
CME review

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T-cell epitopes of aeroallergens

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Objective: To describe the current knowledge of the T-cell epitopes of common aeroallergens, how they were discovered, and implications for future therapy.

Data Sources: PubMed search of English-language articles without date limits pertaining to T-cell epitopes of aeroallergens included on a standard skin test panel.

Study Selection: A total of 127 articles were screened based on the results of the PubMed search and cross-indexed as needed. The highest quality and most clinically relevant articles were included for discussion.

Results: Of the 47 allergen extracts included on the standard skin test panel at our institution, T-cell epitopes have been described for 13. Immunodominant epitopes have been used for peptide immunotherapy trials.

Conclusions: T-cell epitopes have been characterized for a minority of common aeroallergens. However, knowledge is rapidly expanding and can lay the groundwork for therapies that specifically target T cells.

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INTRODUCTION

Clinical allergists are adept at assessing the humoral response to allergens by testing for specific IgE, but most allergists are unable to evaluate T-cell response at the peptide level. This article provides a primer for practicing allergists to explore some of the exciting discoveries in the field of cellular response to peptides. We hope this information can facilitate understanding of emerging diagnostic and therapeutic tools in our specialty.

Much of the early understanding of allergy focused on humoral immunity before knowledge of cell-mediated mechanisms expanded. Although many of the practicing allergist's tools detect the presence of specific IgE, knowledge of the cellular arm's role in allergy has increased since the discov-

ery of IgE in 1968.¹ In 1975, Geha and colleagues² showed that B cells do not produce antibodies specific for ragweed antigen E (later called Amb a 1) without T-cell help. Interleukin 4 was established as a critical factor that T cells produce to induce IgE production by B cells in 1988.³ Compartmentalization of CD4⁺ T_H cells into T_H1 and T_H2 systems was also established in the 1970s and 1980s.⁴ Reciprocity between the T_H1 and T_H2 systems, as well as demonstration of specific suppressor cells generated during immunotherapy,⁵ suggested mechanisms for the efficacy of allergen immunotherapy. Current understanding of its mechanisms includes a shift from a T_H2 to a T_H1 cytokine profile, generation of T-regulatory cells (Tregs), and possibly through generation of allergen specific IgG antibodies.⁶ Tregs often express the transcription factor Foxp3, which can be useful in determining Treg response to specific peptides.

Despite the importance of T cells in mediating allergic diseases, no tests or therapies that specifically target T cells are available to the clinical allergist for IgE-mediated disease. Currently, allergen immunotherapy uses commercial allergen extracts that are complex mixtures of several types of molecules, including the relevant major allergens. These proteins,

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by definition, are capable of binding IgE. During allergen immunotherapy, these proteins are incorporated by antigen presenting cells (APCs) and presented as peptides to T cells. Proteins in immunotherapy have the ability to both decrease allergic symptoms (through Tregs) and cause anaphylaxis. Allergens with diminished IgE binding (or simply peptides) could be used in immunotherapy, modulating the immune response without the risk of anaphylaxis. For example, Litwin et al⁷ demonstrated the effectiveness of immunotherapy using enzymatically degraded ragweed allergen.

Enzymatic degradation is a concern in formulating allergen immunotherapy.⁶ Allergens with high proteolytic activity (usually mold extracts) are placed in separate vials from other allergens out of concern that they could degrade other allergens. This practice is based on studies showing decreased binding of IgE to degraded allergens.^{8,9} How this degradation affects T-cell recognition of allergens is unknown. The purpose of this article is to determine what is known about the T-cell epitopes of common aeroallergens, including how they were discovered and possible implications on future therapy to guide the practicing allergist as new information emerges.

METHODS

PubMed was searched using the phrase *T cell epitopes of* (common name of allergen), (scientific name of allergen), or (major allergen) for each selected allergen without date limits. No common name was used for molds. Articles were cross-referenced as needed. Relevant English-language articles were selected for discussion. The queried allergens were chosen from the allergen extracts used for the standard skin prick test panel at Wilford Hall Medical Center, San Antonio, Texas.

RESULTS

A total of 127 relevant articles were screened based on the described search terms. Table 1 summarizes the results for the common aeroallergens for which T-cell epitopes have been described. Table 2 lists the common aeroallergens for which T-cell epitopes have not been described and lists the search terms used for the literature search. T-cell epitopes have been described for 13 of the 47 selected allergen extracts. In addition, T-cell epitopes are defined for Japanese cedar and cypress. These trees are not included for testing at Wilford Hall Medical Center but are homologous with mountain cedar. Notably, T-cell epitopes are characterized for all of the common indoor allergens. Dust mite revealed the most articles, followed by birch and cat.

