Future therapies for food allergies

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Food allergy is an increasingly prevalent problem in westernized countries, and there is an unmet medical need for an effective form of therapy.

A number of therapeutic strategies are under investigation targeting foods that most frequently provoke severe IgE-mediated anaphylactic reactions (peanut, tree nuts, and shellfish) or are most common in children, such as cow's milk and hen's egg.

The current management of food allergy is limited to strict dietary avoidance, nutritional counseling, and emergency treatment of adverse reactions.

In this review we will focus on efforts to treat IgE-mediated forms of food allergy

Food allergies seriously alter the quality of life of patients with food allergy and their families. Fortunately, about 85% of children allergic to foods such as cow's milk, egg, wheat and other cereal grains, and soy "outgrow" (develop tolerance) their allergy, whereas only 15% to 20% of children allergic to peanut, tree nuts, fish, and shellfish will show spontaneous tolerance

Currently, there are no diagnostic tests (eg, serum food allergen–specific IgE antibody measurement or skin prick tests) that reliably predict the potential for spontaneous development of oral tolerance

However, 2 recent reports in children with multiple food allergies noted that few children with peak cow's milk– or egg white–specific IgE antibody levels of 50 kUA/L or greater outgrow their allergy by their late teenage years.

In addition, recent studies using peptide microarray assays to determine the diversity and affinity of IgE binding to sequential epitopes on major food allergens (eg, peanut, cow's milk, and egg white) might be useful in determining the severity and persistence of food allergy in affected patients

IMMUNOTHERAPEUTIC APPROACHES FOR TREATING FOOD ALLERGY

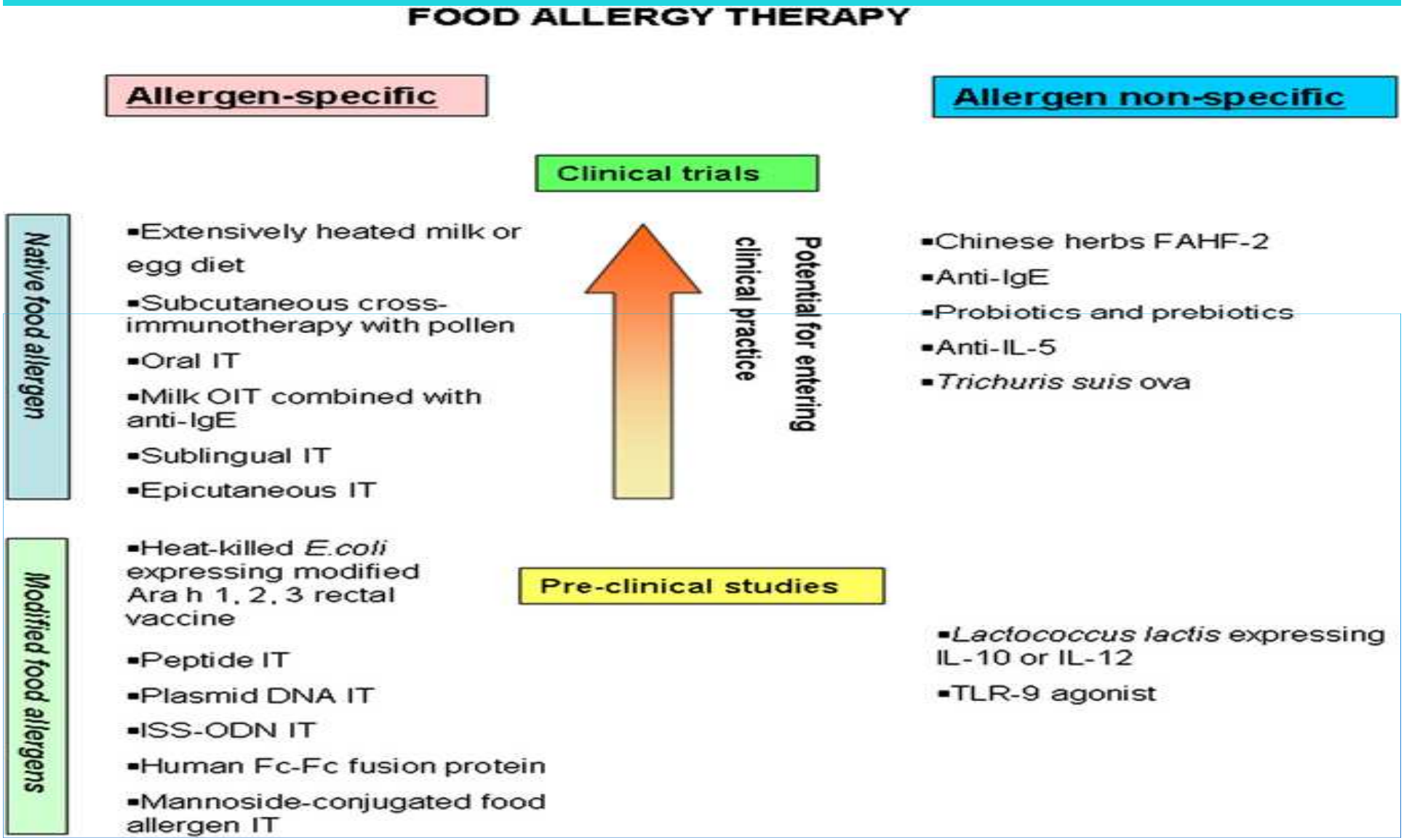
Patients with food allergy can be divided into 3 basic phenotypes: transient food allergy, persistent food allergy, and food-pollen (oral allergy) syndrome.
Based on developing evidence, it appears that each of these forms of IgE-mediated food allergy is the result of different immunologic mechanisms and therefore is likely to require different immunotherapeutic approaches to bring about resolution.

