

Fighting Food Allergy

Current Approaches

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ABSTRACT: Food allergy is defined as an adverse immunologic reaction to allergens present in food and is associated with symptoms ranging from gastrointestinal discomfort to anaphylactic shock and death. The increase in prevalence and potential fatality of disease has led to increased efforts to find effective therapies and prophylaxis. While specific immunotherapy (SIT) is effective in desensitization against inhalant allergens, it is unadvised against food allergy because of the high risk of adverse side effects. A review of the recent literature shows that various approaches have been taken to develop safer and more effective SIT regimens. Here we discuss the use of recombinant allergens, peptides, DNA vaccines, immunostimulatory DNA sequences, and other bacterial products in SIT. In addition, we review nonspecific therapies such as anti-IgE administration and cytokine therapy as well as natural therapies such as probiotics and Chinese herbal medications. In conclusion, anti-IgE treatment and SIT using hypoallergenic recombinant allergens in combination with Th1-inducing adjuvants appear the most promising approaches. New initiatives to increase our understanding of the pathophysiology and immunologic mechanisms of food allergy along with the molecular characterization of food allergens should pave the way towards safer and more effective ways of combating this debilitating and potentially life-threatening disease.

KEYWORDS: food allergy; recombinant allergens; cytokines; immunotherapy; natural therapy; murine models; immunostimulatory DNA; CpG; DNA vaccine

INTRODUCTION

The steady increase in allergic disease has intensified the need for successful therapeutic approaches. Up to 4% of adults and 8% of children are food allergic, with an estimated 30,000 food-induced anaphylactic events seen annually in the United States alone, 150 of them fatal. Fish, shellfish, soybean, wheat, egg, milk, peanuts, and tree nuts cause the majority of all allergic reactions to foods¹⁻⁴ with seafood allergy the most common in the United States⁵ and nuts causing over 90% of fatalities.^{6,7} Currently, strict avoidance of the allergenic foods is the only way to prevent

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reactions, but about 50% of affected individuals experience accidental exposure and reactions every 3–5 years, with hidden allergens in restaurant and processed food often to blame.^{8–10}

Food allergy is defined as an adverse immunologic reaction to allergenic molecules present in foods, with reactions ranging from mild discomfort, urticaria, and allergic asthma to life-threatening anaphylactic shock.^{2,3} The acute symptoms of allergy are usually due to the release of inflammatory mediators by mast cells and basophils, including histamine, platelet-activating factor, leukotrienes, mast cell proteases, and cytokines. These mediators are released when allergen binds to IgE antibody attached to FcεRI receptors on the cell surface, causing degranulation. Studies show a skewing towards a Th2 response in food allergy, with elevated interleukin (IL)-4, IL-5, and IL-13 levels, whereas tolerant individuals have higher levels of the Th1 cytokines interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha, and the regulatory cytokine IL-10.^{11–15}

SPECIFIC IMMUNOTHERAPY

Specific immunotherapy to inhalant allergens has proven to be highly successful.^{16,17} Injections of allergen over a long period of time leads to reduced sensitivity to allergen, which is correlated with a switch from a Th2 type response to a Th1 or regulatory type response, with raised levels of IFN-γ, the regulatory cytokine IL-10, and so-called “blocking” IgG antibodies.^{18–22} It was recently shown that sublingual immunotherapy produces significantly fewer side effects than injections, with equivalent efficacy.^{16,23,24} In addition, there are some indications that specific immunotherapy may abrogate symptoms due to oral allergy syndrome, a condition in which patients with pollen allergy experience reactions upon ingestion of food containing cross-reactive allergens.^{25–29} It is estimated that up to 50% of patients with pollen allergy experience oral allergy syndrome. This so-called class II food allergy is generally mediated by less stable allergens (e.g., Bet vs 8 in peanuts)³⁰ and is drawing increased attention due to the steady rise in the prevalence of inhalant allergies. However, results of desensitization trials are inconclusive.^{25–29} Cross-reactivity between related allergens (peanut and soybean) has been used in a murine model as a safe way to desensitize peanut-allergic mice.³¹ Nevertheless, at this stage, specific immunotherapy against food allergy in humans is currently not viable because of the high risk of adverse reactions and limited efficacy.^{7,32,33} Much research is therefore going into making immunotherapy safer and more efficacious by altering the various components: the antigens, the adjuvants, and the delivery systems.³⁴

RECOMBINANT PROTEINS AND PEPTIDES

Currently, specific immunotherapy relies on crude or commercial allergen extracts that contain proteins and allergens in variable proportions, increasing the risk of unwanted side effects, as in patients treated for house dust-mite allergy who developed anaphylactic reactions to snails due to cross-reactivity of allergens.^{35,36} The use of defined and purified recombinant allergens in immunotherapy would resolve these issues.^{37–39} In addition, current recombinant technology allows the

TABLE 1. Specific immunotherapy in food allergy

Allergy	Treatment	Approach	Relevance	Molecular effects	Clinical effects	Ref.
Peanut	Peanut	Rush therapy (injection)	Human	Increased oral tolerance	Considerable systemic reactions	32
Peanut	Peanut	Rush therapy (injection)	Human	Increased oral tolerance	Considerable systemic reactions	33
Apple (oral allergy syndrome)	rBet v1 (Birch pollen)	SIT	Human	IgG4 upregulated; regulatory T cells not altered	Symptom reduction in food challenge (DBPCFC)	148
Apple (oral allergy syndrome)	Birch pollen	SIT (comparing subcutaneous with sublingual)	Human	Specific IgE reduced	No symptom reduction	149
Peanut	Modified Ara h 1-3	Allergen plus heat-killed <i>L. monocytogenes</i> ; subcutaneous injection	Mouse	Th2 cytokines reduced; specific IgE reduced	Reduced anaphylactic reactions	150
Peanut	Modified Ara h 1-3	Allergen plus heat-killed <i>E. coli</i> ; rectal sensitization	Mouse	Th2 cytokines and IgE reduced	Reduced symptoms	151
Peanut	Soya extract	Desensitization, intra-peritoneal, with soya extract	Mouse	Th2 cytokines and IgG1 reduced	Reduced anaphylactic reactions	31
Ovalbumin	Ovalbumin	Allergen plus heat-killed <i>Lactobacillus casei</i> strain Shirota (LcS)	Mouse	Th1 skewed response; specific IgE/IgG1 reduced	Reduced symptoms	152
Milk	Beta-lactoglobulin (BLG)	Carrageenan	Mouse	Reduced antigen-specific proliferative response	Reduced symptoms	153
Peanut	Peanut	Allergen plus heat-killed <i>Listeria monocytogenes</i>	Dog	Specific IgE reduced; Skin prick reactivity reduced	Reduced symptoms	66

