed Th2-T cell-driven allergic inflammation in the skin and nasal mucosa and that this was due to either immune deviation in favour of Th1 responses and/or the induction of a population of regulatory T cells (1). These immunological findings prompted the hypothesis that immunotherapy, unlike conventional anti-allergic drugs, was disease-modifying. In 1999, we showed subcutaneous grass pollen immunotherapy to be highly effective in severe hayfever and 3 years of treatment could induce at least 3-4 years disease remission accompanied by prolonged suppression of target organ sensitivity, a decrease in cutaneous Th2 responses and persistent IgG-blocking activity that correlated with the clinical response to treatment (2, 3).</p> <p>Despite high efficacy, the injection route was associated with 10-20% mild-moderate systemic allergic reactions and the risk of anaphylaxis. Consequently, Professor Durham and colleagues performed a double-blind trial of a sublingual (under the tongue) grass pollen allergen extract in liquid form from ALK Denmark that gave promising results (4). The same allergen extract was used by ALK to produce a fast-dissolving daily sublingual tablet (Grazax®). Professor Durham co-</p>

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developed and was principal investigator on a Europe-wide study in 2006 that showed that sublingual tablet immunotherapy was similarly effective (5). We showed that the mechanism was shown to be very similar (suppression of Th2 responses, induction of IgG4 and IgA2 blocking antibodies). Additionally we demonstrated the induction by immunotherapy of phenotypic T regulatory cells at the site of vaccine delivery within the sublingual mucosa by use of triple immunofluorescence studies of sublingual mucosal biopsies (4). During a 5 year follow up, 3 years double-blind treatment with sublingual grass allergy tablets was shown to result in prolonged benefit that persisted for 2 years after discontinuation and associated with persistent blocking antibody responses (6).

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

- (1) Durham, S.R., Walker, S.M., Varga, E.M., Jacobson, M.R., O'Brien, F., Noble, W., Till, S.J., Hamid, Q.A., Nouri-Aria, K.T. (1999). Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*, 341 (7), 468-75. [DOI](#): Times cited: 632 (as at 5<sup>th</sup> November 2013 on ISI Web of Science). Journal Impact Factor: 51.65.
- (2) James, L.K., Shamji, M.H., Walker, S.M., Wilson, D.R., Wachholz, P.A., Francis, J.N., Jacobson, M.R., Kimber, I., Till, S.J., Durham, S.R. (2011). Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol*, 127, 509-516. [DOI](#): Times cited: 36 (as at 5<sup>th</sup> November 2013 on ISI Web of Science). Journal Impact Factor: 12.04.
- (3) Durham, S.R., Ying, S., Varney, V.A., Jacobson, M.R., Sudderick, R.M., Mackay, I.S., Kay, A.B., Hamid, Q.A. (1996). Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J Allergy Clin Immunol*, 97 (6), 1356-1365. [DOI](#). Times cited: 271 (as at 5<sup>th</sup> November 2013 on ISI Web of Science). Journal Impact Factor: 12.04.
- (4) Scadding, G.W., Shamji, M.H., Jacobson, M.R., Lee, D.I., Wilson, D., Lima, M.T., Pitkin, L., Pilette, C., Nouri-Aria, K., Durham, S.R. (2010). Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells. *Clin Exp Allergy*, 40, 598-606. [DOI](#). Times cited: 59 (as at 5<sup>th</sup> November 2013 on ISI Web of Science). Journal Impact Factor: 4.78.
- (5) Dahl, R., Kapp, A., Colombo, G., de Monchy, J.G., Rak, S., Emminger, W., Rivas, M.F., Ribel, M., Durham, S.R. (2006). Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*, 118, 434-440. [DOI](#). Times cited: 192 (as at 5<sup>th</sup> November 2013 on ISI Web of Science). Journal Impact Factor: 12.04.
- (6) Durham, S.R., Emminger, W., Kapp, A. et al (2012). SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*, 129, 717-725. [DOI](#). Times cited: 32 (as at 5<sup>th</sup> November 2013 on ISI Web of Science). Journal Impact Factor: 12.04.

