

## Editorial

# Allergens in 1998: from molecular biology to improved patient care

Allergens are antigens that react to specific IgE antibodies. Since the discovery by Charles Blackley in the 1860s that pollens can cause allergic diseases, the number of allergenic substances which have been identified has increased enormously. Originating from a wide range of higher animals, insects, plants, and fungi, allergens are low-molecular-weight chemicals. They include proteins or glycoproteins from inhalant allergens, foods, drugs, or insect venoms; haptens from occupational agents or drugs; and, more rarely, glycans, as in the case of allergy to *Candida albicans*.

The first purified allergens were obtained in the 1960s by protein chemistry (1). However, major advances have been made recently in allergen characterization and sequence determination by chemical, immunochemical, biochemical, and molecular biology techniques (2). Tremendous progress has been made in identifying, cloning, and expressing the major allergens since 1988 when the first cDNA sequence of an allergen was published (3). The cDNAs of a large number of important allergens have now been isolated and sequenced, including mites, insects, Hymenoptera venoms, animal proteins, pollens, molds, and foods (4, 5). Recombinant cDNA technology has considerably increased our knowledge of allergens, since this powerful tool can provide large numbers of identical cloned allergens.

These new technologies make it possible to characterize the structure of allergens and are improving the standardization of allergen extracts (6), and they are likely to improve the diagnosis and treatment of allergic patients. Just a few examples may indicate how our allergy practice will be modified by this technology. Bet v 1, the major allergen of birch pollen, is one of the most studied allergens and a member of a multigene family. Several Bet v 1 isoforms and homologous proteins from closely related species (alder, hazel, and hornbeam) have been isolated and their cDNAs cloned and characterized. This considerable degree of heterogeneity has been attributed to glycosylation (or other post-translational modifications) or to isogenes coding for Bet v 1 isoforms and/or allelic variants (7). It was shown that individual

birch trees produce various subsets of isoallergens which display differences in reactivity to both IgE antibodies and T cells in man (8). Recombinant isoforms of Cor a 1, the major allergen of hazel pollen which shares great homology with Bet v 1, show different reactivities to allergen-specific T-cell clones (9). Analysis of IgE and T-cell reactivity of isoforms of the major birch-pollen allergen Bet v 1 suggests a potential use of hypoallergenic isoforms for immunotherapy (10). X-ray crystal structures of Bet v 1, birch-pollen profilin, and Phl p 2 have been studied (11, 12), and new forms of immunotherapy may be found, since a detailed description of the major reactive epitopes may help to design tight-binding monovalent ligands which can prevent receptor aggregation and thereby reduce the allergic response. Another promising strategy to increase the safety of immunotherapy is through the use of allergen derivatives which do not cause anaphylaxis. Such hypoallergenic isoforms have been produced *in vitro* for Der p 2 and Bet v 1 by site-directed mutagenesis (13-15).

These molecular biology-based approaches have also improved our knowledge of cross-reactivity among allergens. Identification of allergens in fruits and vegetables showed IgE cross-reactivities with the important birch-pollen allergens Bet v 1 and Bet v 2 (birch profilin) (16). Many other cross-reactive antigens have also been identified and characterized. Depending on the main cross-reactive allergen, different symptoms may be observed. Bet v 1 in apples, cherries, peaches, and plums mainly causes mild symptoms such as oral allergy syndrome. However, Bet v 1 associated with other allergens may cause generalized symptoms. Sensitization to Bet v 2 is more often associated with generalized symptoms; in particular, urticaria and angioedema.

Most allergens have associated activities with potent biologic functions. Most allergens can be divided into several broad groups based either on their demonstrable biologic activity or significant homology with proteins of known function (17). They include enzymes, enzyme inhibitors, proteins involved in transport, and regulatory proteins. Profilins, ubiquitous, low-molecular-weight (13 000-

15 000  $M_r$ ) actin-binding proteins (18), regulate the formation of F-actin structures *in vivo*, and are localized to specific cellular regions through interaction with proline-rich sequences closely associated with actin filaments. They were shown to be crucial for cytoskeletal rearrangements such as those essential to the process of pollen tube growth (19). The major birch-pollen allergen, Bet v 1, shows ribonuclease activity (20); it may include a subset of defense-related genes that are activated in the presence of microbial pathogens (21) and may be involved in anther ontogeny (22). Most mite allergens are associated with enzymatic activities. Many of these are digestive enzymes (23), the specificities of which may differ depending upon the substrate on which the mites are growing; e.g., human skin scales for mites of the *Dermatophagoides* genus or grain and fungi for storage mites.

In view of the explosion of information generated by the identification, cloning, and expression of allergens, it seems appropriate, in 1998, to begin a series of articles on allergens which will be published in subsequent issues of *Allergy*. These articles will deal with the newer concepts of allergen chemistry, molecular biology, and genetics. Moreover, some papers will be of more clinically relevant interest to readers.

In the papers of this series, the same nomenclature will be used, and we report here a summary to help the reader. Allergen nomenclature has been standardized by the WHO/IUIS Allergen Nomenclature Subcommittee (24). Allergens are designated according to the taxonomic name of their source as follows: the first three letters of the genus name, space, the first letter of the species name, space, and an Arabic numeral. The numbers are assigned to the allergens in the order of their identification, and the same number is generally used to designate homologous allergens of the related species. For example, Der p 1 was the first *Dermatophagoides pteronyssinus* allergen identified, and Der f 1 refers to the homologous allergen of *D. farinae*. If necessary, an additional letter is added to the genus or species name abbreviation to avoid ambiguity; e.g., a distinction is made between antigen 5 of *Vespula vulgaris* and that of *V. vidua* with *Ves v 5* and *Ves vi 5*. Moreover, isoallergens and variants are indicated by an additional four numerals, the first two identifying the isoallergen and the second two the variant. Thus, Amb a 1.01 is an isoallergen and Amb a 1.0101 is a variant. The revised nomenclature was published in 1995 and is given together with the proposed nomenclature systems for allergen genes, mRNAs, and cDNA, as well as for recombinant synthetic peptides of allergenic interest. In the revised allergen nomenclature, a definition of "major" and

"minor" allergens has been proposed. When over 50% of the patients tested have the corresponding allergen-specific IgE, allergens can be considered "major".

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