construction of hypoallergenic derivatives of natural allergens, which should reduce the adverse effects of immunotherapy. Such allergens should not be able to activate cells via crosslinking of IgE antibodies, but should preserve T-cell epitopes (immunogenicity) and activate B cells to induce blocking IgG antibodies. Hypoallergenic derivatives of the major birch pollen allergen Bet v1 have been extensively studied. Recombinant Bet v1 (rBet v1) and even rBet v1 fragments induced blocking IgG antibodies in animal models and were even able to shift a type Th2 immune response towards a Th1 phenotype.⁴⁰ Recent patient trials with rBet v1 were successful.³⁸ A range of recombinant food allergens has been produced and successfully tested in animal models (TABLE 1).⁴¹⁻⁴⁴ However, no human immunotherapy trials have been performed with recombinant food allergens. Another approach has been to use synthetic peptides of allergen T-cell epitopes in specific therapy. This approach seemed to induce a regulatory T-cell response rather than a Th1 response and worked to some extent, but allergic reactions were reported during the therapy.^{45,46}

ADJUVANTS

A variety of traditional adjuvants (e.g., aluminium hydroxide) have been used in immunotherapy without detailed understanding of their molecular mechanisms.⁴⁷ Now new adjuvants with stronger Th1-inducing properties are being investigated.

Immunostimulatory DNA

Bacterial CpG motifs, unmethylated dinucleotides flanked by specific sequences, are recognized by the mammalian immune system via toll-like receptor 9 (and possibly other pattern-recognition receptors) and trigger a Th1 response.⁴⁸⁻⁵¹ The same is true of synthetic oligodeoxynucleotides containing such CpG motifs (CpG-ODN).^{50,52,53} Experiments in murine models of allergic asthma, rhino-sinusitis, and conjunctivitis show that administration of CpG-ODN prevents symptoms and reduces already established disease by reducing Th2 and IgE.⁵⁴⁻⁵⁷ Allergen/CpG-ODN conjugates have been shown to be less allergenic and more immunogenic than native allergen.^{58,59} The major allergen from ragweed, Amb a 1, linked to an immunostimulatory DNA sequence promoted Th1 cytokine expression and downregulated Th2 expression *in vitro*,⁶⁰ reversed established airway hyperreactivity in a murine model of asthma,^{61,62} and yielded promising results in Phase II clinical trials.⁶³ Although no food allergen-CpG conjugates have been tested, a similar approach using Th1-inducing heat-killed bacteria has yielded good results in mice^{64,65} and allergic dogs.⁶⁶

Monophosphoryl Lipid A

Another bacterial derivative undergoing testing is 3-deacylated monophosphoryl lipid A (MPL), a detoxified form of lipid A derived from the lipopolysaccharide of *Salmonella minnesota* R595. Its effects as a Th1-inducing immunostimulatory adjuvant have been described in several publications.^{67,68} Clinical trials using MPL as an adjuvant in immunotherapy for grass allergy demonstrated that MPL was efficacious, needing only four injections to induce antibody changes normally requiring lengthy injection schedules,⁶⁹ and that MPL induced strong blocking IgG responses.⁷⁰ It has not been tested in any food allergy vaccines.

DELIVERY SYSTEMS

Several routes of administration are under consideration for use in food allergy vaccines.

Microencapsulation

Oral administration of antigens usually leads to tolerance and has been effective in decreasing allergic sensitization to antibiotics and other medications.^{71,72} Obviously, native food allergens cannot be administered in this way, but it may be possible with hypoallergenic or CpG-conjugated derivatives. Microencapsulation provides a promising way of delivering allergens without degradation in the stomach,⁷³ thereby inducing oral tolerance, and it has already been applied in clinical trials.⁷⁴

DNA Vaccines

Plasmid DNA injected intramuscularly, intraperitoneally, or with a gene gun results in transcription and translation of encoded genes and elicits an antibody response in the host.⁷⁵⁻⁷⁷ This method of immunization, known as a DNA vaccine, preferentially induces a Th1 immune response and suppression of IgE.^{78,79} These effects appear to be mediated by both CD8⁺ and CD4⁺ cells,^{77,80,81} and plasmid DNA requires immunostimulatory sequences (CpG) for optimal immunogenicity.⁸²⁻⁸⁶ Several allergens have been tested in DNA vaccines in murine models, including Ara h 2 (peanut), bovine beta-lactoglobulin (cow's milk), Cry j 1 (Japanese cedar), phospholipase A2 (bee venom), Der f 11 and Der p 1 (dust mites), and Bet v 1 and Phl p 2 (grass).^{80,83-85,87-90} Most studies found elicitation of a Th1 response and increased IL-10. Mice vaccinated against phospholipase A2 were protected against fatal anaphylaxis after allergen challenge,⁸³ whereas mice receiving an oral DNA vaccine containing the peanut allergen Ara h 2 orally⁸⁷ experienced significantly less severe and delayed allergic reactions upon subsequent sensitization and challenge. However, prophylactic effects, while promising, are not sufficient to aid patients who have existing food allergy. In mice pre-sensitized to phospholipase A, therapeutic gene vaccination prevented only 30% of mice from experiencing anaphylaxis.⁸³ However, DNA vaccination provides the option of co-delivering genes or adjuvant molecules with immunomodulatory properties together with the antigen sequence.⁸⁶ Vaccination of mice with a plasmid containing the cDNA for OVA fused to the cDNA of IL-18, a potent Th1 inducer, reversed established airway hyper-reactivity, while a plasmid containing OVA alone had only a prophylactic effect.⁹¹

NONSPECIFIC IMMUNOTHERAPY

While specific immunotherapy aims to correct the underlying immunologic mechanisms leading to allergy, nonspecific therapy targeting Th2 cytokines or anti-IgE may help abrogate symptoms and could be useful in minimizing the side effects associated with conventional immunotherapy.