DISCUSSION

Birch

T-cell epitopes of birch have been well characterized. Ebner and colleagues¹⁰ identified 7 T-cell epitopes by stimulating T cells from birch-allergic patients with a panel of 75 overlapping dodecapeptides based on the known Bet v 1 amino acid

sequence. This work was further refined, showing that several regions have T-cell specificities but that Bet v 1_{142 to 156} is the dominant epitope for 61% of patients.¹¹ Furthermore, Bet v 1_{142 to 156} was compared with the corresponding amino acid sequence of several foods that are commonly cross-reactive with birch in the oral allergy syndrome. Bet v 1_{142 to 156}-specific T-cell lines (TCLs) were stimulated with the peptide sequences from the selected foods, and 71% of these TCLs proliferated in response to 1 or more of the food peptides.

A Bet v 1_{141 to 155} tetramer has been used to further define the expression of birch-specific T cells.¹² The frequency of Bet v 1_{141 to 155}-specific T cells was much higher during the pollen season than in the winter season (10^{-3} vs 10^{-6} of circulating CD4⁺ T cells, respectively) and were expressed in all patients after stimulation. However, Foxp3^{bright} CD4⁺ cells specific to birch were found at much higher levels in healthy patients compared with birch-allergic patients.

Alder

Peptides that are cross-reactive among the related species birch, hazel, and alder have been demonstrated.¹³ Sequences of Cor a 1 (hazel) and Aln g 1 (European alder), corresponding to T-cell epitopes of birch, stimulated birch-reactive T-cell clones (TCCs).

Olive

Several T-cell-reactive peptides of Ole e 1 have been described in both patients who produce specific IgE to Ole e 1 and in patients who do not.¹⁴ High concentrations of the overlapping peptides do not inhibit IgE binding to Ole e 1, suggesting different B- and T-cell epitopes. In general, one would expect peptides possibly to bind linear, but not conformational, IgE epitopes. Peptides that bind linear IgE epitopes would not be good candidates for use in peptide immunotherapy because they could cause anaphylaxis similar to native allergen extracts.

Japanese Cedar and Cypress

T-cell epitopes of mountain cedar have not been identified, but mountain cedar is clinically cross-reactive with Japanese cedar and there is a high degree of sequence homology among the major allergens of mountain cedar, Japanese cedar, and Japanese cypress.¹⁵ Significantly fewer patients with HLA-DR4 have mountain cedar allergy compared with patients with other HLA types, implying a difference in how different major histocompatibility complex (MHC) molecules present mountain cedar peptides.¹⁶ T-cell epitopes of the major allergens of Japanese cedar, Cry j 1 and Cry j 2, have been well described, and T-cell proliferation was demonstrated using a synthetic peptide containing 5 major T-cell epitopes, termed *cry-consensus*, as indicated in Table 1.¹⁷ Several T-cell epitopes have also been identified for Japanese cypress.¹⁸ Cry j 1 peptide fragments have been expressed in transgenic rice seed as a possible means of oral immunotherapy.¹⁹

Table 1. Common Aeroallergens With Discovered T-Cell Epitopes

Allergen extracts	Major allergens	Immunodominant T-cell epitope(s) ^a	Methods
Trees			
Red alder (<i>Alnus rubra</i>)	Aln ru	Partially described ^b	Human TCL stimulation
Birch (<i>Betula verrucosa</i>)	Bet v 1	142–156	
Arizona cypress (<i>Cupressus arizonica</i>)	Cup a 1	Not described ^c	
Mountain cedar (<i>Juniperus ashei</i> ; also <i>Juniperus sabinoides</i>)	Jun a 1	Not described ^d	
Japanese cypress (<i>Chamaecyparis obtusa</i>) ^e	Cha o 1	11–30, 211–230, 251–270, 331–350	Human TCL stimulation
Japanese cedar (<i>Cryptomeria japonica</i>) ^e	Cry j 1, Cry j 2	211–225, 108–120 (for Cry j 1), 182–200, 344–355, 66–80 (for Cry j 2)	Human PBMC stimulation
Olive (<i>Olea europaea</i>)	Ole e	91–102, 109–130 (in sensitized patients)	Human PBMC stimulation
Grasses			
Bermuda (<i>Cynodon dactylon</i>)	Cyn d 1	109–128, 181–209, 217–241	Human TCL stimulation
Ryegrass (<i>Lolium perenne</i>)	Lol p 1	190–210, 19–38	Human PBMC and TCL stimulation
Timothy (<i>Phleum pratense</i>)	Phl p 1	Multiple (Phl p 1), 16–42, 94–120, 136–150, 181–207, 238–252 (Phl p 5b)	Human TCL and TCC (Phl p 1) and TCC (Phl p 5b)
Weeds			
Ragweed (giant, short, western; <i>Ambrosia</i> spp)	Amb a 1	51–65 (for Amb a 3), 21–37 (Amb a 5), 21–34, 27–40 (Amb t 5)	Mouse lymph node cell stimulation
Sagebrush or mugwort (Douglas; <i>Artemisia vulgaris</i>)	Art v 1	25–36 (minimal epitopes contain region 28–32)	Human TCL and TCC stimulation
Molds			
<i>Aspergillus fumigatus</i>	Asp f 1	46–65, 106–125, ³¹ 36–84, 115–130, 135–146 ³²	Human TCC ³¹ and PBMC ³² stimulation
Indoor Allergens			
House dust mite (<i>Dermatophagoides pteronyssinus</i>)	Der p	Many, see text	Mouse and human
House dust mite (<i>Dermatophagoides farinae</i>)	Der f	18–38, 44–64, 75–94, 128–148, 137–157, 155–175, 200–217, 206–223	Human TCL stimulation
Cat (<i>Felis domesticus</i>)	Fel d 1	7–33, 29–55 of chain 1, 1–20 of chain 2	Chain 1 epitopes used for immunotherapy, ^{42,43} chain 2 epitope described in atopic dermatitis using cytokine profiles ⁴⁵
Dog (<i>Canis familiaris</i>)	Can f 1	15–30, 33–48, 49–64, 73–88, 107–122, 123–138, 141–156	Human TCL and TCC stimulation
Cockroach mix (German, American; <i>Blattella germanica</i> , <i>Periplaneta americana</i>)	Bla g 1, Per a 1	91–110, 161–180, 151–170 (for Bla g 5)	Described for German cockroach in transgenic mice