Persistent food allergy might present a more challenging situation.

Patients with the persistent form of food allergy are likely to have a less favorable response to therapy, including failure to desensitize, failure to have oral tolerance, need for a more prolonged treatment course, and development of more serious adverse reactions during therapy.

As experience with various treatment regimens increases, we will be better equipped to counsel patients about optimal individualized therapeutic options.

Approaches being pursued are both food allergen specific and nonspecific



Modified recombinant allergen immunotherapy for food allergy

The risk of an immediate allergic reaction during immunotherapy can be decreased by modifying the IgE antibody–binding sites (epitopes) with point mutations introduced by site-directed mutagenesis or with protein polymerization

Modified recombinant allergen immunotherapy for food allergy

Therapy	Mechanism of action	Effects	Comments
Clinical			
Heat-killed bacteria mixed with or containing modified peanut proteins Li et al, 2003[63]	Upregulation of T_H1 and regulatory T-cell cytokine responses	Protection against peanut-induced anaphylaxis in mice, lasting up to 10 wk after treatment	Concern for toxicity of bacterial adjuvants, excessive T_H1 stimulation, and potential for autoimmunity. Heat-killed *E coli* expressing modified peanut allergens administered rectally is viewed as the safest approach for future human studies. A phase I clinical trial in adults with peanut allergy is ongoing.
Preclinical (murine models)			
Peptide immunotherapy Li et al, 2001[64]	Overlapping peptides (10-20 amino acids long) that represent the entire sequence of allergen. Binding to mast cells is eliminated, and T-cell responses are preserved.	Protection against peanut-induced anaphylaxis in mice	Improved safety profile compared with conventional immunotherapy; does not require identification of IgE-binding epitopes
pDNA immunotherapy Li et al, 1999[65]	Induces prolonged humoral and cellular responses caused by CpG motifs in the DNA backbone	Protection against peanut-induced anaphylaxis in sensitized AKR/J mice but induction of anaphylaxis in C3H/HeJ ($H\text{-}2^K$) mice; no effect on peanut-specific IgE antibody levels	Serious concerns regarding safety in view of strain-dependent effects in mice and concern for excessive T_H1 stimulation and autoimmunity
ISS immunotherapy (ISS-ODN) Srivastava et al, 2001[66]	Potent stimulation of T_H1 through activation of antigen-presenting cells, natural killer cells, and B cells; increased T_H1 cytokine levels	Protection against peanut sensitization in mice	Not shown to reverse established peanut allergy, concern for excessive T_H1 stimulation, and potential for autoimmunity
Engineered recombinant peanut immunotherapy Srivastava et al, 2002[62]	Binding to mast cells eliminated or markedly decreased, T-cell responses comparable with those to native peanut allergens	Protection against peanut-induced anaphylaxis in mice	Improved safety profile compared with conventional immunotherapy, requires identification of IgE-binding sites
Human immunoglobulin Fc-Fc fusion protein Zhang et al, 2004[67] Kepley et al, 2004[68] Zhu et al, 2005[69]	Fusion protein cross-links the high-affinity FcεRI and low-affinity FCγRIIb receptors on mast cells and basophils.	Fusion protein inhibits degranulation of mast cells and basophils.	A human γ-allergen fusion protein, the Fc–Fel d 1 fusion protein, inhibited Fel d 1–mediated degranulation in purified human basophils from patients with cat allergy and blocked the allergic responses in a murine model. A similar approach can be used for food allergy.
Sugar-conjugated BSA Zhou et al, 2010[70]	Mannoside-conjugated BSA (Man_{51}-BSA) targeted lamina propria dendritic cells expressing SIGNR-1 and promoted $CD4^+$ type 1 regulatory T cells.	Mice sensitized with Man_{51}-BSA were protected from anaphylaxis during an oral challenge with BSA and Man_{51}-BSA.	Sugar-modified food allergens might be used to induce oral tolerance by targeting SIGNR-1 and lamina propria dendritic cells.