Anti-IgE Therapy

Blocking humanized anti-IgE antibody (Omalizumab/Xolair) has been successfully used in patients with moderate to severe allergic asthma (TABLE 2). TNX-901, another anti-IgE antibody, was tested in 84 peanut-allergic patients in clinical trials.⁹² TNX-901 reduced serum IgE levels and successfully increased the sensitivity threshold to peanuts from an average of half a peanut to almost nine peanuts. While patients would still have to eliminate peanuts from the diet, TNX-901 therapy would ensure protection from accidental ingestion or exposure, which is the cause of most fatalities.^{7,8,93} In addition, anti-IgE administered during specific immunotherapy for food may reduce the risk of anaphylaxis.^{94,95} On other fronts, an inhibitor of the IgE receptor on mast cells, R112, is in Phase I/II trials for allergic rhinitis,⁹⁶ and preclinical experiments are being conducted on a human IgG-IgE Fc fusion protein that inhibits mast cells, basophils, and B cells^{97,98} (TABLE 2). These drugs may also have application in food allergy.

Cytokines

Cytokines and anticytokine monoclonal antibodies have been tested in clinical trials in a number of diseases (Cutler & Brombacher, this issue), but to date they have not been tested against food allergies. However, cytokines have been targeted in other allergic diseases such as asthma and atopic dermatitis (TABLE 2), which have similar underlying mechanisms. IL-4, which signals via the IL-4R alpha, is known to be important for the generation of Th2 cytokines such as IL-5, IL-9, and IL-13⁹⁹ and IgE production,¹⁰⁰ although recent studies have found that a Th2 response occurred even in the absence of the IL-4R alpha in *Leishmania major* infection.¹⁰¹ This redundancy perhaps explains the disappointing results in clinical trials using anti-IL-4 monoclonal antibodies to treat asthma (TABLE 2). However, trials of a recombinant human soluble IL-4R antagonist did show some clinical benefits in asthma.¹⁰² It is now known that IL-13, which also binds to the IL-4R α , is the central mediator of allergic asthma¹⁰³⁻¹⁰⁵ and increases susceptibility to fatal anaphylaxis.¹⁰⁶ Furthermore, fatal anaphylaxis caused by food allergy in humans is often associated with a history of asthma,⁷ and murine studies showed that helminth-induced protection against peanut allergy via IL-10 correlated with a fivefold decrease in IL-13.¹⁰⁷ Phase I trials using anti-IL-13 against asthma and development of anti-IL-13 receptor are currently underway.¹⁰⁸ Antibodies against other cytokines include anti-IL-5 for eosinophilia (phase II for asthma and atopic dermatitis),^{109,110} anti-IL-9 (phase I for asthma),¹¹¹ and anti-eotaxin 1 (phase I/IIa for rhinitis)¹¹² (TABLE 2). A few cytokines with anti-allergic properties have also been tested in clinical trials. Murine models show that IL-10 is crucial for tolerance and successful immunotherapy^{107,113-115} and that IFN- γ plays a role in oral tolerance.¹¹⁶ Recombinant IL-10 has been produced but not tested against allergies, although it is in phase III trials for colitis,^{117,118} (TABLE 2). Recombinant IFN- γ has shown promising results in phase II trials for dermatitis,^{119, 120} with patients interestingly showing improvement in allergic rhinitis and conjunctivitis as well as skin symptoms.¹¹⁹ Phase I trials of recombinant IL-12, a Th1-promoting cytokine, were halted due to inefficacy and adverse side effects.¹²¹ In a murine model, oral administration of liposome-encapsulated rIL-12 had both preventative and therapeutic effects on peanut allergy.¹²² It is likely that some kind of cytokine combination therapy would be required.

TABLE 2. Nonspecific immunotherapy in allergy

Target	Active principal	Generic name/ code	Company	Application	Status	Ref.
IgE	Humanized anti-IgE	Xolair (omalizumab)	Genentech, Novartis, Tanox	Peanut allergy Asthma	Phase II	154
					Approved	153
IgE	Humanized anti-IgE	TNX-901	Tanox, Genen-tech, Novartis	Peanut allergy	Phase II	92
FcεRI	FcεRI inhibitor	R112	Rigel	Allergic rhinitis	Phase II	96
FcεRI and FcγRII	Human IgG-IgE Fc fusion protein	GE2	Biogen-Idec Inc.	Allergy	Preclinical	97, 98
IL-4	Humanized anti-IL-4 mAb	SB240683	PDL/GSK	Asthma	Phase II halted	156
IL-5	Humanized anti-IL-5	SCH-55700	Celltech/Schering-Plough	Asthma / Allergy	Phase II	157
IL-5	Humanized anti-IL-5	Mepolizumab	GSK	Asthma	Phase II	109, 110,
				Atopic dermatitis	Phase II	158
IL-9	Anti-IL-9 mAb	IL-9 mAb	Genaera / MedImmune	Asthma	Phase I	111
IL-4R	IL-4R antagonist	Bay 16-9996	Bayer	Asthma	Phase II halted	159
IL-4R	IL-4R antagonist	Altrakinept/ Nuvance	Immunex Corp.	Asthma	Phase II	102
IL-4 / IL-13	Recombinant IL-4Rα/IL-13Rα/Fc fusion	IL-4/IL-13 trap	Regeneron	Asthma	Phase I	160, 161
IL-13	Anti-IL-13 human IgG4	CAT-354	Cambridge Antibody Technology	Asthma	Phase I	108
IL-13Rα	Anti-IL-13 receptor alpha 1	IL-13 receptor α 1	Amrad / Merck	Asthma	Preclinical	162
Eotaxin	Anti-eotaxin1	CAT213	Cambridge Antibody Technology	Rhinitis	Phase I/IIa	112
—	Recombinant IL-10	Ilodecakin / Tenovil	Schering-Plough	No trials in allergy Colitis	Phase III	117, 163
—	Recombinant IL-12	rIL-12	Genetic Institute	Asthma	Phase I halted	121
—	Recombinant IFN-γ	Actimmune	Intermune Pharma	Atopic dermatitis	Phase II	164