Abbreviations: TCL, T-cell line; PBMC, peripheral blood mononuclear cell; TCC, T-cell clone.

^a Numbers refer to position in amino acid sequence.

^b Partially described for European alder (*Alnus glutinosa*).

^c Described for Japanese cypress (*Chamaecyparis obtusa*).

^d Described for Japanese cedar (*Cryptomeria japonica*).

^e Japanese cypress and cedar are not included on the skin test panel at Wilford Hall Medical Center.

Bermuda Grass

T cells from Bermuda grass-allergic patients are reactive, with overlapping peptides comprising most of the Cyn d 1 sequence.²⁰ This study also included proliferation responses before and after immunotherapy containing 50% Bermuda grass and 50% 7-grass mix. Proliferation in response to

Bermuda grass pollen and Cyn d 1 decreased significantly after immunotherapy.

Ryegrass

Two groups performed T-cell epitope mapping of Lol p 1 in 1993.^{21,22} They both used overlapping peptides for epitope

Table 2. Common Aeroallergens Without Discovered T-Cell Epitopes

Allergen extracts	Major allergens
Trees	
White ash (<i>Fraxinus americana</i>)	Fra am
Box elder-maple mix (<i>Acer negundo</i> , <i>Acer</i> spp)	Ace n
Common cottonwood (<i>Populus deltoides</i>)	Pop d
American elm (<i>Ulmus americana</i>)	Ulm a
Hackberry (<i>Celtis occidentalis</i>)	Cel o
Mesquite (<i>Prosopis glandulosa</i>)	Pro g
Mulberry mix (red and white; <i>Morus rubra</i> , <i>Morus alba</i>)	Mor r, Mor a
Oak mix (red, white, and live; <i>Quercus rubra</i> , <i>Quercus alba</i> , <i>Quercus virginiana</i>)	Que ru, Que a 1, Que v
Queen palm (<i>Arecastrum romanzoffianum</i>)	Are r
Pecan (<i>Carya illinoensis</i>)	Car i
American sycamore (<i>Platanus occidentalis</i>)	Pla oc
Black walnut (<i>Juglans nigra</i>)	Jug n 1
Grasses	
Bahia (<i>Paspalum notatum</i>)	Pas n
Johnson (<i>Sorghum halepense</i>)	Sor h 1
Weeds	
Burning bush (<i>Kochia scoparia</i>)	Koc s
Cocklebur (rough or common; <i>Xanthium strumarium</i>)	Xan st
Yellow dock-sheep sorrel mix (<i>Rumex crispus</i> , <i>Rumex acetosella</i>)	Rum c, Rum a
Lamb's quarters (<i>Chenopodium album</i>)	Che a 1
Burweed marshelder-poverty mix (<i>Iva xanthifolia</i> , <i>Iva axillaris</i>)	Iva x, Iva ax
Stinging nettle (<i>Urtica dioica</i>)	Urt d ^a
Pigweed (careless weed; <i>Amaranthus palmeri</i>)	Ama p
English plantain (<i>Plantago lanceolata</i>)	Pla l
Russian thistle (<i>Salsola kali</i>)	Sal k
Molds	
<i>Alternaria alternata</i> (also <i>Alternaria tenuis</i>)	Alt a 1
<i>Aspergillus niger</i>	Asp n
<i>Curvularia spicifera</i>	Cur sp
<i>Epicoccum nigrum</i> (also <i>Epicoccum purpurascens</i>)	Epi p
<i>Fusarium oxysporum vasinfectum</i>	Fus o
<i>Helminthosporium interseminatum</i> (<i>Drechslera</i> spp)	Dre s
<i>Hormodendrum cladosporioides</i> (also <i>Hormodendrum hordei</i>)	Hor h
<i>Penicillium notatum</i> (also <i>Penicillium chrysogenum</i>)	Pen ch