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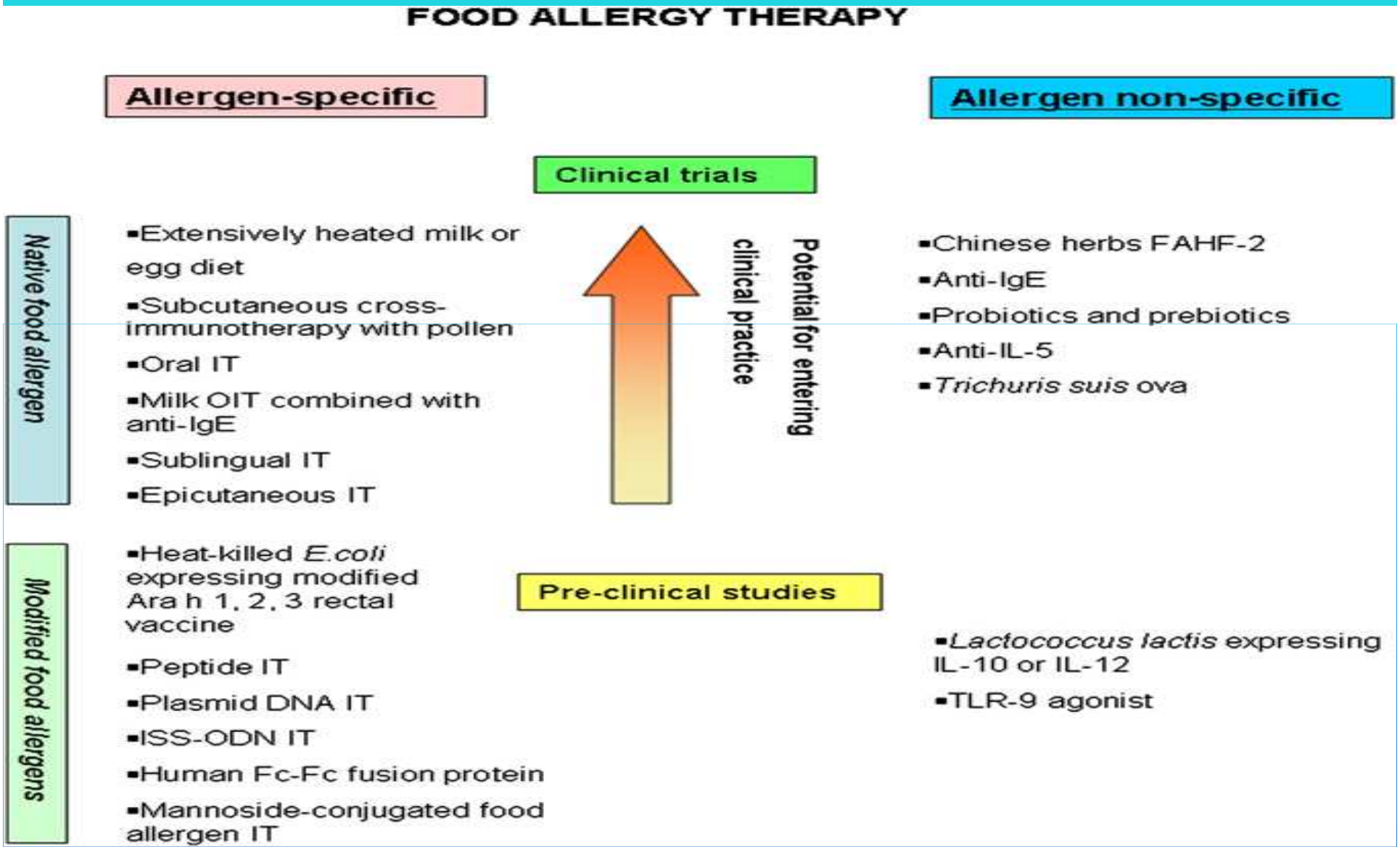