TABLE 3. Natural therapies in food allergy

Allergy	Model / application	Treatment	Relevance	Molecular effects	Clinical effects	Ref.
Peanut	Oral peanut sensitization using cholera toxin	Chinese herbal formula FAHF-1	Mouse	Reduced specific IgE, mast cell degranulation, histamine, Th2 cytokines	Abolished anaphylactic reactions	127
Peanut	Oral peanut sensitization using cholera toxin	Chinese herbal formula FAHF-2	Mouse	Reduced specific IgE, Th2 cytokines, enhanced IFN- γ	Abolished anaphylactic reactions	126
Cow's milk	Infants with cow's milk allergy and IgE-associated dermatitis (plus conventional treatment)	<i>Lactobacillus rhamnosus</i> GG or probiotic mix	Human	Increase in IFN- γ secretion	Alleviated skin symptoms	142
Various	Children with moderate to severe atopic dermatitis	<i>Lactobacillus rhamnosus</i> or <i>Lactobacillus reuteri</i>	Human	Decreased eosinophil cationic protein, decreased lactulose to mannitol ratio (stabilization of gut permeability); no change in cytokine production	Improvement in eczema, symptom scores, decreased gastrointestinal symptoms	143, 144
Various	Children with atopic dermatitis	<i>Lactobacillus rhamnosus</i> GG	Human	Elevated serum IL-10	—	138
—	Pregnant mothers, then infants for 6 months	<i>Lactobacillus</i> GG	Human	—	Frequency of atopy halved in infants at age 2 and 4	145, 165
—	Newborns	Probiotic <i>E.coli</i> strain	Human	—	Significant reduction in prevalence of allergies at ages 10 and 20	147
Cow's milk	Rat pups fed cow's milk	<i>Lactobacillus</i> GG	Rat	—	Restored aberrant gut permeability	139
Peanut	Oral peanut sensitization	Antibiotic treatment to remove intestinal flora	Mouse	Increased specific IgE, increased histamine and mast cell degranulation after challenge	Removing flora rendered mice susceptible to peanut-induced anaphylaxis. Reconstitution reversed the effect	140

NATURAL THERAPIES

A few authors have reviewed nonallopathic therapies for allergy, including herbal remedies, homeopathy, and acupuncture.^{123–125} In prevention or therapy of food allergies, the most promising results have been obtained using Chinese herbal formulas or probiotics (TABLE 3). In murine models of peanut allergy, the formulas FAHF-1 and FAHF-2 completely blocked anaphylaxis and downregulated Th2 and IgE responses without any apparent toxicity.^{126,127} The effects of probiotics, live microorganisms that are thought to exert beneficial effects on the host by improving gut microflora,^{128,129} are more controversial.^{130–135} It is thought that probiotic administration promotes a change in the local microflora and mucosal immune response and corrects aberrations in gut permeability.^{134,136–139} Murine models found that toll-like receptor 4-dependent signals provided by macrobiotics inhibited the development of allergic responses to food,¹⁴⁰ whereas disruption in this microbiota enhanced the allergic response to OVA and to mold spores.¹⁴¹ Clinical trials have demonstrated that probiotic therapy may help to alleviate atopic dermatitis and gastrointestinal symptoms caused by food allergy.^{136,142–144} In addition, when probiotics were given to expectant mothers with a familial history of atopy as well as postnatally for 6 months to their infants, the frequency of atopic eczema in the treated infants was half that of the placebo group.^{145,146} Another study found that administration of a probiotic *Escherichia coli* strain after birth resulted in a reduced incidence of allergies recorded at the ages of 10 and 20.¹⁴⁷ It is therefore possible that probiotics may have a role in the prevention of food allergy. However, such effects appear to be species-specific, and further research is needed.^{132,133}

CONCLUSIONS

Several novel therapeutic and prophylactic therapies against food allergy are under investigation. To date, anti-IgE treatment and specific immunotherapy using hypoallergenic recombinant allergens together with Th1-inducing adjuvants such as CpG DNA or heat-killed bacteria appear the most promising. New initiatives to increase our understanding of the pathophysiology and immunologic mechanisms of food allergy along with the molecular characterization of food allergens should pave the way towards safer and more effective ways of combatting this debilitating and potentially life-threatening disease.

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REFERENCES

1. HELM, R.M. & A.W. BURKS. 2000. Mechanisms of food allergy. *Curr. Opin. Immunol.* **12**: 647–653.
2. SAMPSON, H.A. 2003. Food allergy. *J. Allergy Clin. Immunol.* **111**: S540–547.

3. SAMPSON, H.A. 2004. Update on food allergy. *J. Allergy Clin. Immunol.* **113**: 805–819.
4. SAMPSON, H.A. 2004. Food-induced anaphylaxis. *Novartis Found Symp.* **257**: 161–171.
5. SICHERER, S.H., A. MUNOZ-FURLONG & H.A. SAMPSON. 2004. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J. Allergy Clin. Immunol.* **114**: 159–165.
6. SKOLNICK, H.S. *et al.* 2001. The natural history of peanut allergy. *J. Allergy Clin. Immunol.* **107**: 367–374.
7. BOCK, S.A., A. MUNOZ-FURLONG & H.A. SAMPSON. 2001. Fatalities due to anaphylactic reactions to foods. *J. Allergy Clin. Immunol.* **107**: 191–193.
8. PERRY, T.T. *et al.* 2004. Distribution of peanut allergen in the environment. *J. Allergy Clin. Immunol.* **113**: 973–976.
9. MONERET-VAUTRIN, D.A. & G. KANNY. 2004. Update on threshold doses of food allergens: implications for patients and the food industry. *Curr. Opin. Allergy Clin. Immunol.* **4**: 215–219.
10. MORISSET, M. *et al.* 2003. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clin. Exp. Allergy* **33**: 1046–1051.
11. TURCANU, V., S.J. MALEKI & G. LACK. 2003. Characterization of lymphocyte responses to peanuts in normal children, peanut-allergic children, and allergic children who acquired tolerance to peanuts. *J. Clin. Invest.* **111**: 1065–1072.
12. SCHADE, R.P. *et al.* 2003. The cow's milk protein-specific T cell response in infancy and childhood. *Clin. Exp. Allergy* **33**: 725–730.
13. TIEMESSEN, M.M. *et al.* 2004. Cow's milk-specific T-cell reactivity of children with and without persistent cow's milk allergy: key role for IL-10. *J. Allergy Clin. Immunol.* **113**: 932–939.
14. ANDRE, F., J. PENE & C. ANDRE. 1996. Interleukin-4 and interferon-gamma production by peripheral blood mononuclear cells from food-allergic patients. *Allergy* **51**: 350–355.
15. NOMA, T. *et al.* 1996. Cytokine production in children outgrowing hen egg allergy. *Clin. Exp. Allergy* **26**: 1298–307.
16. WILSON, D.R., M.T. LIMA & S.R. DURHAM. 2005. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* **60**: 4–12.
17. SCHMIDT-WEBER, C.B. & K. BLASER. 2004. Immunological mechanisms in specific immunotherapy. *Springer Semin. Immunopathol.* **25**: 377–390.
18. VARNEY, V.A. *et al.* 2003. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin. Exp. Allergy* **33**: 1076–1082.
19. DURHAM, S.R. *et al.* 1996. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4⁺ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J. Allergy Clin. Immunol.* **97**: 1356–1365.
20. WACHHOLZ, P.A. *et al.* 2002. Grass pollen immunotherapy for hayfever is associated with increases in local nasal but not peripheral Th1:Th2 cytokine ratios. *Immunology* **105**: 56–62.
21. ROLLAND, J. & R. O'HEHIR. 1998. Immunotherapy of allergy: anergy, deletion, and immune deviation. *Curr. Opin. Immunol.* **10**: 640–645.
22. NASSER, S.M. *et al.* 2001. Interleukin-10 levels increase in cutaneous biopsies of patients undergoing wasp venom immunotherapy. *Eur. J. Immunol.* **31**: 3704–3713.
23. BUFE, A. *et al.* 2004. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* **59**: 498–504.
24. PASSALACQUA, G. *et al.* 2004. Efficacy and safety of sublingual immunotherapy. *Ann. Allergy Asthma Immunol.* **93**: 3–12.
25. MA, S.H., S.H. SICHERER & A. NOWAK-WĘGRZYN. 2003. A survey on the management of pollen-food allergy syndrome in allergy practices. *J. Allergy Clin. Immunol.* **112**: 784–788.
26. HANSEN, K.S. *et al.* 2004. Food allergy to apple and specific immunotherapy with birch pollen. *Molec. Nutr. Food Res.* **48**: 441–448.