## Key funding:

- Medical Research Council (MRC; 1992-1994; £78,500), Principal Investigator (PI), S. Durham, Effects of treatment on inflammatory cells and cytokines in summer hayfever.
- MRC (1996-1999; £250,826), PI S. Durham, Do long lived "Th1-type" lymphocyte responses after pollen immunotherapy modify local nasal IgE/IgG4 synthesis?
- National Asthma Campaign (Asthma UK) (2000-2002; £83,031), PI S. Durham, Do IgG antibodies induced by grass pollen immunotherapy inhibit IgE-facilitated allergen presentation to T cells?
- Asthma UK (2006-2008; £125,385), PI S. Durham and H. Gould, A definitive investigation of the protective role of IgG4 in allergen immunotherapy.
- MRC (2007-2010; £179,981), PI S. Durham, A novel serum-based assay of 'functional' IgG inhibitory activity is surrogate and/or predictive of the clinical response to allergen immunotherapy for hayfever.
- Immune Tolerance Network / National Institute of Allergy and Infectious Diseases (NIAID) USA (2011-2016; £4,250,138), Single centre Study. PI S. Durham, A randomized, double-blind,

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single-center, placebo-controlled study of sublingual immunotherapy and subcutaneous immunotherapy.

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

Impacts include: health and welfare, commercial, production, international development, public policy and services

Main beneficiaries include: national/international guideline committees, World Health Organisation (WHO), regulatory bodies [US Food and Drugs Administration (FDA)], European Medicines Agency [EMA], and industry (ALK, Merck and Torii pharmaceuticals).

Allergic rhinitis (“hayfever”) affects 1 in 4 in the UK and has a major impact on work/school performance and quality of life. Community surveys in primary care show that at least 40% of sufferers remain uncontrolled despite use of antihistamines and intranasal steroids. Research from Imperial has had an impact on this unmet need as allergen immunotherapy is highly effective in patients who fail to respond to usual anti-allergic drugs. The sublingual tablet approach is novel, more convenient and safer than the subcutaneous route and has disease modifying properties that result in long-term disease remission.

The UK and Europe-wide regulatory approval of Grazax® sublingual tablets represents the first registration of an allergy vaccine in Europe for 35 years. The EMA (2013) quotes Imperial’s study as evidence of long-term efficacy of sublingual tablet immunotherapy in adults [1; see page 3] and have stated that in future all paediatric investigational plans for immunotherapy products should include a study to demonstrate long-term efficacy in children [1; see page 4]. Imperial’s long-term study of Grazax resulted in the German regulatory authorities accepting alteration of the Grazax® product label to include an indication for long-term efficacy and disease modifying effect.

Imperial’s research is frequently quoted in international guidelines as primary evidence for efficacy and long-term benefits of allergen immunotherapy. The WHO position paper on sublingual immunotherapy (2009) quotes Professor Durham’s work on the long-term benefits of immunotherapy and recommends the earlier introduction of immunotherapy in the treatment paradigm for allergic rhinitis [2; see page 269]. Similarly Professor Durham’s work is quoted in the British Society (BSACI) position paper on allergen Immunotherapy (2011), the European Allergic Rhinitis and its Impact on Asthma (ARIA) revised guideline (2010) and in the British Thoracic Society and Scottish ‘Sign’ Asthma Guideline (2012) [3; see page 33]. Imperial’s work has been showcased by the charity Asthma UK as a key impact of their research funding strategy over the past 15 years (2012) [4].

An independent budget impact analysis (2013) showed that Grazax® was cost saving compared to subcutaneous immunotherapy, saving approximately €1291 per patient per treatment course. This also implies that an additional 40% of patients could be treated sublingually without influencing the current cost for the subcutaneous treatment [5]. Another analysis concluded that sublingual immunotherapy with Grazax was cost-effective compared with standard pharmacologic management of patients with rhinoconjunctivitis and co-existing asthma [6]. The estimated cost per QALY (Quality of Life Year) gained with Grazax® was £4319, which is highly cost-effective. The long-term benefits after withdrawal of treatment have stimulated another major pharmaceutical company (Stallergenes, France) to independently research and corroborate these findings using an alternative grass allergen tablet (Oralair®) thereby expanding the availability of effective alternatives [7].