Chinese herbs FAHF-2

Wang J, Patil SP, Yang N, et al.
Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, doubleblinded, placebo-controlled, dose escalation, phase 1 study.
Ann Allergy Asthm Immunol 2010;105:75-84.

Upregulation of TH1 cytokines:
IFN-g, IL-12
Downregulation of TH2 cytokines:
IL-4, IL-5, IL-13
Decreased
allergen-specific IgE levels
and
T-cell proliferation to peanut

Reverses allergic inflammation in the airways, protects mice from peanut-induced anaphylaxis for prolonged periods of time

Current studies focus on identification of the crucial active herbal components in the 9-herb formula and establishing optimal dosing in human phase I and II trials.

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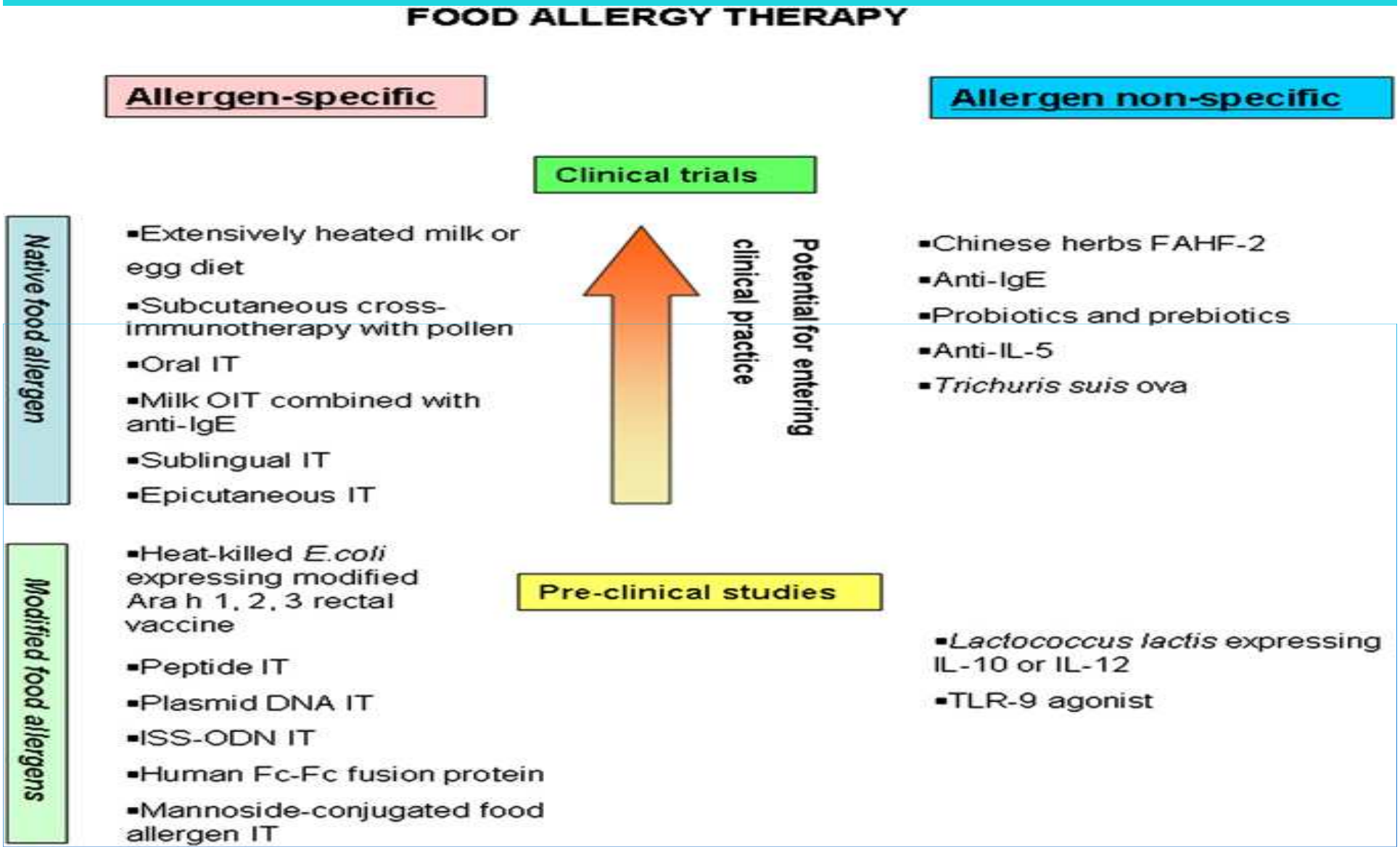