27. BOLHAAR, S.T.H.P. *et al.* 2004. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin. Exp. Allergy* **34**: 761–769.
28. KELSO, J.M. 2000. Pollen-food allergy syndrome. *Clin. Exp. Allergy* **30**: 905–907.
29. BUCHER, X. *et al.* 2004. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy* **59**: 1272–1276.
30. MITTAG, D. *et al.* 2004. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J. Allergy Clin. Immunol.* **114**: 1410–1417.
31. PONS, L. *et al.* 2004. Soy immunotherapy for peanut-allergic mice: modulation of the peanut-allergic response. *J. Allergy Clin. Immunol.* **114**: 915–921.
32. OPPENHEIMER, J.J. *et al.* 1992. Treatment of peanut allergy with rush immunotherapy. *J. Allergy Clin. Immunol.* **90**: 256–262.
33. NELSON, H.S. *et al.* 1997. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J. Allergy Clin. Immunol.* **99**: 744–751.
34. BURKS, W., S.B. LEHRER & G.A. BANNON. 2004. New approaches for treatment of peanut allergy: chances for a cure. *Clin. Rev. Allergy Immunol.* **27**: 191–196.
35. VAN REE, R. *et al.* 1996. Possible induction of food allergy during mite immunotherapy. *Allergy* **51**: 108–113.
36. PAJNO, G.B. *et al.* 2002. Harmful effect of immunotherapy in children with combined snail and mite allergy. *J. Allergy Clin. Immunol.* **109**: 627–629.
37. VALENTA, R. 2002. Recombinant allergen-based concepts for diagnosis and therapy of Type I allergy. *Allergy* **57**: 66–67.
38. NIEDERBERGER, V. *et al.* 2004. Vaccination with genetically engineered allergens prevents progression of allergic disease. *Proc. Natl. Acad. Sci. USA* **101**: 14677–14682.
39. BOHLE, B. & S. VIETHS. 2004. Improving diagnostic tests for food allergy with recombinant allergens. *Methods* **32**: 292–299.
40. VRTALA, S. *et al.* 2000. T cell epitope-containing hypoallergenic recombinant fragments of the major birch pollen allergen, Bet v 1, induce blocking antibodies. *J. Immunol.* **165**: 6653–6659.
41. RENZ, H. 1999. How can animal models lead to improved specific immunotherapy (SIT)? *Allergy* **54**: 39–40.
42. HERZ, U. *et al.* 1996. The relevance of murine animal models to study the development of allergic bronchial asthma. *Immunol. Cell Biol.* **74**: 209–217.
43. HERZ, U., H. RENZ & U. WIEDERMANN. 2004. Animal models of type I allergy using recombinant allergens. *Methods* **32**: 271–280.
44. HELM, R.M. & A.W. BURKS. 2002. Animal models of food allergy. *Curr. Opin. Allergy Clin. Immunol.* **2**: 541–546.
45. HASELDEN, B.M., A.B. KAY & M. LARCHE. 2000. Peptide-mediated immune responses in specific immunotherapy. *Int. Arch. Allergy Immunol.* **122**: 229–237.
46. NORMAN, P. S. 1996. Clinical experience with treatment of allergies with T cell epitope containing peptides. *Adv. Exp. Med. Biol.* **409**: 457–461.
47. WILCOCK, L.K., J.N. FRANCIS & S.R. DURHAM. 2004. Aluminium hydroxide down-regulates T helper 2 responses by allergen-stimulated human peripheral blood mononuclear cells. *Clin. Exp. Allergy* **34**: 1373–1378.
48. BAUER, M. *et al.* 2001. Bacterial CpG-DNA triggers activation and maturation of human CD11c⁺, CD123⁺ dendritic cells. *J. Immunol.* **166**: 5000–5007.
49. BAUER, S. *et al.* 2001. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. *Proc. Natl. Acad. Sci. USA* **98**: 9237–9242.
50. HARTMAN, G., G.J. WEINER & A.M. KRIEG. 1999. CpG DNA: a potent signal for growth, activation, and maturation of human dendritic cells. *Proc. Natl. Acad. Sci. USA* **96**: 9305–9310.
51. STACEY, K.J. *et al.* 2000. Macrophage activation by immunostimulatory DNA. *Curr. Top. Microbiol. Immunol.* **247**: 41–58.
52. CHU, R.S. *et al.* 1997. CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity. *J. Exp. Med.* **186**: 1623–1631.
53. LIANG, H. *et al.* 1996. Activation of human B cells by phosphorothioate oligodeoxynucleotides. *J. Clin. Invest.* **98**: 1119–1129.

