

Review article

The future of immunotherapy. Report of a National Institute of Allergy and Infectious Diseases (NIAID), Division of Allergy, Immunology and Transplantation (DAIT) Workshop

Recent advances in the molecular sciences make possible new and innovative immunotherapeutic approaches to the treatment of human asthma and allergic disorders. In 2005, the National Institute of Allergy and Infectious Diseases, Division of Allergy, Immunology and Transplantation, sponsored a workshop entitled *Immunological Basis of Antigen-specific Asthma/Allergies Therapeutic Strategies Meeting*. International experts in the field of asthma and allergy immunotherapy discussed the current state of immunotherapy, and made recommendations for future areas of research aimed at advancing our knowledge and understanding of immunotherapy for asthma and allergic diseases. The workshop recommendations are presented herein.

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Key words: allergens; clinical trials; immunotherapy; subcutaneous immunotherapy; sublingual immunotherapy.

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Accepted for publication 11 August 2006

On November 14, 2005, the National Institute of Allergy and Infectious Diseases (NIAID), Division of Allergy, Immunology and Transplantation (DAIT) sponsored a workshop entitled *Immunological Basis of Antigen-specific Asthma/Allergies Therapeutic Strategies Meeting*. NIAID is a component of the National Institutes of Health (NIH). Workshop participants included international experts in the field of asthma and allergy immunotherapy. Keynote presentations were made by Dr David H. Broide of the University of California at San Diego on *Basic Immunology Relevant to Allergen Immunotherapy*, by Dr Martin D. Chapman from Indoor Biotechnologies, Inc., on *Allergens Relevant to Allergen Immunotherapy*, and by Dr Philip S. Norman of the Johns Hopkins Asthma and Allergy Center, on *Allergen Immunotherapy*. These presentations were followed by three roundtable discussions on immunotherapy topics including basic immunology, allergens, and clinical applications. The roundtable discussions focused on developing recommendations for future areas of research that will advance our knowledge

and understanding of immunotherapy for asthma and allergic diseases and identify barriers to such advancement.

Basic immunology roundtable

Co-chairs: Dr Dale T. Umetsu (Children's Hospital, Boston, MA) and Dr Judith A. Woodfolk (University of Virginia Health System, Charlottesville, VA)

Participants discussed the mechanisms of immunotherapy for immunoglobulin E-mediated disorders, including blocking antibodies, immunomodulation, tolerance induction by activation of regulatory T cells, T-cell anergy, and/or clonal deletion, and the role of innate immunity. It was noted that appropriate reagents and resources must become available to ensure the success of future immunotherapeutic research and clinical trials. Low frequencies of antigen-specific T cells in human blood make them difficult to isolate and characterize.

Therefore, it will be necessary to develop new techniques and technologies to identify and assess immune mechanisms associated with immunotherapy, such as major histocompatibility complex (MHC) tetramers.

Two primary methods of immunotherapy were discussed – subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In particular, the panelists recognized the need for studies that define the molecular and cellular mechanisms of SLIT. It is necessary to determine if the safety and effectiveness characteristic of SLIT can be attributed to distinct dendritic cell subsets and/or very low numbers of mast cells under the tongue.

The panelists suggested that the mechanism of immunotherapy could be separated into distinct early and late responses. For example, some effects might be observed shortly after beginning therapy (e.g. mast cell FcγRII-mediated inhibitory signaling, antibody effects, immune deviation, actions of regulatory T cells) and some effects could occur later during the course of therapy (e.g. antibody-independent immune tolerance and/or clonal T-cell deletion and/or anergy). The innate immune system is also likely to play a separate, but key, role during both phases of the response to immunotherapy.

Recommendations made by members of the panel include:

- 1 more fully characterize the role of dendritic cells in the host response to immunotherapy;
- 2 design and conduct clinical studies to determine and clarify the roles of T-regulatory cell subsets in mediating harmful immune responses to specific allergens in allergic subjects and in mediating tolerance, anergy or clonal T-cell deletion in response to immunotherapy;
- 3 clinical trials should include the use of chemically defined and standardized immunotherapeutic allergens coupled to an assessment of host immune mechanisms, using contemporary immunologic methods, in response to allergen immunotherapy;
- 4 expand chemical characterization of known and novel allergens: establish a repository of standardized allergens; develop MHC tetramers to T-cell epitopes, in particular epitopes recognized by T cells in an MHC class II-dependent manner; and comprehensively identify (map) the T-cell epitopes of clinically important allergens;
- 5 conduct clinical studies to define the molecular and cellular immune mechanisms involved in early host responses vs long-term or late-phase responses;
- 6 improve methods for translating findings in allergen immunotherapy clinical studies to clinical practice; and
- 7 encourage and foster the use of animal models to identify molecular and cellular mechanisms of interest and as important systems for preclinical testing to support clinical studies.