Humanized monoclonal anti–IgE

Humanized monoclonal murine anti-IgE IgG1 antibodies have been produced that bind to the constant region (third domain of the Fc region) of IgE antibody molecules and prevent IgE from binding to high-affinity FceRI receptors expressed on the surface of mast cells and basophils and low-affinity FceRII receptors expressed on B cells, dendritic cells, and intestinal epithelial cells.

With the decrease in free IgE molecules caused by anti-IgE therapy, the expression of FceRI receptors on mast cells and basophils is downregulated, resulting in decreased activation and release of histamine and other inflammatory mediators.

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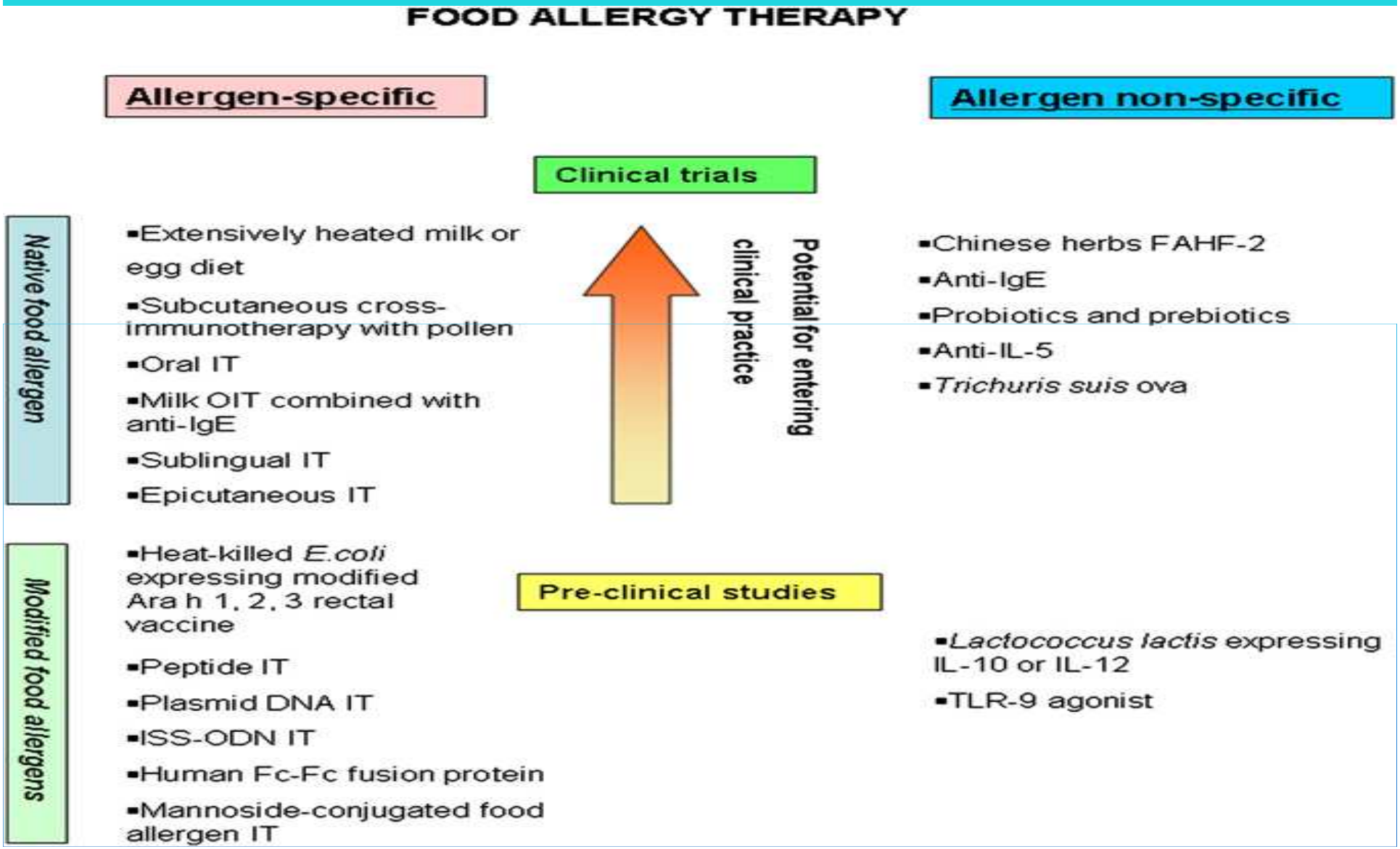