54. KLINE, J.N. *et al.* 1998. Modulation of airway inflammation by CpG oligodeoxynucleotides in a murine model of asthma. *J. Immunol.* **160**: 2555–2559.
55. KLINE, J.N. *et al.* 1999. CpG oligodeoxynucleotides do not require TH1 cytokines to prevent eosinophilic airway inflammation in a murine model of asthma. *J. Allergy Clin. Immunol.* **104**: 1258–1264.
56. SEREBRISKY, D. *et al.* 2000. CpG oligodeoxynucleotides can reverse Th2-associated allergic airway responses and alter the B7.1/B7.2 expression in a murine model of asthma. *J. Immunol.* **165**: 5906–5912.
57. MAGONE, M.T. *et al.* 2000. Systemic or mucosal administration of immunostimulatory DNA inhibits early and late phases of murine allergic conjunctivitis. *Eur. J. Immunol.* **30**: 1841–1850.
58. HORNER, A.A. *et al.* 2002. Immunostimulatory DNA-based therapeutics for experimental and clinical allergy. *Allergy* **57** (Suppl 72): 24–29.
59. TIGHE, H. *et al.* 2000. Conjugation of immunostimulatory DNA to the short ragweed allergen Amb a 1 enhances its immunogenicity and reduces its allergenicity. *J. Allergy Clin. Immunol.* **106**: 124–134.
60. SIMONS, F.E. *et al.* 2004. Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA. *J. Allergy Clin. Immunol.* **113**: 1144–1151.
61. MARSHALL, J.D. *et al.* 2001. Immunostimulatory sequence DNA linked to the Amb a 1 allergen promotes T(H)1 cytokine expression while downregulating T(H)2 cytokine expression in PBMCs from human patients with ragweed allergy. *J. Allergy Clin. Immunol.* **108**: 191–197.
62. SANTELIZ, J.V. *et al.* 2002. Amb a 1-linked CpG oligodeoxynucleotides reverse established airway hyperresponsiveness in a murine model of asthma. *J. Allergy Clin. Immunol.* **109**: 455–462.
63. TULIC, M.K. *et al.* 2004. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J. Allergy Clin. Immunol.* **113**: 235–241.
64. LI, X.M. *et al.* 2003. Persistent protective effect of heat-killed *Escherichia coli* producing “engineered,” recombinant peanut proteins in a murine model of peanut allergy. *J. Allergy Clin. Immunol.* **112**: 159–167.
65. LI, X.M. *et al.* 2003. Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J. Immunol.* **170**: 3289–3295.
66. FRICK, O.L. *et al.* 2005. Allergen immunotherapy with heat-killed *Listeria monocytogenes* alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* **60**: 243–250.
67. BALDRICK, P., D. RICHARDSON & A.W. WHEELER. 2001. Safety evaluation of a glutaraldehyde modified tyrosine adsorbed housedust mite extract containing monophosphoryl lipid A (MPL) adjuvant: a new allergy vaccine for dust mite allergy. *Vaccine* **20**: 737–743.
68. WHEELER, A.W., J.S. MARSHALL & J.T. ULRICH. 2001. A Th1-inducing adjuvant, MPL, enhances antibody profiles in experimental animals suggesting it has the potential to improve the efficacy of allergy vaccines. *Int. Arch. Allergy Immunol.* **126**: 135–139.
69. DRACHENBERG, K.J. *et al.* 2001. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* **56**: 498–505.
70. MOTHES, N. *et al.* 2003. Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by therapy-induced blocking antibodies. *Clin. Exp. Allergy* **33**: 1198–2008.
71. STEVENSON, D.D. 2000. Approach to the patient with a history of adverse reactions to aspirin or NSAIDs: diagnosis and treatment. *Allergy Asthma Proc.* **21**: 25–31.
72. STEVENSON, D.D. 2003. Aspirin desensitization in patients with AERD. *Clin. Rev. Allergy Immunol.* **24**: 159–168.
73. LITWIN, A. *et al.* 1996. Immunologic effects of encapsulated short ragweed extract: a potent new agent for oral immunotherapy. *Ann. Allergy Asthma Immunol.* **77**: 132–138.

74. TEPAŠ, E.C. *et al.* 2004. Clinical efficacy of microencapsulated timothy grass pollen extract in grass-allergic individuals. *Ann. Allergy Asthma Immunol.* **92**: 25–31.
75. TANG, D.C., M. DEVIT & S.A. JOHNSTON. 1992. Genetic immunization is a simple method for eliciting an immune response. *Nature* **356**: 152–154.
76. ULMER, J.B. *et al.* 1993. Heterologous protection against influenza by injection of DNA encoding a viral protein. *Science* **259**: 1745–1749.
77. HSU, C.H. *et al.* 1996. Immunoprophylaxis of allergen-induced immunoglobulin E synthesis and airway hyperresponsiveness *in vivo* by genetic immunization. *Nat. Med.* **2**: 540–544.
78. RAZ, E. *et al.* 1996. Preferential induction of a Th1 immune response and inhibition of specific IgE antibody formation by plasmid DNA immunization. *Proc. Natl. Acad. Sci. USA* **93**: 5141–5145.
79. YOSHIDA, A. *et al.* 2000. Advantage of gene gun-mediated over intramuscular inoculation of plasmid DNA vaccine in reproducible induction of specific immune responses. *Vaccine* **18**: 1725–1729.
80. PENG, H.J. *et al.* 2002. Induction of specific Th1 responses and suppression of IgE antibody formation by vaccination with plasmid DNA encoding Der f 11. *Vaccine* **20**: 1761–1768.
81. LEE, D.J. *et al.* 1997. Inhibition of IgE antibody formation by plasmid DNA immunization is mediated by both CD4+ and CD8+ T cells. *Int. Arch. Allergy Immunol.* **113**: 227–230.
82. SATO, Y. *et al.* 1996. Immunostimulatory DNA sequences necessary for effective intradermal gene immunization. *Science* **273**: 352–354.
83. JILEK, S. *et al.* 2001. Antigen-independent suppression of the allergic immune response to bee venom phospholipase A(2) by DNA vaccination in CBA/J mice. *J. Immunol.* **166**: 3612–3621.
84. HOCHREITER, R. *et al.* 2003. TH1-promoting DNA immunization against allergens modulates the ratio of IgG1/IgG2a but does not affect the anaphylactic potential of IgG1 antibodies: no evidence for the synthesis of nonanaphylactic IgG1. *J. Allergy Clin. Immunol.* **112**: 579–584.
85. ADEL-PATIENT, K. *et al.* 2001. Genetic immunisation with bovine beta-lactoglobulin cDNA induces a preventive and persistent inhibition of specific anti-BLG IgE response in mice. *Int. Arch. Allergy Immunol.* **126**: 59–67.
86. HARTL, A. *et al.* 2004. DNA vaccines for allergy treatment. *Methods* **32**: 328–339.
87. ROY, K. *et al.* 1999. Oral gene delivery with chitosan--DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. *Nat. Med.* **5**: 387–391.
88. LUDWIG-PORTUGALL, I. *et al.* 2004. Prevention of long-term IgE antibody production by gene gun-mediated DNA vaccination. *J. Allergy Clin. Immunol.* **114**: 951–957.
89. TODA, M. *et al.* 2000. Inhibition of immunoglobulin E response to Japanese cedar pollen allergen (Cry j 1) in mice by DNA immunization: different outcomes dependent on the plasmid DNA inoculation method. *Immunology* **99**: 179–186.
90. KWON, S.S., N. KIM & T.J. YOO. 2001. The effect of vaccination with DNA encoding murine T-cell epitopes on the Der p 1 and 2 induced immunoglobulin E synthesis. *Allergy* **56**: 741–748.
91. MAECKER, H.T. *et al.* 2001. Vaccination with allergen-IL-18 fusion DNA protects against, and reverses established, airway hyperreactivity in a murine asthma model. *J. Immunol.* **166**: 959–965.
92. LEUNG, D.Y. *et al.* 2003. Effect of anti-IgE therapy in patients with peanut allergy. *N. Engl. J. Med.* **348**: 986–993.
93. WENSING, M. *et al.* 2002. The range of minimum provoking doses in hazelnut-allergic patients as determined by double-blind, placebo-controlled food challenges. *Clin. Exp. Allergy* **32**: 1757–1762.
94. HAMELMANN, E., C. ROLINCK-WERNINGHAUS & U. WAHN. 2003. Is there a role for anti-IgE in combination with specific allergen immunotherapy? *Curr. Opin. Allergy Clin. Immunol.* **3**: 501–510.
95. Kuehr, J. *et al.* 2002. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* **109**: 274–280.