^a Described as a superantigen.

mapping, but 1 group²¹ used peripheral blood mononuclear cells and the other²² used CD4⁺ TCCs developed from rye-specific TCLs. They produced similar results, showing that multiple T-cell reactive epitopes exist within Lol p 1, the bulk of which reside approximately at Lol p 1_{190 to 210}. The most frequently recognized peptide in a later study was Lol p 1_{19 to 38}, although the region Lol p 1_{190 to 209} (the most frequent in the prior studies) was the second most frequently recognized region.²³

Timothy Grass

Several T-cell epitopes of Phl p 1 have been identified with a wide distribution across the amino acid sequence.²⁴ The Phl p 5b sequence has been engineered with the intention of destroying IgE epitopes while preserving T-cell epitopes.²⁵ Five immunodominant T-cell epitopes were mapped. B-cell epitopes were surmised based on velvet grass pollen, which is

homologous to timothy grass. Site-directed mutagenesis was used to disrupt areas that bind IgE while preserving T-cell epitopes. Most of the mutated peptides retained the ability to proliferate T cells, even though IgE recognition of the mutants was greatly reduced.

Ragweed

Relatively little information is available regarding the T-cell epitopes of ragweed allergens. T-cell epitopes in mice have been characterized for Amb a 3,²⁶ Amb a 5, and Amb t 5.^{27,28}

Sagebrush and Mugwort

The immunodominant T-cell epitope of Art v 1 has been defined in great detail.²⁹ In this study, 49 of 51 patients (96%) showed T-cell reactivity to Art v 1_{25 to 36}. Further mapping using truncated peptides narrowed this region further, showing that minimal epitopes were 5 to 10 amino acids in length and contained the central region Art v 1_{28 to 32}. Mugwort

pollen allergy was also found to be associated with HLA-DRB1*01 in the white, Austrian study population.

Stinging Nettle (Urtica)

T-cell epitopes of Urt d have not been identified; however, *Urtica dioica* agglutinin is a superantigen that has been used in a murine model of lupus.³⁰

Aspergillus fumigatus

In a study using TCCs from 3 patients with allergic bronchopulmonary aspergillosis, 5 T-cell epitopes were discovered, with most cells responding to Asp f 1_{46 to 65} and Asp f 1_{106 to 125}.³¹ Reactive clones were limited to HLA-DR2 or HLA-DR5. Another study using peripheral blood mononuclear cells showed that many epitopes stimulated proliferation, but Asp f 1_{36 to 84}, Asp f 1_{115 to 130}, and Asp f 1_{135 to 146} were most pronounced.³²

House Dust Mite

A wide body of literature exists for T-cell epitopes of the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Der p 1 was discovered first and is the best described, followed by Der p 2. T-cell epitopes of *D farinae* have not been studied extensively.

TCCs from 2 patients allergic to *D pteronyssinus* reacted primarily to Der p 1_{45 to 67}, Der p 1_{94 to 104}, and Der p 1_{117 to 143} in an early study.³³ Two other studies examined TCCs from 1 patient allergic to *D pteronyssinus* and found that they were reactive to Der p 1_{101 to 119}, Der p 1_{110 to 131}, Der p 1_{111 to 134}, and Der p 1_{120 to 143}.^{34,35} A larger-scale study involving 18 *D pteronyssinus*-allergic patients showed even more disparate results.³⁶ TCCs reacted most frequently to Der p 1_{1 to 56}, along with several other areas in the sequence. A more recent study³⁷ used a mouse model of *D pteronyssinus* sensitization to determine if a single peptide epitope can induce tolerance. Mice were sensitized intraperitoneally with *D pteronyssinus* extract, and tolerance was induced by intravenous injection of Der p 1_{114 to 128}. The peptide-treated mice showed significantly less lung eosinophilia.

