Future Therapies for Food Allergy

In the past two decades, food allergy has emerged as an important public health issue in countries with a western lifestyle. Current management of food allergy relies on dietary avoidance and there is no therapy proven to restore permanent oral tolerance to food. This review focuses on novel approaches to allergen-specific therapy for IgE-mediated food allergy. Oral immunotherapy alone or in combination with anti-IgE antibody is likely to advance into clinical practice in the more immediate future. However, these approaches have to be further validated in large clinical trials before entering clinical practice. Diets containing extensively heated (baked) milk and egg for the majority of milk- and egg-allergic patients represent a safer alternative approach to food oral immunotherapy and are already changing the paradigm of strict dietary avoidance for majority of milk and egg-allergic children.

Introduction

Over the past two decades, food allergy has become a major public health problem in societies with western lifestyle [2,26]. Food allergy profoundly affects well-being of an individual patient and his/her family and has a broad social and economic impact. The growing numbers of patients with food allergy highlight the need for the development of accurate diagnostic tests and therapies. This review focuses on novel approaches to diagnosis and therapy for IgE-mediated food allergy.

Current standard management of food allergy involves avoidance of the food, prompt recognition and treatment of allergic reactions, and nutritional support [2]. There are no therapies proven to accelerate the development of oral tolerance or to provide effective protection from accidental exposures. Novel approaches to food allergy therapy can be allergen-specific such as oral, sublingual and epicutaneous immunotherapy with native food allergens or with mutated recombinant proteins [20]. The diet including extensively heated milk and egg proteins in baked foods is an alternative approach to allergen-specific immunomodulation and appears to accelerate development of tolerance to unheated milk and egg compared to children maintaining strict avoidance of milk and egg. The summary of diverse novel approaches to food allergy therapy is presented in Figure 1.

Subcutaneous Immunotherapy

Subcutaneous (SCIT) immunotherapy is recognized as an effective treatment for environmental and venom allergies. In two small pilot studies, aqueous peanut extract-SCIT was administered to adults with peanut allergy [18,22]. SCIT-treated subjects tolerate an increased peanut dose during post-treatment oral food challenges (OFC) and had decreased sensitivity on titrated peanut skin prick test (SPT), whereas untreated control subjects had no improvement. However, adverse reactions were exceedingly common: anaphylaxis occurred with 23% of the doses administered and an average of 9.8 epinephrine injections were given per subject during the SCIT rush phase. Only 3 of 6 subjects achieved the target maintenance dose due to adverse reactions; an average 12.6 epinephrine injections per subject was given during the maintenance phase. In spite of evidence that food-SCIT induced desensitization, the high rate of unpredictable, severe adverse reactions discouraged further evaluation of food-
SCIT. Birch pollen SCIT has been shown to modulate oral allergy syndrome caused by cross-reactive plant foods, e.g., apple. Adults treated with pollen SCIT or sublingual (SLIT) immunotherapy experience variable improvement in oral symptoms and SPT to plant foods. It has been postulated that high-dose birch pollen SCIT is required to exert a beneficial effect on the cross-reactive food allergy [1].

Oval immunotherapy

Oval immunotherapy (OIT) [22] is the most actively investigated novel therapy for food allergy [Table I]. The goal of food allergy therapy is to re-establish permanent oral tolerance, defined as the ability to ingest the food without symptoms despite prolonged periods of avoidance or irregular intake. In contrast, desensitization is an intermediate stage during OIT, which depends on the regular ingestion of the food; when dosage is interrupted or discontinued, the protective effect is lost. Augmentation factors such as viral infection, exercise, use of NSAIDs or menstrual period may trigger reactions to the previously tolerated maintenance dose. The exact mechanisms of permanent tolerance and desensitization have not been determined. Permanent oral tolerance may involve the initial development of regulatory T-cells and immunologic skewing away from the pro-allergic Th2 response, followed by anergy at later stages [29]. Immunologic changes accompanying oral desensitization include decreased reactivity of mast cells and basophils, increased food-specific serum and salivary IgG and IgA antibodies and initially increased but eventually decreased serum food-specific IgE antibodies. The permanence of protection may be tested with intentional interruption of OIT dosing for at least 4 – 12 weeks followed by a food challenge. Early studies showed that a subset of food allergic-subjects could be “desensitized” to milk, egg, fish, fruit, peanut, and celery. However, the majority of subjects who tolerated a maintenance dose, even for a significant period of time, re-developed allergic symptoms if the food was not ingested on a regular basis, indicating that permanent tolerance was not achieved. No adequately controlled trials of OIT have demonstrated the development of permanent tolerance or even long-term desensitization due to therapy as opposed to natural acquisition of tolerance.