On the basis of Imperial’s research, ALK Denmark have changed their strategy in Europe to focus on sublingual rather than subcutaneous immunotherapy. For example, ALK have initiated a 5 year clinical trial of Grazax® in Europe to study the prevention of asthma in childhood (GAP study 2010-2015). They have extended the technology of sublingual allergen tablet immunotherapy to house dust mite allergy; a recent 2013 press release confirmed efficacy in two phase III studies in perennial allergic rhinitis and, importantly, in mite-sensitive adults with asthma [8]. ALK have successfully partnered with Torii pharmaceuticals in Japan to develop a fast-dissolving tablet for Japanese cedar allergy.

Immunotherapy is widely practiced in the USA where there is considerable interest in sublingual immunotherapy (Professor Durham's work is quoted in the American Academy of Allergy, Asthma and Immunology [AAAAI] Practice Parameters, JACI 2010). ALK have successfully partnered with Merck who have the franchise for sublingual tablet immunotherapy within the USA [9]. Merck have completed a pivotal study in adults that has replicated the European data for Grazax® and extended fast-dissolving tablet technology to sublingual immunotherapy for autumnal ragweed pollen allergy.

Professor Durham has increased public awareness of severe hayfever and the research of his group on immunotherapy within the UK, having been interviewed on BBC breakfast television (July 1st 2009) [10] and he recently presented his research on the BBC 'Trust me I'm a Doctor' series (October 24<sup>th</sup> 2013) [10]. His work on immunotherapy was showcased at the MRC Public Science day held at the Science Museum June 15<sup>th</sup> 2013.

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

[1] [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/11/WC500015814.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500015814.pdf). EMA/PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy (2013). [Archived](#) on 5<sup>th</sup> November 2013.

[2] Sub-lingual immunotherapy: World Allergy Organization Position Paper <http://www.waojournal.org/content/pdf/1939-4551-2-11-233.pdf> (see page 269, box 9, pts 6 and 7). [Archived](#) on 5<sup>th</sup> November 2013.

[3] [BTS Sign asthma guideline](#) recommendation for Subcutaneous immunotherapy long-term effects (page 33, recommendation 3.3.3.B and ref 207). [Archived](#) on 5<sup>th</sup> November 2013.

[4] Hanney, S.R., Watt, A., Jones, T.H., Metcalf, L. (2013). Conducting retrospective impact analysis to inform a medical research charity's funding strategies: the case of Asthma UK. *Allergy Asthma Clin Immunol*, 9 (1), 17. [DOI](#).

[5] <http://www.dovepress.com/budget-impact-analysis-of-two-immunotherapy-products-for-treatment-of-peer-reviewed-article-CEOR>. Budget impact analysis showed that grass AIT is a cost-saving alternative to SCIT when treating patients with grass pollen-induced allergic rhinitis. [Archived](#) on 26<sup>th</sup> November 2013.

[6] Nasser, S.M., Vestenbaek, U., Beriot-Mathiot, A., Poulsen, P. B. (2008). Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy*, 63, 1624-1629. [DOI](#).

[7] Didier, A., Malling, H-J, Worm, M., Horak, F., Sussman, G., Melac, M., Soulie, S., Zeldin, R.K. (2013). Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy*, 43 (5), 568-577. [DOI](#).

[8] <http://ir.alk-abello.com/releasedetail.cfm?ReleaseID=776321>

Positive results from pivotal Phase III trial of new allergy immunotherapy tablet against house dust mite-induced allergic asthma (2013). [Archived](#) on 26<sup>th</sup> November 2013.

[9] <http://ir.alk-abello.com/releasedetail.cfm?ReleaseID=751379>

License application for grass allergy immunotherapy tablet accepted for review by FDA Copenhagen (2013). [Archived](#) on 26<sup>th</sup> November 2013.

[10] BBC interview with Professor Durham 'Hope for hayfever vaccine pill' (2009) and <http://www.bbc.co.uk/programmes/p01dgd9c/features/allergies>. BBC 'Trust me I'm a Doctor' series Episode 3 October 24<sup>th</sup> 2013. [Archived](#) on 26<sup>th</sup> November 2013.

Contact: Vice President, Paul Erlich Institute for role of Imperial research in the disease modifying effect of Grazax.