Der p 2 also demonstrates a wide array of defined T-cell epitopes. Twenty-four *D pteronyssinus*-allergic patients responded to multiple epitopes, but 66.7% of them responded to Der p 2_{111 to 129}.³⁸ A DNA vaccine encoding Der p 2_{87 to 129} was shown to have several beneficial effects in a murine model of asthma.³⁹ For *D farinae*, 16 T-cell epitopes were found using Der f 1-reactive TCLs from 6 *D farinae*-allergic donors.⁴⁰

Cat

T-cell epitopes of Fel d 1 have been identified and used for peptide immunotherapy. Fel d 1 has 2 peptide chains. A study including 53 cat-allergic patients defined the epitopes as 9 to 55 and 56 to 69 (chain 1) and 74 to 92 (chain 2).⁴¹ A clinical trial tested peptide immunotherapy using 2 dominant T-cell epitopes of cat allergen.⁴² The 2 peptide sequences were chosen from chain 1 of Fel d 1. The trial had 4 randomized, double-blind arms consisting of placebo and 3 different con-

centrations of the peptides. The high-dose group showed the most improvement in symptom scores during exposure in a specialized cat room. These 2 peptides were tested again in a study of 133 cat-allergic patients, most of whom were current cat owners.⁴³ This trial included 3 arms (placebo, 75 μ g, and 750 μ g) for a total of 8 injections per patient. Asthmatic patients who received the higher dose showed a significant improvement in forced expiratory volume in 1 second at 3 weeks after treatment (but statistical significance was not maintained). Also, most patients in the high-dose peptide group reported improved tolerance to cat exposure. However, 21.7% of the patients in the high-dose group demonstrated IgE to 1 of the treatment peptides. One of the patients who required treatment with epinephrine for a reaction after an injection demonstrated IgE against both treatment peptides (3 patients were treated with epinephrine). This finding demonstrates 1 of the difficulties of peptide immunotherapy: choosing peptides that are immunogenic to T cells but not reactive with IgE.

Peptides from both Fel d 1 chains were used to study the late asthmatic response to inhalation of peptides.⁴⁴ Patients demonstrated tolerance to a second intradermal challenge without a decrease in late-phase forced expiratory volume in 1 second, but inhalational challenge was not tolerogenic. This finding suggests that peptides are able to stimulate T cells directly in the airways, but that peripheral antigen processing by APCs is important in generating tolerance to peptides.

Recently, a peptide from chain 2 of Fel d 1 (1–20) was shown to be immunodominant in patients with atopic dermatitis, as well as control subjects without atopic dermatitis, using interferon γ and interleukin 4 response measured by ELISpot.⁴⁵ Furthermore, this region was restricted to HLA-DQB1*06 and HLA-DPB1*0401, which are common MHC type II serotypes. This study identified an epitope from chain 2 as immunodominant in atopic dermatitis, whereas the cat peptide immunotherapy studies used peptides from chain 1.

Dog

Can f 1_{33 to 48}, Can f 1_{49 to 64}, and Can f 1_{107 to 122} appear immunodominant, and interestingly, the latter sequence has homology with human tear lipocalin.⁴⁶

Cockroach

A transgenic mouse model has been used for T-cell epitope mapping of Bla g 5, 1 of the allergens of German cockroach.⁴⁷ The transgenic T cells proliferated in response to overlapping peptides across the sequence; response was maximal at Bla g 5_{91 to 110} and Bla g 5_{161 to 180}.

Other Allergens

A detailed description of other allergens is beyond the scope of this article, but T-cell epitopes have also been identified for honeybee,⁴⁸ rubber elongation factor (Hev b 1),⁴⁹ peanut,⁵⁰ cow's milk β -lactoglobulin,⁵¹ cow dander allergen (Bos d 2),⁵² rat,⁵³ and horse.⁵⁴ This list is not exhaustive.

CONCLUSION

Of the 47 allergen extracts used as search terms, 13 have T-cell epitopes identified. Only 24 of the 47 major allergens (contained in the allergen extracts on our standard skin test panel that were used as search terms) have published amino acid sequences; therefore, much of the basic biochemistry of allergens is unknown.⁵⁵ As more is discovered about the cellular response to allergens, T-cell-targeted diagnostic tools and therapies will be developed, allowing clinical allergists to move beyond the lexicon of IgE. In addition, whether T-cell epitopes and T-cell recognition of allergens are affected by enzymatic degradation of allergen extracts would be valuable information.

Some allergens seem to have clearly dominant T-cell epitopes, whereas others have epitopes spread diffusely throughout the sequence. Most studies make use of allergen-specific TCLs from which TCCs are drawn. T cells are stimulated with panels of overlapping peptides encompassing the amino acid sequence of the allergen of interest. T-cell proliferation is usually measured using tritiated thymidine incorporation. MHC class II serotypes, which vary by race and population, add further complexity to the system. Immunodominant T-cell epitopes may vary for different MHC serotypes. Furthermore, the selected panel of peptides may differ from in vivo antigen processing by APCs.

Peptide immunotherapy has been elusive but remains promising. Shorter, more focused courses of immunotherapy may be possible, with less risk of anaphylaxis. However, T-cell epitopes may also contain B-cell epitopes, so therapeutic peptides must be selected and engineered carefully. Further insights will allow allergists to target T cells in the future.