96. www.rigel.com/rigel/pr_1091415726.
97. ZHU, D. *et al.* 2002. A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation. *Nat. Med.* **8**: 518–521.
98. ZHANG, K. *et al.* 2004. Inhibition of allergen-specific IgE reactivity by a human Ig Fc gamma-Fc epsilon bifunctional fusion protein. *J. Allergy Clin. Immunol.* **114**: 321–327.
99. KOPF, M. *et al.* 1993. Disruption of the murine IL-4 gene blocks Th2 cytokine responses. *Nature* **362**: 245–248.
100. MAGNAN, A. *et al.* 2000. Relationships between natural T cells, atopy, IgE levels, and IL-4 production. *Allergy* **55**: 286–290.
101. MOHRS, M. *et al.* 1999. Differences between IL-4- and IL-4 receptor alpha-deficient mice in chronic leishmaniasis reveal a protective role for IL-13 receptor signaling. *J. Immunol.* **162**: 7302–7308.
102. BORISH, L.C. *et al.* 2001. Efficacy of soluble IL-4 receptor for the treatment of adults with asthma. *J. Allergy Clin. Immunol.* **107**: 963–970.
103. GRUNIG, G. *et al.* 1998. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* **282**: 2261–2263.
104. WALTER, D.M. *et al.* 2001. Critical role for IL-13 in the development of allergen-induced airway hyperreactivity. *J. Immunol.* **167**: 4668–4675.
105. WILLS-KARP, M. *et al.* 1998. Interleukin-13: central mediator of allergic asthma. *Science* **282**: 2258–2261.
106. FALLON, P.G. *et al.* 2001. IL-13 overexpression predisposes to anaphylaxis following antigen sensitization. *J. Immunol.* **166**: 2712–2716.
107. BASHIR, M.E. *et al.* 2002. An enteric helminth infection protects against an allergic response to dietary antigen. *J. Immunol.* **169**: 3284–3292.
108. www.bioportfolio.com/news/cat_8.htm.
109. LECKIE, M.J. *et al.* 2000. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* **356**: 2144–2148.
110. PHIPPS, S. *et al.* 2004. Intravenous anti-IL-5 monoclonal antibody reduces eosinophils and tenascin deposition in allergen-challenged human atopic skin. *J. Invest. Dermatol.* **122**: 1406–1412.
111. www.mediumimmune.com/pipeline/il9.asp.
112. http://www.cambridgeantibody.com/html/technology_products/product_pipeline/cat_213_treatment_for_allergies_including_asthma.
113. VISSERS, J.L. *et al.* 2004. Allergen immunotherapy induces a suppressive memory response mediated by IL-10 in a mouse asthma model. *J. Allergy Clin. Immunol.* **113**: 1204–1210.
114. FROSSARD, C.P. *et al.* 2004. Lymphocytes in Peyer patches regulate clinical tolerance in a murine model of food allergy. *J. Allergy Clin. Immunol.* **113**: 958–964.
115. AKBARI, O., R.H. DEKRUYFF & D.T. UMETSU. 2001. Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. *Nat. Immunol.* **2**: 725–731.
116. LEE, H.O. *et al.* 2000. Interferon gamma induction during oral tolerance reduces T-cell migration to sites of inflammation. *Gastroenterology* **119**: 129–138.
117. DUMONT, F.J. 2003. Therapeutic potential of IL-10 and its viral homologues: an update. *Exp. Opin. Therapeutic Patents* **13**: 1551–1577.
118. FRANCIS, J.N., S.J. TILL & S.R. DURHAM. 2003. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. *J. Allergy Clin. Immunol.* **111**: 1255–1261.
119. STEVENS, S.R. *et al.* 1998. Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. *Arch. Dermatol.* **134**: 799–804.
120. NOH, G.W. & K.Y. LEE. 1998. Blood eosinophils and serum IgE as predictors for prognosis of interferon-gamma therapy in atopic dermatitis. *Allergy* **53**: 1202–1207.
121. BRYAN, S.A. *et al.* 2000. Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* **356**: 2149–2153.

