Allergology International (1998) **47**: 159–161

Editorial

Future of allergen-specific immunotherapy

Takeru Ishikawa

On 27–29 January 1997 a workshop regarding allergen-specific immunotherapy was held at WHO headquarters in Geneva, Switzerland in order to establish a position paper which might represent international consensus. A total of 22 participants from 11 countries met to discuss standardization of the concept, therapeutic methods, as well as the future of immunotherapy. The meeting was co-chaired by J Bousquet, RF Lockey and H-J Malling.

At the beginning of the meeting, we discussed the term 'allergen vaccine', which appeared in the title of the position paper, 'Allergen immunotherapy: Therapeutic vaccines for allergic diseases'. Despite some reservations the committee agreed to use the term 'allergen vaccine'. The idea of the allergen immunotherapy, which was first tried by Curtis in 1890 on patients with pollenosis, originated in a 'vaccine' to protect immunologically against out-coming foreign bodies. Polatino, horse antiserum to pollen allergen, which was developed by Dunbar in 1903, really originated from an idea of antiserum vaccine against microorganisms, and even allergen-specific hyposensitization therapy tried by Noon in 1911,[1] was also based on the concept of vaccination against pollen-toxins.

The purpose of immunotherapy should be the primary or secondary prevention of hyperreactivity by the induction of hypo-responsiveness to the allergenic substances, which are causative to IgE antibody production. Therefore, there may be some differences in the concept between immunotherapy to allergic diseases and vaccination. However, a mechanism producing clinical effectiveness has not conclusively been clarified yet. Each of the theories proposed by successive researchers, such as theories of blocking antibodies, suppressor T cells, shift to Th1 from Th2 dominance and tolerance/anergy, are still considerable candidates for explaining immunological effectiveness.

From a practical point of view, standardization of the allergens, efficacy, risk and indication of immunotherapy were discussed and revised several times, and finally a consensus was reached by the co-chairpersons on the proposed draft, which will be published in the near future. Among them, other routes for the application of allergens besides subcutaneous injection,[2–4] such as oral, sublingual, nasal and bronchial, drew my attention. Although many reports were tabled concerning this, more extensive studies may be needed to establish the methodology because this form of therapy may result in discomfort and inconvenience given the frequent injections. In addition, the direct application of allergen, either native or modified, to the local tissue may be more promising for controlling mucosal immune response.

In the last section of the meeting, several future strategies for immunotherapy were proposed, such as active immunotherapy using nonanaphylactic allergens; allergen-fragments or peptides; IgE-binding haptens of major allergens for passive saturation of effector cells; plasmid DNA immunization; allergen-specific antibodies and antibody fragments for passive therapy in the allergic effector organs; and immunotherapy with humanized anti-IgE monoclonal antibodies or IgE-mimotopes.

I would like to take the opportunity to comment on allergen peptides for active immunotherapy. The recent development of chemistry has accelerated study on the analysis of responsible allergenic epitopes in peptide levels. Furthermore, a mechanism of conversation between T cell receptor (TCR) and antigen presenting cells (APC) expressing antigen epitope cognate with MHC molecule, HLA in humans, has now been clarified. In addition, results of the studies informed us of an important fact: that the activated T cell, through the specific antigen stimulation, releases various cytokines which modulate the immune reaction. The recognition system is common to most of immune reactions including autoimmune, cancer immune, as well as immune response to out-coming antigenic substances such as micro-organisms, allergens and so on. Regarding IgE mediated allergies, it has been understood that HLA class II is essential to specific recognition of TCR as a restriction molecule. Also, the HLA class II allergen peptide complexes stimulate Th2, releasing characteristic cytokines, such as IL-3, 4, 5, 6, 10, 13 and so on. It has been generally accepted that the allergic

Correspondence: Allergy and Immunology Centre of Kyushu, 3-20-1 Hattanda, Kumamoto 862-0934, Kumamoto, Japan.

target tissues are dominantly infiltrated by activated Th2.

Th1, on the other hand, is characterized by released cytokines, such as IL-2, IL-3, IFN-γ, TNF-β, TNF-α, GM-CSF and so on. In addition, as is well known, IFN-γ inhibits the production of IgG1 and IgE elicited by IL-4. Therefore, in this sense the purpose of allergen immunotherapy may be the induction of a Th1 dominant state, shifted from Th2 in the allergic targets.

Sloan-Lancaster et al.[5] and Briner et al.[6] have documented that antigen specific T-cell anergy could be induced by an injection of antigen under a certain condition in mice. Furthermore, clinical trials have already been undertaken using synthetic allergen peptides derived from cat dander allergen Fel d1 in the USA,[7] which might be based theoretically on the induction of allergen specific T cell anergy. In this sense, the induction of anergy or tolerance to a specific allergen must be an aim of the immunotherapy.

Considering these two theories, there is some confusion regarding which allergen epitope should be used for the immunotherapy: responsible epitope to stimulate Th1 releasing IFN-γ,[8] or responsible epitope to stimulate Th2 inducing T cell anergy.