Probiotics

- Probiotics are live bacteria or their components that have beneficial effects on the health of the host, presumably by improving intestinal microbial balance. The major sources of probiotics are dairy products that contain Lactobacillus and Bifidobacterium species.

- **Potential mechanisms of probiotic immunomodulation include increased synthesis of IgA and IL-10, suppression of TNF-a, inhibition of casein-induced T-cell activation and circulating soluble CD4, and Toll-like receptor 4 signaling.**

Clinical trials of probiotics have focused on the prevention and treatment of atopic dermatitis, which includes a large subset of children with food allergy.

It has been hypothesized that the defective skin barrier resulting from atopic inflammation predisposes infants to IgE-mediated responses to food and environmental allergens.

Prenatal supplementation of mothers and postnatal supplementation of infants during the first 6 months of life have been reported to decrease the prevalence of atopic dermatitis at 2 and 7 years of age, without any effect on IgE sensitization to food or environmental allergens.

Other studies have not replicated this finding.

Prebiotics

Prebiotics are oligosaccharides that promote probiotic colonization of the gastrointestinal tract.

In a large clinical trial of 830 healthy term infants at low risk for atopy, the cumulative prevalence of atopic dermatitis at 1 year of age was reportedly 5.7% infants in the prebiotic group compared with 9.7% infants in the control group (P=0.04).

Gruber C, van SM, Mosca F, et al. Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. J Allergy Clin Immunol 2010;126:791-7.

However a double-blind, randomized, placebo-controlled trial in 119 infants with cow's milk allergy treated with a mix of 2 probiotics for 12 months showed no benefit for cow's milk allergy.

Hol J, van Leer EH, Elink Schuurman BE, et al. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlledtrial. J Allergy Clin Immunol 2008;121:1448-54.