122. LEE, S.Y. *et al.* 2001. Oral administration of IL-12 suppresses anaphylactic reactions in a murine model of peanut hypersensitivity. *Clin. Immunol.* **101**: 220–228.
123. ZIMENT, I. & D.P. TASHKIN. 2000. Alternative medicine for allergy and asthma. *J. Allergy Clin. Immunol.* **106**: 603–614.
124. NIGGEMANN, B. & C. GRUBER. 2003. Side-effects of complementary and alternative medicine. *Allergy* **58**: 707–716.
125. BIELORY, L. & K. LUPOLI. 1999. Herbal interventions in asthma and allergy. *J. Asthma* **36**: 1–65.
126. SRIVASTAVA, K.D. *et al.* 2005. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J. Allergy Clin. Immunol.* **115**: 171–178.
127. LI, X.M. *et al.* 2001. Food allergy herbal formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. *J. Allergy Clin. Immunol.* **108**: 639–646.
128. FULLER, R. 1991. Probiotics in human medicine. *Gut* **32**: 439–442.
129. DUGAS, B. *et al.* 1999. Immunity and probiotics. *Immunol. Today* **20**: 387–390.
130. KIRJAVAINEN, P.V. & G.R. GIBSON. 1999. Healthy gut microflora and allergy: factors influencing development of the microbiota. *Ann. Med.* **31**: 288–292.
131. MATRICARDI, P.M. 2002. Probiotics against allergy: data, doubts, and perspectives. *Allergy* **57**: 185–187.
132. VANDERHOOF, J.A. & R.J. YOUNG. 2004. Current and potential uses of probiotics. *Ann. Allergy Asthma Immunol.* **93**: S33–S37.
133. PAGANELLI, R. *et al.* 2002. Probiotics and food-allergic diseases. *Allergy* **57** (Suppl 72): 97–99.
134. O'Sullivan, G.C. *et al.* 2005. Probiotics: an emerging therapy. *Curr. Pharm. Des.* **11**: 3–10.
135. BROWN, A.C. & A. VALIERE. 2004. Probiotics and medical nutrition therapy. *Nutr. Clin. Care* **7**: 56–68.
136. MIRAGLIA DEL GIUDICE, M., JR., M.G. DE LUCA & C. CAPRISTO. 2002. Probiotics and atopic dermatitis. A new strategy in atopic dermatitis. *Dig. Liver Dis.* **34** (Suppl 2): S68–S71.
137. SIMON, G.L. & S.L. GORBACH. 1984. Intestinal flora in health and disease. *Gastroenterology* **86**: 174–193.
138. PESSI, T. *et al.* 2000. Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clin. Exp. Allergy* **30**: 1804–1808.
139. PESSI, T. *et al.* 1998. Probiotics reinforce mucosal degradation of antigens in rats: implications for therapeutic use of probiotics. *J. Nutr.* **128**: 2313–2318.
140. BASHIR, M.E. *et al.* 2004. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *J. Immunol.* **172**: 6978–6987.
141. NOVERR, M.C. *et al.* 2005. Development of allergic airway disease in mice following antibiotic therapy and fungal microbiota increase: role of host genetics, antigen, and interleukin-13. *Infect. Immun.* **73**: 30–38.
142. POHJAVUORI, E. *et al.* 2004. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. *J. Allergy Clin. Immunol.* **114**: 131–136.
143. ROSENFELDT, V. *et al.* 2004. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J. Pediatr.* **145**: 612–616.
144. ROSENFELDT, V. *et al.* 2003. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *J. Allergy Clin. Immunol.* **111**: 389–395.
145. KALLIOMAKI, M. *et al.* 2001. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* **357**: 1076–1079.
146. KALLIOMAKI, M. *et al.* 2003. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* **361**: 1869–1871.
147. LODINOVA-ZADNIKOVA, R., B. CUKROWSKA & H. TLASKALOVA-HOGENOVA. 2003. Oral administration of probiotic *Escherichia coli* after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years). *Int. Arch. Allergy Immunol.* **131**: 209–211.
148. BOLHAAR, S.T. *et al.* 2004. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin. Exp. Allergy* **34**: 761–769.

149. HANSEN, K.S. *et al.* 2004. Food allergy to apple and specific immunotherapy with birch pollen. *Mol. Nutr. Food Res.* **48**: 441–448.
150. LI, X.M. *et al.* 2003. Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J. Immunol.* **170**: 3289–3295.
151. LI, X.M. *et al.* 2003. Persistent protective effect of heat-killed *Escherichia coli* producing “engineered,” recombinant peanut proteins in a murine model of peanut allergy. *J. Allergy Clin. Immunol.* **112**: 159–167.
152. SHIDA, K. *et al.* 2002. *Lactobacillus casei* strain Shirota suppresses serum immunoglobulin E and immunoglobulin G1 responses and systemic anaphylaxis in a food allergy model. *Clin. Exp. Allergy* **32**: 563–570.
153. FROSSARD, C.P., C. HAUSER & P.A. EIGENMANN. 2001. Oral carrageenan induces antigen-dependent oral tolerance: prevention of anaphylaxis and induction of lymphocyte anergy in a murine model of food allergy. *Pediatr. Res.* **49**: 417–422.
154. www.foodallergy.org/research/antiigetherapy.html.
155. WALKER, S. *et al.* 2004. Anti-IgE for chronic asthma in adults and children. The Cochrane Library, Issue 4.
156. www.pdl.com/applications/press_releases.cfm?newsId=68.
157. KIPS, J.C. *et al.* 2003. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study 164/rccm.200206-5250C. *Am. J. Respir. Crit. Care Med.* **167**: 1655–1659.
158. FLOOD-PAGE, P. *et al.* 2003. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J. Clin. Invest.* **112**: 1029–1036.
159. FITCH, N. *et al.* 2001. Preclinical evaluation of BAY 16-9966 a dual IL-4/IL-13 receptor antagonist. *J. Allergy Clin. Immunol.* **107**: S61–S61.
160. ECONOMIDES, A.N. *et al.* 2003. Cytokine traps: multi-component, high-affinity blockers of cytokine action. *Nat. Med.* **9**: 47–52.
161. www.regn.com/products/product_candidate.asp?v_c_id=8.
162. www.amrad.com.au/Filesa1%20-%20Aug%202004.pdf.
163. ASADULLAH, K., W. STERRY & H.D. VOLK. 2003. Interleukin-10 therapy: review of a new approach. *Pharmacol. Rev.* **55**: 241–269.
164. CHANG, T.T. & S.R. STEVENS. 2002. Atopic dermatitis: the role of recombinant interferon-gamma therapy. *Am. J. Clin. Dermatol.* **3**: 175–183.
165. KALLIOMAKI, M. & E. ISOLAURI. 2003. Role of intestinal flora in the development of allergy. *Curr. Opin. Allergy Clin. Immunol.* **3**: 15–20.