REFERENCES

1. Hamilton DG. Science behind the discovery of IgE. *J Allergy Clin Immunol.* 2005;115:648–652.
2. Geha RS, Colten HR, Schneeberger E, Merler E. Cooperation between human thymus-derived and bone marrow-derived lymphocytes in the antibody response to ragweed antigen E in vitro. *J Clin Invest.* 1975; 56:386–390.
3. Del Prete G, Maggi E, Parronchi P, et al. IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. *J Immunol.* 1988;140:4193–4198.
4. Mosmann TR, Coffman RL. T_H1 and T_H2 cells: different patterns of lymphokine secretion lead to different functional properties. *Ann Rev Immunol.* 1989;7:145–173.
5. Rocklin RE, Sheffer AL, Greineder DK, Melmon KL. Generation of antigen-specific suppressor cells during allergy desensitization. *N Engl J Med.* 1980;302:1213–1219.
6. Cox L, Li JT, Nelson H, Lockey R, eds. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol.* 2007;120: S1–S85.
7. Litwin A, Pesce AJ, Fischer T, Michael M, Michael JG. Regulation of the human immune response to ragweed pollen by immunotherapy: a controlled trial comparing the effect of immunosuppressive peptic fragments of short ragweed with standard treatment. *Clin Exp Allergy.* 1990;457–465.
8. Nelson HS, Ikle D, Buchmeier A. Studies of allergen extract stability: the effects of dilution and mixing. *J Allergy Clin Immunol.* 1996;98: 382–388.
9. Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability of standardized grass, dust mite, cat, and short ragweed allergens after mixing with mold or cockroach extracts. *Ann Allergy Asthma Immunol.* 2007;99:151–160.
10. Ebner C, Szépfalusi Z, Ferreira F, et al. Identification of multiple T cell epitopes on Bet v 1, the major birch pollen allergen, using specific T cell clones and overlapping peptides. *J Immunol.* 1993;150:1047–1054.
11. Jahn-Schmid B, Radakovics A, Lüttkopf D, et al. Bet v 1_{142–156} is the dominant T-cell epitope of the major birch pollen allergen and important for cross-reactivity with Bet v 1-related food allergens. *J Allergy Clin Immunol.* 2005;116:213–219.
12. Van Overtvelt L, Wambre E, Maillère B, et al. Assessment of Bet v 1-specific CD4⁺ T cell responses in allergic and nonallergic individuals using MHC class II peptide tetramers. *J Immunol.* 2008;180: 4514–4522.
13. Ebner C, Ferreira F, Hoffmann K, et al. T cell clones specific for Bet v 1, the major birch pollen allergen, crossreact with the major allergens of hazel, Cor a I, and alder, Aln g I. *Mol Immunol.* 1993;30:1323–1329.
14. Cárđaba B, Del Pozo V, Jurado A, et al. Olive pollen allergy: searching for immunodominant T-cell epitopes on the Ole e 1 molecule. *Clin Exp Allergy.* 1998;28:413–422.
15. Midoro-Horiuti T, Goldblum RM, Kurosky A, Goetz DW, Brooks EG. Isolation and characterization of the mountain cedar (*Juniperus ashei*) pollen major allergen, Jun a 1. *J Allergy Clin Immunol.* 1999;104: 608–612.
16. Reid MJ, Nish WA, Whisman BA, et al. HLA-DR4-associated nonresponsiveness to mountain-cedar allergen. *J Allergy Clin Immunol.* 1992; 89:593–598.
17. Sone T, Morikubo K, Miyahara M, et al. T cell epitopes in Japanese cedar (*Cryptomeria japonica*) pollen allergens: choice of the major T cell epitopes in Cry j 1 and Cry j 2 toward design of the peptide-based immunotherapeutics for the management of Japanese cedar pollinosis. *J Immunol.* 1998;161:448–457.
18. Sone T, Dairiki K, Morikubo K, et al. Identification of human T cell epitopes in Japanese cypress pollen allergen, Cha o 1, elucidates the intrinsic mechanism of cross-allergenicity between Cha o 1 and Cry j 1, the major allergen of Japanese cedar pollen, at the T cell level. *Clin Exp Allergy.* 2005;35:664–671.
19. Yang L, Suzuki K, Hirose S, Wakasa Y, Takaiwa F. Development of transgenic rice seed accumulating a major Japanese cedar pollen allergen (Cry j 1) structurally disrupted for oral immunotherapy. *Plant Biotechnol J.* 2007;5:815–826.
20. Eusebius NP, Papalia L, Suphioglu C, et al. Oligoclonal analysis of the atopic T cell response to the group 1 allergen *Cynodon dactylon* (Bermuda grass) pollen: pre- and post-allergen-specific-immunotherapy. *Int Arch Allergy Immunol.* 2002;127:234–244.
21. Bungo Poor Fard GA, Latchman Y, Rodda S, Geysen M, Roitt I, Brostoff J. T cell epitopes of the major fraction of rye grass *Lolium perenne* (Lop p I) defined using overlapping peptides in vitro and in vivo. I. Isoallergen clone1A. *Clin Exp Immunol.* 1993;94:111–116.
22. Spiegelberg HL, Beck L, Stevenson DD, Ishioka GY. Recognition of T cell epitopes and lymphokine secretion by rye grass allergen *Lolium perenne* 1-specific human T cell clones. *J Immunol.* 1994;152: 4706–4711.
23. Burton MD, Papalia L, Eusebius NP, O'Hehir RE, Rolland JM. Characterization of the human T cell response to rye grass pollen allergens Lol p 1 and Lol p 5. *Allergy.* 2002;57:1136–1144.
24. Schenk S, Breiteneder H, Susani M, et al. T-cell epitopes of Phl p 1, the 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;96:986–996.
25. Schramm G, Kahlert H, Suck R, et al. "Allergen engineering": variants of the timothy grass pollen allergen Phl p 5b with reduced IgE-binding capacity but conserved T cell reactivity. *J Immunol.* 1999;162: 2406–2414.
26. Kurisaki J, Atassi H, Atassi MZ. T cell recognition of ragweed allergen Ra3: localization of the full T cell recognition profile by synthetic overlapping peptides representing the entire protein chain. *Eur J Immunol.* 1986;16:236–240.