OIT dosing schedule

During OIT, food is mixed with a vehicle and ingested in gradually increasing doses. Dose escalations occur in a controlled setting. Most studies include an initial rush rapid dose escalation day that is followed by further dose escalation on bi-weekly basis until maintenance dose is achieved. Daily ingestion of tolerated doses during the build-up and maintenance phases occurs at home.

OIT safety

OIT is associated with acute adverse allergic reactions in virtually all patients, which are more common during dose escalation than during maintenance. However, systemic reactions may occur at previously tolerated doses in the setting of exercise or viral illness. The risk of an allergic reaction to a previously tolerated dose of food is associated with physical exertion after dosing, dosing on empty stomach, dosing during menses, concurrent febrile illness, and sub-optimally controlled asthma. Some patients complain of gastrointestinal discomfort associated with OIT dosing and several studies have described the onset of symptoms consistent with eosinophilic esophagitis in 10% - 20% of treated subjects.

Patterns of response to food oral immunotherapy

Figure 2 summarizes success rates during each phase of OIT. Overall, approximately 50 - 77% of the treated subjects tolerate the daily maintenance dose, usually about 2-5 g of the food protein [22]. It is unclear, which factors determine response to OIT. It is possible that desensitization failure is associated with the most severe food allergy phenotype, as opposed to desensitization success that may be associated with a milder, transient phenotype and higher chances of spontaneous resolution of food allergy.

High quality trials of food OIT

Although numerous studies of food OIT have been conducted to date, only a few adhered to a rigorous design, as recently critically reviewed by meta-analyses [9,21,25]. Selected high-quality clinical trials are presented in detail in Table I.

SLIT and OIT combined with SLIT

Several clinical trials of SLIT with milk, peanut, hazelnut and peach extracts have been conducted [6,7,8,10] [Table II]. In SLIT, food allergen extract is kept in the mouth for 2-3 minutes and then spit out or swallowed. The starting dose is usually 100-1000-fold lower than in OIT, but SLIT is generally better tolerated than OIT and the rate of systemic adverse reactions is lower, but the degree of desensitization appears to be less than with OIT.

In a single-center clinical trial, 30 children (aged 6-17 years) with milk allergy were randomized to sublingual immunotherapy (SLIT) or OIT followed by OIT [11]. Following therapy, 1 of 10 subjects in the SLIT-group, 6 of 10 subjects in the SLIT/ oral OIT-group, and 8 of 10 subjects in the...
Table I