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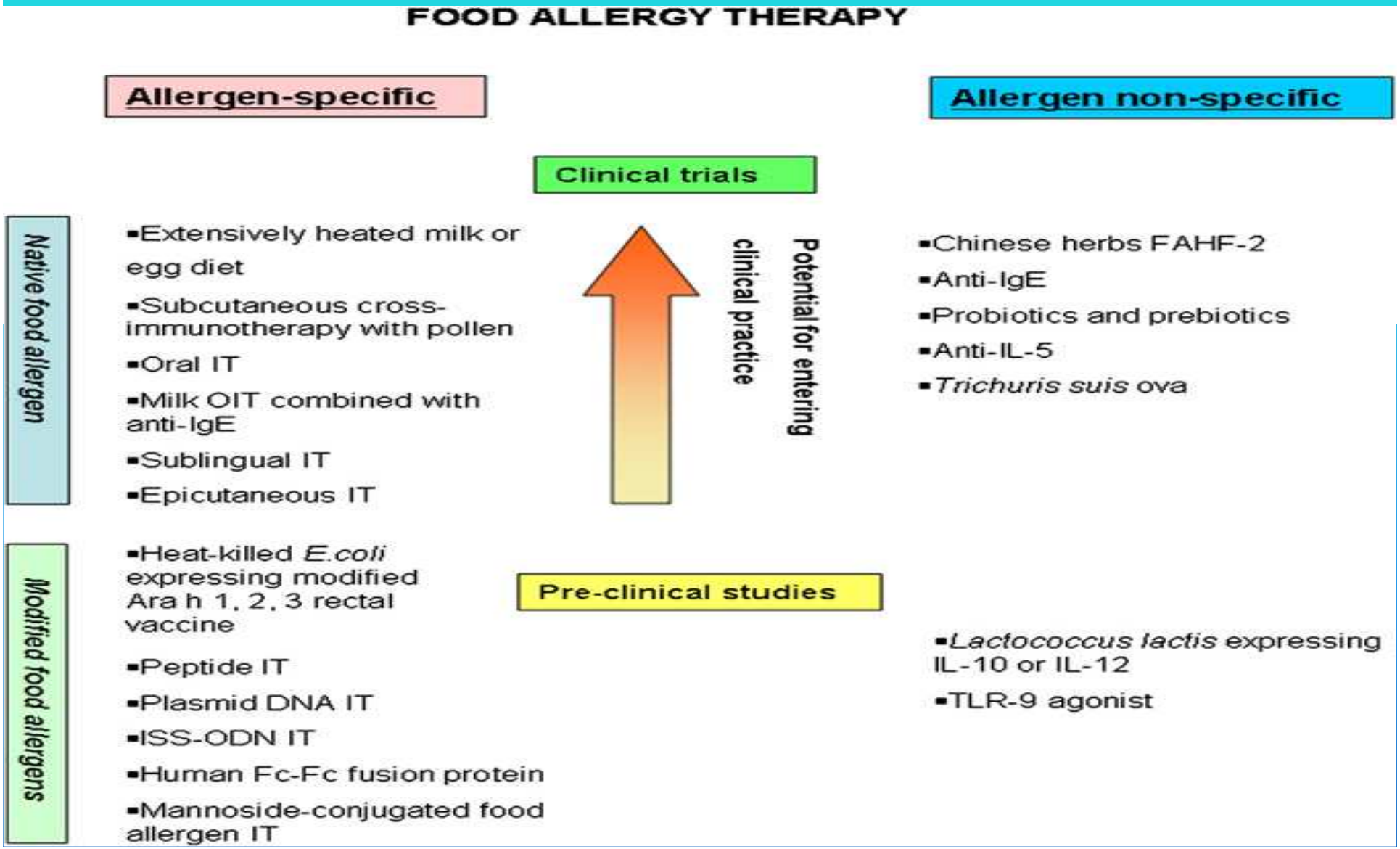

Anti–IL–5 antibody (mepolizumab) in patients with eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a disorder of mixed pathophysiology, with both IgE-mediated and non–IgE-mediated mechanisms involved.

A subset of subjects with EoE is responsive to food elimination, especially in children.

Considering the pivotal role of IL-5 in the accumulation of eosinophils in the esophageal tissue, treatment with an anti–IL-5 mAb was investigated in a randomized, placebo-controlled, double-blind trial.

Adults with active EoE were randomized to receive 750 mg of mepolizumab (n = 5) or placebo (n = 6). A significant reduction of mean esophageal eosinophilia was seen in the mepolizumab treated group (-54%) compared with the placebo group (-5%) after the first dose (P 5.03), but limited improvement of clinical symptoms was observed.

Mepolizumab was well tolerated and had an acceptable safety profile.

Currently, mepolizumab is being evaluated in children with EoE.

"An ounce of prevention is worth a pound of cure"
(Benjamin Franklin, 1706–1790)

A reassessment of neonatal feeding studies prompted the European and American pediatric societies to alter previous feeding guidelines for mothers and newborns. In recognition of an apparent lack of effect of intrauterine and early-life avoidance of peanut feeding, the guidelines no longer stress allergen avoidance by mothers during pregnancy or while breast feeding or by their newborns

Greer FR, Sicherer SH, Burks AW.

Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas.

Pediatrics 2008;121:183-91.

In addition, epidemiologic observations and studies in animal models have highlighted the potential for sensitization to peanut and egg white through cutaneous contact.

This route favors a TH2-skewed immune response and specific IgE production, which suggests a need for early oral introduction to counter the effect of cutaneous exposure.

However, in a recent study of infants at high risk of peanut allergy, a direct correlation was found between the degree of sensitization in infants and the amount of peanut consumed by their mothers during the third trimester of pregnancy.

Several ongoing studies should help clarify these issues over the next several years.

CONCLUSIONS

- *Among the plethora of novel approaches, the strategies most likely to advance into clinical practice include the Chinese herbal formula FAHF-2 and OIT alone or in combination with anti-IgE antibody.*
- *Diets containing extensively heated (baked) milk and egg represent an alternative approach to food OIT and are already changing the paradigm of strict dietary avoidance for patients with food allergy*
- *The exponential increase in research activity on food allergy and the concerted efforts in major centers worldwide give hope that an effective treatment for food allergy is within reach.*