27. Zhu X, Greenstein JL, Rogers BL, Kuo M. T cell epitope mapping of ragweed pollen allergen *Ambrosia artemisiifolia* (Amb a 5) and *Ambrosia trifida* (Amb t 5) and the role of free sulfhydryl groups in T cell recognition. *J Immunol.* 1995;155:5064–5073.
28. Chapoval SP, Neeno T, Krco CJ, Marietta EV, Harders J, David CS. HLA-DQ6 and HLA-DQ8 transgenic mice respond to ragweed allergens and recognize a distinct set of epitopes on short and giant ragweed group 5 antigens. *J Immunol.* 1998;161:2032–2037.
29. Jahn-Schmid B, Fischer GF, Bohle B, et al. Antigen presentation of the immunodominant T-cell epitope of the major mugwort pollen allergen, Art v 1, is associated with the expression of HLA-DRB1*01. *J Allergy Clin Immunol.* 2005;115:399–404.
30. Musette P, Galelli A, Chabre H, et al. Urtica dioica agglutinin, a V β 8.3-specific superantigen, prevents the development of the systemic lupus erythematosus-like pathology of MRL *lpr/lpr* mice. *Eur J Immunol.* 1996;26:1707–1711.
31. Chauhan B, Knutsen AP, Hutcheson PS, Slavin RG, Bellone CJ. T cell subsets, epitope mapping, and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. *J Clin Invest.* 1996;97:2324–2331.
32. Kurup VP, Banerjee B, Murali PS, et al. Immunodominant peptide epitopes of allergen, Asp f 1 from the fungus *Aspergillus fumigatus*. *Peptides.* 1998;19:1469–1477.
33. Yssel H, Johnson KE, Schneider PV, et al. T cell activation-inducing epitopes of the house dust mite allergen Der p 1. *J Immunol.* 1992;148:738–745.
34. Higgins JA, Lamb JR, Marsh SGE, et al. Peptide-induced nonresponsiveness of HLA-DP restricted human T cells reactive with *Dermatophagoides* spp. (house dust mite). *J Allergy Clin Immunol.* 1992;90:749–756.
35. Higgins JA, Thorpe CJ, Hayball JD, O'Hehir RE, Lamb JR. Overlapping T-cell epitopes in the group I allergen of *Dermatophagoides* species restricted by HLA-DP and HLA-DR class II molecules. *J Allergy Clin Immunol.* 1994;93:891–899.
36. O'Brien RM, Thomas WR, Tait FD. An immunogenetic analysis of T-cell reactive regions the major allergen from the house dust mite, Der p 1, with recombinant truncated fragments. *J Allergy Clin Immunol.* 1994;93:628–634.
37. Zuleger CL, Gao X, Burger MS, Chu Q, Payne LG, Chen D. Peptide induces CD4+CD25+ and IL-10+ T cells and protection in airway allergy models. *Vaccine.* 2005;23:3181–3186.
38. O'Brien RM, Thomas WR, Nicholson I, Lamb JR, Tait BD. An immunogenetic analysis of the T-cell recognition of the major house dust mite allergen Der p 2: identification of high- and low-responder HLA-DQ alleles and localization of T-cell epitopes. *Immunology.* 1995;86:176–182.
39. Kim CH, Ahn JH, Kim SJ, et al. Co-administration of vaccination with DNA encoding T cell epitope on the Der p and BCG inhibited airway remodeling in a murine model of chronic asthma. *J Asthma.* 2006;43:345–353.
40. Matsuoka T, Kohrogi H, Ando M, Nishimura Y, Matsushita S. *Dermatophagoides farinae*-1-derived peptides and HLA molecules recognized by T cells from atopic individuals. *Int Arch Allergy Immunol.* 1997;112:365–370.
41. Counsell CM, Bond JF, Ohman JL, Greenstein JL, Garman RD. Definition of the human T-cell epitopes of Fel d 1, the major allergen of the domestic cat. *J Allergy Clin Immunol.* 1996;98:884–894.
42. Norman PS, Ohman JL, Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med.* 1996;154:1623–1628.
43. Maguire P, Nicodemus C, Robinson D, Aaronson D, Umetsu DT. The safety and efficacy of ALLERVAX CAT in cat allergic patients. *Clin Immunol.* 1999;93:222–231.