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Success rate*</th>
<th>Immunologic changes</th>
<th>Side effects/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow milk OIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skripak 2008 [27] randomized, placebo controlled clinical trial;</td>
<td>n=20; active to placebo 2:1 ratio; age 6-17 years</td>
<td>19 subjects completed treatment; post-OIT, the median cumulative dose of milk inducing a reaction in the active group increased from 40 mg to 5140 mg; there was no change in the placebo group, P=.003.</td>
<td>Milk-IgE levels did not change in either group. Milk-IgG levels increased significantly in the OIT-group, with a predominant milk-IgG4 increase.</td>
<td>The median frequency of side effects was 35% in the active group compared to 1% in the placebo group. Blinded study [27]: mild oral pruritus median 16% doses/child gastrointestinal median 2% doses/child Epinephrine: 0.2% of total doses; 2 doses during build-up and 2 doses during home maintenance (in 4 subjects) Open label home study [17]: 1-3 months: 2.5-96.4% of doses per subject; &gt;3 months: 0-79% /subject % total doses with reactions: Oral pruritus: 17% Gastrointestinal: 3.7% Respiratory: 0.9% Cutaneous: 0.8% Multisystem: 5.5% Epinephrine: 6 reactions in 4 subjects. 1 subject developed EoE.</td>
</tr>
<tr>
<td>Narisetty 2009 [17] open label follow up study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keet 2012 [11] Randomized clinical trial comparing milk OIT and SLIT</td>
<td>N=30, 6-17 years</td>
<td>1/10 in the SLIT group, 6/10 subjects in the SLIT/OITB group, and 8/10 subjects in the OITA group passed the 8-g challenge (P = .002, SLIT vs OIT).</td>
<td>Titrated CM skin prick tests, basophil CD63 and CD203c expression decreased; CM-IgG4 increased in all groups; CM-IgG and spontaneous histamine release decreased in only the OIT group.</td>
<td>After screening DBPCFC and initial SLIT escalation, subjects continued SLIT escalation to 7 mg daily OR began OIT to either 1000 mg (the OITB group) or 2000 mg (the OITA group) of milk protein. OFC to 8 g of milk protein was done after 12 and 60 weeks of maintenance. If the 60-week OFC was asymptomatic, IT was stopped, OFC repeated 1 and 6 weeks later. OIT was caused more systemic side effects than SLIT. After avoidance, 6 of 15 subjects (6/ 15 subjects in the OITB and 3/8 subjects in the OITA group) regained reactivity, 2 after only 1 week.</td>
</tr>
<tr>
<td>Nadeau 2011 [16] Small phase I trial, uncontrolled open label study of rapid milk oral desensitization combined with omalizumab</td>
<td>n=11, 7-17 years</td>
<td>9/10 tolerated 1000 mg milk protein on initial rush day; 1 subject dropped out due to gastrointestinal symptoms; 9 subjects who reached a daily dose of 2000 mg passed the DBPCFC and an open challenge.</td>
<td>Following a week of milk OIT, the CD4(+) T-cell response to milk was reduced indicating anergy, or deletion. Following 3 months of daily milk-OIT, the CD4(+) T-cell response returned, with a shift from IL-4 to IFN-γ. Milk-IgE decreased; milk-IgG4 increased 15-fold.</td>
<td>Following 9 weeks of omalizumab, milk-OIT begun. Omalizumab was discontinued at week 16; milk-OIT was continued DBPCFC was performed after 24 weeks. The mean frequency for total reactions reported by week 24 was 1.6%; most were mild; 0.3% were moderate; 0.1% severe.</td>
</tr>
<tr>
<td>Peanut OIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varshney, 2011 [28]</td>
<td>n=28; age 1-16 years Subjects randomized 19:9 to OIT or placebo for 48 weeks.</td>
<td>During the initial day of rapid dose escalation, 26 out of 28 (93%) children reached the maximum cumulative dose of 12mg of peanut protein or placebo. 16 children received the full course of peanut OIT and all tolerated 5 g of peanut protein following OIT.</td>
<td>Compared to placebo, peanut OIT group showed reductions in SPT size (P &lt; .001), IL-5 (P = .01), and IL-13 (P = .02) and increases in peanut-specific IgG4 (P &lt; .001). The ratio of forkhead box protein 3 (FoxP3)(hi); FoxP3(intermediate) CD4+ CD25+ T cells increased at the time of OFC (P = .04) in peanut OIT subjects.</td>
<td>Adverse reactions were common, but most reactions were mild. In the mild arm, 47% (n = 9) of subjects experienced adverse reactions during the initial day escalation; during the build-up phase adverse reactions occurred following 1.2% of 407 build-up doses. None of the placebo subjects required treatment during initial day escalation or build-up dosing, however 3 (33%) were treated with epinephrine during the final peanut DBPCFC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mo challenge: 55% active group passed; 0% placebo passed</td>
<td>22 mo challenge: 75% active group passed (desensitized) 24 mo challenge (6-8 weeks off OIT): 28% active group passed (sustained unresponsiveness) Small wheal diameters on skin-prick testing and increases in egg-specific IgG4 antibody levels were associated with passing the oral food challenge at 24 months. The results of this clinical trial raise concerns about the long-term protection (sustained unresponsiveness) afforded by OIT. It remains to be determined whether a higher maintenance dose and longer duration of OIT might improve the rates of sustained unresponsiveness</td>
<td></td>
</tr>
</tbody>
</table>

Symbols: *Success rate defined as regular ingestion of the tested food for at least 6 months; $ One of each Apple, peach, lettuce, orange, beans and corn; Abbreviations: MILK, cow’s milk; SPT, skin prick test; DBPCFC, double-blind, placebo-controlled food challenge; OIT, oral food challenge; EoE, eosinophilic esophagitis Reprinted with permission from Nowak-Wegrzyn A., Sampson H.A.: Future therapies for food allergies. J Allergy Clinical Immunol. 2011, 127(3), 558-73.
Table II  
Clinical trials in specific-food SLIT.  
Badania kliniczne dotyczące podjęczej immunoterapii w alergii pokarmowej.