Allergens roundtable

Co-chairs: Dr Robyn O'Hehir (The Alfred Hospital, Melbourne, Australia), Dr Jay Slater (Food and Drug Administration Center for Biologicals and Evaluation Research, Rockville, MD), and Dr David Golden (Johns Hopkins University, Baltimore, MD)

The panel identified a number of issues to address in order to facilitate the selection and use of allergens in immunotherapy, including: measuring potency; optimizing formulation; and assessing the relative efficacy of single vs multiple allergen preparations. Despite the extensive body of work focused on the characterization and purification of allergens, there is still much left to discover. For example, the minimum amount of allergen and the structural elements required to induce immunologic tolerance are not well understood. Ongoing work focuses on the purification of crude allergen mixes, identification of immunodominant proteins, creation of recombinant allergens, and the production of small allergen peptides. The importance of understanding the contribution of immunostimulatory contaminants, such as lipopolysaccharide (LPS or endotoxin) to the potency of allergen preparations was also discussed. Significantly, recombinant allergen preparations appear to have 20- to 100-fold less LPS than allergen extracts, yet recombinant allergen immunotherapy remains clinically effective. It was noted that the goal of the European Union's CREATE program (<http://macehead.nuigalway.ie/create/>) is the development of allergen standards and currently, the IDEAL50 method is used to standardize allergens.

The panel noted that, to date, no specific laboratory assay is sufficiently accurate to replace skin testing to assess the success of immunotherapy, and recommended that future clinical research focus on identifying biomarkers of disease. In addition, the optimal combination of allergens (e.g. single vs multiple allergens) has yet to be determined and should be included in the criteria for selecting allergens for immunotherapeutics.

Recommendations made by members of the panel include:

- 1 conduct basic research that will lead to the development of improved methods for measuring allergen potency;
- 2 conduct clinical studies that will determine when to use a single allergen or multiple allergens, for immunotherapy;
- 3 conduct clinical studies that would facilitate the identification and prioritization of allergens from clinically relevant sources (e.g. tree and grass pollens, dust mites, dogs, cat, cockroaches, and nuts);
- 4 determine whether LPS contamination in allergen preparations has any significant effect on clinical efficacy of the preparations;

- 5 develop methods to manufacture standardized recombinant allergens that are clinically relevant for use in immunotherapeutic trials under good clinical practice (GCP); and
- 6 continue epitope mapping of allergens to facilitate the development of new reagents, assays, biomarkers of disease, and new immunotherapeutic approaches.

Clinical applications roundtable

Co-chairs: Dr Harold Nelson (National Jewish Medical and Research Center, Denver, CO) and Dr Jean Bousquet (Hospital Arnaud de Villeneuve, Montpellier, France)

The panel discussed the existing data on immunotherapy with an emphasis on the variations between diseases and conflicting clinical results. Immunotherapy is effective for allergic rhinitis and clinical improvement persists for years after therapy is stopped. A Cochrane database review of the use of SCIT in asthma found an association between immunotherapy and reductions in symptoms, medication use, and bronchial hyperreactivity (1). In contrast, a carefully controlled trial in allergic asthmatic children found a striking placebo effect and little to no improvement induced by immunotherapy (2). Other asthma studies, principally from Europe that looked at the use of SLIT have also yielded conflicting results. More promising results using SCIT in children with allergic rhinitis found that therapy can prevent the development of asthma, rather than simply control symptoms (PAT-study; 3). The panel noted that the ability to compare various immunotherapy studies has been hindered by differences in the populations studied, allergens used, duration of therapy, and outcomes measured.

Recommendations made by members of the panel include:

- 1 conduct well-designed immunotherapy clinical trials using standardized allergens to investigate: (i) control of asthma disease symptoms; (ii) prevention of the

- development of asthma; (iii) identification of subgroups who would most benefit from immunotherapy; and (iv) determination of the benefits or problems with using single vs multiple allergen immunotherapy;
- 2 develop biomarkers to use as outcome measures of successful immunotherapy-induced immune tolerance;
- 3 the potential benefits of SLIT must be considered in the context of monosensitized vs polysensitized patients, underscoring the need for a clinical trial using SLIT in young children sensitized to single and multiple allergens; and
- 4 the utility of SLIT in reducing the symptoms, or the initial development, of asthma should be thoroughly investigated, including whether SLIT can benefit both atopic and nonatopic asthma patients.

Conclusions

In order to advance clinical trials using chemically well-defined allergens and reagents, support is needed for core facilities that will use innovative techniques to isolate, purify, and identify novel allergens from various sources. Additionally, funds are needed to support the identification and characterization of peptides containing T-cell epitopes that induce anergy in allergen-specific effector T cells, or activate allergen-specific regulatory T cells.

The panel identified the need for future clinical trials to examine and compare the clinical effectiveness of SCIT and SLIT particularly with respect to clinical effectiveness, the short-term and long-term therapeutic benefits and the underlying mechanisms associated with these benefits.

Acknowledgment

The authors are indebted to the efforts of the workshop Co-chairs and the workshop panel members.

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