PERSPECTIVE

A human touch

Stephen Holgate argues for a return to more human-centred studies of allergy and asthma.

Since the discovery of immunoglobulin E (IgE) almost half a century ago, there has been a massive expansion in knowledge about how IgE antibodies work. Research has unravelled IgE's role in a myriad of cellular and molecular targets driving inflammatory responses and underlying complex allergic disorders. This knowledge might have been expected to lead to novel preventative and therapeutic pathways — unfortunately, this has not been the case.

The dramatic rise in allergy and asthma worldwide has increased the clinical need for treatment, but research focusing heavily on IgE as the main malefactor in allergies has not been translated into widespread patient benefit.

Part of the reason lies in inherent limitations of the animal models on which researchers have so heavily depended.

Most pharma effort in drug discovery for allergy has been directed at asthma. Almost all novel therapeutics for asthma are developed using mice and, to a lesser extent, non-human primates, to investigate whether they inhibit antigen-driven models of lung inflammation. While such acute or chronic models result in a strong immune response by the T helper 2 lymphocytes (Th2) in the lungs, they fail to take account of the many other exposures that are now known to cause human asthma: genetic susceptibility; viral infection; air pollutants; and drugs such as aspirin and paracetamol.

A compounding problem with animal models is the widespread use of ovalbumen as a sensitizing antigen in trials on rodents. Ovalbumen is not a natural inhalant allergen and does not prime airway dendritic cells the same way as dust mites, pollens and other allergens do in human asthma.

Traditional therapy of allergic disease has in large part relied on the abatement of symptoms with H_1-antihistamines (rhinoconjunctivitis, food allergy, urticaria), adrenaline (anaphylaxis) or β2–adrenoceptor agonists (asthma), and the suppression of inflammation with corticosteroids. Besides improving the pharmacology of known drugs, the only novel asthma therapies to emerge are leukotriene inhibitors (for example, montelukast) and the non-anaphylactogenic anti-IgE, omalizumab, both of which are directed at targets identified well over 40 years ago.

There have been disappointments with a wide range of biologics targeting activating receptors on T cells, cytokines, chemokines, adhesion molecules and inflammatory mediators. Having shown convincing efficacy in *in-vitro* cell systems and animal models, and possibly some level of efficacy in acute allergen challenge in mild asthma, all of these have fallen short of expectations when trialled in human asthma. In moderate–severe asthma, where the unmet therapeutic need is greatest, trials of novel biologics have revealed only small subgroups in which efficacy has been shown or is suggestive.

RESEARCH FOCUSING HEAVILY ON IgE HAS NOT BEEN TRANSLATED INTO WIDESPREAD PATIENT BENEFIT – PARTLY DUE TO THE LIMITATIONS OF ANIMAL MODELS.

Most of the potential new therapeutics have been directed towards aspects of the Th2 pathway, and yet gene profiling of epithelial cells of asthmatic patients indicates that in only half of cases could they be classified as Th2 predominant. Indeed, the premise that asthma is primarily an allergic condition is a concept now being challenged, and attention is shifting to impaired innate immunity sensitizing a person to allergy.

In the future, it is essential that asthma is not treated as a single disorder, but rather defined by causative pathways. We need new diagnostic biomarkers to identify patients most likely to respond to highly selective biologics, such as anti-IL-5 biologic (mepolizumab) and anti-IL-13 (lebrikizumab). These therapies are only active in particular subtypes of asthma, when the molecules they target lie on a causative disease pathway.

Forms of allergic disease affecting organs other than the lungs have taken second place to asthma in therapeutic research, despite the large and increasing unmet clinical need. Repositioning the biologics for use in diseases other than asthma, however, is leading to some therapeutic success. Omalizumab has shown benefits in a range of diseases, including: IgE autoimmune urticaria; recalcitrant atopic dermatitis; allergic bronchopulmonary aspergillosis; and therapy-resistant systemic mast cell activation disease. It can also provide protection against anaphylaxis during food allergen immunotherapy. There have been successes, too, with mepolizumab for eosinophilic oesophagitis, Churg-Strauss syndrome and other hypereosinophilic disorders.

The *World Allergy Organization White Book on Allergy* stresses that allergy and asthma have not only increased in prevalence, but also in severity and complexity — with attendant health costs. Recognizing that they are reaching worrying proportions, it is necessary to focus more on studying all these diseases as they occur in humans, using well-phenotyped patients, biomarkers and experimental medicine approaches. Understanding the pathobiology of the disease in well-phenotyped humans will then enable a direct assessment of clinical efficacy, using relevant disease-related stressors besides allergen challenge, such as viruses and pollutants. A different type of more open and trusting relationship is also needed between academia and industry, where greater collaboration is encouraged in the pre-competitive space. The current model of blockbuster drug discovery is unsustainable. ■

Stephen Holgate *is UK Medical Research Council Clinical Professor at the University of Southampton, Honorary Consultant Physician at the Southampton University Hospital NHS Trust and Chairman of the UK Respiratory Research Collaborative.*
e-mail: s.holgate@soton.ac.uk