44. Ali FR, Oldfield WLG, Higashi N, Larché M, Kay AB. Late asthmatic reactions induced by inhalation of allergen-derived T cell peptides. *Am J Respir Crit Care Med.* 2004;169:20–26.
45. Bateman EAL, Ardern-Jones MR, Ogg GS. Identification of an immunodominant region of Fel d 1 and characterization of constituent epitopes. *Clin Exp Allergy.* 2008;38:1760–1768.
46. Immonen AK, Taivainen AH, Närviäinen ATO, et al. Use of multiple peptides containing T cell epitopes is a feasible approach for peptide-based immunotherapy in Can f 1 allergy. *Immunology.* 2006;120:38–46.
47. Papouchado BG, Chapoval SP, Marietta EV, Weiler CR, David CS. HLA-DQ/human CD4-restricted immune response to cockroach allergens in transgenic mice. *Tissue Antigens.* 2000;55:303–311.
48. Müller U, Akdis CA, Fricker M, et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. *J Allergy Clin Immunol.* 1998;101:747–754.
49. Raulf-Heimsoth M, Chen Z, Rihs HP, Kalbacher H, Liebers V, Baur X. Analysis of T-cell reactive regions and HLA-DR4 binding motifs on the latex allergen Hev b 1 (rubber elongation factor). *Clin Exp Allergy.* 1998;28:339–348.
50. Glaspole IN, de Leon MP, Rolland JM, O'Hehir RE. Characterization of the T-cell epitopes of a major peanut allergen, Ara h 2. *Allergy.* 2005;60:35–40.
51. Inoue R, Matsushita S, Kaneko H, Shinoda S, Sakaguchi H, Nishimura Y, Kondo N. Identification of beta-lactoglobulin-derived peptides and class II HLA molecules recognized by T cells from patients with milk allergy. *Clin Exp Allergy.* 2001;7:1126–1134.
52. Zeiler T, Mäntytjärvi R, Rautiainen J, et al. T cell epitopes of a lipocalin allergen colocalize with the conserved regions of the molecule. *J Immunol.* 1999;162:1415–1422.
53. Jeal H, Draper A, Harris J, Taylor AN, Cullinan P, Jones M. Determination of the T cell epitopes of the lipocalin allergen, Rat n 1. *Clin Exp Allergy.* 2004;34:1919–1925.
54. Immonen A, Kinnunen T, Sirven P, et al. The major horse allergen Equ c 1 contains one immunodominant region of T cell epitopes. *Clin Exp Allergy.* 2007;37:939–947.
55. International Union of Immunological Societies, Allergen Nomenclature Sub-committee. Allergen Nomenclature. <http://www.allergen.org>. Accessed June 28, 2008.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Letz AG, Calabria CW. 2009;102:445–452.

CME Test Questions

1. T-cell epitopes have been characterized for which of the following allergens?
 - a. mountain cedar
 - b. birch
 - c. Russian thistle
 - d. oak
 - e. *Urtica*
2. Which of the following allergens presents the widest body of literature for T-cell epitopes?
 - a. cat
 - b. ragweed
 - c. birch
 - d. house dust mite
 - e. cockroach
3. Peptide immunotherapy has been performed in a double-blind, placebo-controlled trial for which allergen?
 - a. cat
 - b. olive
 - c. sagebrush or mugwort
 - d. cockroach
 - e. birch
4. T cells recognize allergens by
 - a. their native conformations in 3-dimensional space
 - b. native proteins presented by antigen-presenting cells
 - c. linear peptides presented by antigen-presenting cells
 - d. both b and c
 - e. dimerization with Foxp3
5. Which of the following is NOT a difficulty in identifying immunodominant T-cell epitopes?
 - a. differences between in vivo antigen processing by antigen-presenting cells and synthesized panels of peptides
 - b. variability in major histocompatibility presentation of peptides
 - c. limited knowledge of amino acid sequences of many allergens
 - d. recognition of peptides by T-cell clones compared with T cells in vivo
 - e. lack of reliable proliferation assays

Answers found on page 499.