There have been reports of established cloned or lined T cells reacting to various allergen peptides derived from dermatophagoides,[9] ragweed,[10] cat dander,[11] rye grass,[12] timothy,[13] birch pollen,[14] Japanese cedar pollen[15] and so on. Their cytokine production profile indicated that the clones or lines were mostly Th2 dominant. However, it has often been observed that multiple epitopes in allergen peptides react to T cells from one individual, and that the reacting epitope is different from patient to patient. We also confirmed that T cell lines from 12 patients allergic to Japanese cedar pollen reacted to various overlapping peptides derived from the purified Japanese cedar pollen allergen, Cry j1.[16] In addition, cytokine release profiles found in this experiment indicated that the one definite peptide did not always stimulate the same type of T cell, either Th1 or Th2. For instance, one peptide activated Th2 from one individual and released dominantly IL-4; however, the same peptide proliferated Th1 from another individual and released IFN-γ. Therefore, it can be said that multiple T cell epitopes in each allergen may complicate immunotherapy, as has been pointed out by van Neerven.[11] As seen in the clinical trial of immunotherapy to Fel d1 sensitive patients, multiple peptides may have to be used as the therapeutic allergens for more than 80% of patients treated. However, it remains debatable whether Th1 or Th2 should be targeted.

Thus, peptides as a T cell epitope have several practical merits in immunotherapy; nonanaphylactic allergen, capacity to use a large amount of antigen, and high accuracy of antigen standardization. These merits may provide the variety of routes for application of peptide allergens, namely oral, sublingual, nasal or bronchial as well as intradermal injection, mentioned above. However, study on drug carrier technology may be important in facilitating more effective absorption of peptide molecules from the airway or alimentary mucosa.

Therefore, further basic and practical studies still need to be undertaken in order to establish the exact effect of the peptide immunotherapy, as well as to establish methods of inducing hyporesponsiveness against allergens while avoiding any side-effects.

References

1 Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911; **i**: 1572–3.

2 Mowat AM. Oral tolerance and regulation of immunity to dietary antigens. In: Ogra PL, Mestecky J, Lamm ME, Strober W, McGhee JR, Bienenstock J, eds. *Handbook of Mucosal Immunology*. London: Academic Press, 1994: 185–201.

3 Malling H-J. Sublingual immunotherapy. *Clin. Exp. Allergy* 1996; **26**: 1228–31.

4 Welsh PW, Butterfield JH, Yunginger JW *et al.* Allergen-controlled study of intranasal immunotherapy for ragweed hay fever. *J. Allergy Clin. Immunol.* 1983; **71**: 454–60.

5 Sloan-Lancaster J, Shaw AS, Rothbard JB *et al.* Partial T cell signaling: altered phospho-ζ and lack of Zap 70 recruitment in APC-induced T cell anergy. *Cell* 1994; **79**: 913–22.

6 Briner TJ, Kuo MC, Keating KM *et al.* Peripheral T-cell tolerance induced in naive and primed mice by subcutaneous injection of peptides from the major cat allergen Fel d1. *Proc. Natl Acad. Sci. USA* 1993; **90**: 7608–12.

7 Norman PS, Nicodemus CF, Creticos PS *et al.* Clinical and immunologic effects of component peptides in Allervax Cat. *Int. Arch. Allergy Immunol.* 1997; **113**: 224–6.

8 Lack G, Nelson HS, Amran D *et al.* Rush immunotherapy results in allergen-specific alterations in lymphocyte function and interferon-γ production in CD4+ T cells. *J. Allergy Clin Immunol.* 1997; **99**: 530–8.

9 Yssle H, Johnson KE, Schneider PV *et al.* T cell activation-inducing epitopes of the house dust mite allergen Der p1: Proliferation and lymphokine production patterns by Der p1-specific CD4+ T cell clones. *J. Immunol.* 1992; **148**: 738–45.

10 Huang SK, Zwollo P, Marsh DG. Class II major histocompatibility complex restriction of human T cell responses to short ragweed allergen, Amb aV. *Eur. J. Immunol.* 1991; **21**: 1469–73.

11 van Neerven RJJ, van d Pole MM, van Milligen FJ *et al.* Characterization of cat dander specific T lymphocytes from

atopic patients. *J. Immunol.* 1994; **152**: 4203–10.
12 Spiegelberg HL, Beck K, Stevenson DD *et al.* Recognition of T cell epitopes and lymphokine secretion by rye grass allergen Lokium perenne I-specific human T cell clones. *J. Immunol.* 1994; **153**: 4706–11.
13 Shenk S, Breiteneder H, Susani M *et al.* T cell epitopes of Phl p1, major pollen allergen of timothy grass (Phleum pratense): Evidence for crossreacting and non-crossreacting T-cell epitopes within grass group I allergens. *J. Allergy Clin. Immunol.* 1995; **96**: 986–96.
14 Ebner C, Szepfalusi Z, Ferreira F *et al.* Identification of multiple T cell epitopes on Bet v1, the major birch pollen allergen, using specific T cell clones and overlapping peptides. *J. Immunol.* 1993; **150**: 1047–54.
15 Ikagawa S, Matsushita S, Chen Yu-Z *et al.* Single amino acid substitutions of a Japanese cedar pollen allergen (Cry j1)-derived peptide induced alterations in human T cell responses and T cell receptor antagonism. *J. Allergy Clin. Immunol.* 1996; **97**: 53–64.
16 Ishikawa T, Ikagawa S, Masuyama K *et al.* Human T cell response to antigen peptides of Japanese cedar pollen (Cry j1). *Int. Arch. Allergy Immunol.* 1996; **113**: 255–7.