<table>
<thead>
<tr>
<th>Food/Study</th>
<th>Subjects</th>
<th>Success rate</th>
<th>Immunologic changes</th>
<th>Side effects/comments</th>
</tr>
</thead>
</table>
| HAZELNUT  
Enrique 2005, 2008 [6,7] randomized, double-blind, placebo-controlled trial | n=23, adults, (54.5%) with allergy symptoms to hazelnut | 50% of SLIT-subjects tolerated 20 g of hazelnut during follow-up DBPCFC, versus 9% in the placebo group. | Levels of serum hazelnut-IgG4 and total serum IL-10 increased only in the SLIT-group, but there were no differences in hazelnut-IgE levels pre- and post-SLIT. | All SLIT-subjects reached the max dose with a 4-day rush-protocol, followed by a daily maintenance dose (182.8 µg of Cor a 1 and 121.9 µg of Cor a 8, major hazelnut allergens). After 5 months, the mean threshold dose of hazelnut increased from 2.3 g to 11.6 g in the active group (P = 0.02) compared to 3.5 g to 4.1 g in placebo (non-significant). |
| PEACH ( Pru p 3)  
Fernandez-Rivas 2009 [8] randomized double-blind placebo-controlled trial | n=37, adults | In the SLIT-treated subjects (n=37), the threshold doses of Pru p 3 for local reactions (usually oral pruritus) during a DBPCFC were 9-times higher and for systemic reactions (usually transient gastrointestinal discomfort or mild rhinitis) were 3-times higher following 6 months of SLIT compared to pre-SLIT threshold doses. In contrast, the placebo-treated subjects experienced no significant changes in their threshold doses of Pru p 3. | Specific IgE to recombinant Pru p 3 increased both in the active (P < .001) and placebo (P = .03) groups, although the increase remained only significant at 6 months in the active group (active 4.2, P = 0.08; placebo 4.0, P = 0.08, T-test). IgG4 to native Pru p 3 increased significantly in the active group (P = .007) but not in the placebo group (P = 0.2). | Peach SLIT was well tolerated. |
| Fleischer 2013 [10] Multicenter randomized, double-blind, placebo controlled clinical trial | n=40, 12-37 years old | After 44 weeks of SLIT, 14/20 (70%) subjects receiving peanut SLIT were responders compared to 3/20 (15%) subjects receiving placebo (P<.001). In peanut-SLIT responders, median SICD increased from 3.5mg to 496mg after 44 weeks, and to 996 mg after 60 weeks of SLIT. | There were modest increases in peanut IgG4 and decrease in basophil activation in SLIT treated subjects. There were no significant changes in peanut-IgE and skin prick test wheal size in treated subjects, at baseline and week 44. | Peanut SLIT safely induced a modest level of desensitization in a majority of subjects compared to placebo. Longer duration of therapy showed statistically significant increases in the tolerated dose of peanut. Of 10,885 peanut doses through week 44, 63.1% were symptom-free; excluding oral/pharyngeal symptoms, 95.2% were symptom-free. |

OITA-group passed the 8-g challenge (p = 0.002; SLIT vs. OIT). After discontinuing treatment, 6 of 15 subjects (3 of 6 subjects in the OITB-group and 3 of 8 subjects in the OITA-group) reacted to milk challenge, 2 only after 1 week, indicating loss of desensitized state. Systemic reactions were more common during OIT than during SLIT. In this trial, milk OIT was more efficacious for desensitization to milk than SLIT alone but was associated with more systemic side effects.

Oral immunotherapy combined with anti-IgE monoclonal antibody

Anti-IgE monoclonal antibody has been tested for peanut allergy in one study and showed an increased threshold of response to peanut in the subjects treated with the highest dose [14]. Pre-treatment with anti-IgE monoclonal antibody is expected to improve safety of food OIT by lowering the circulating IgE. Monoclonal anti-IgE antibodies may enhance efficacy of food OIT by down-regulating the expression of IgE receptor on antigen presenting cells and facilitated antigen presentation.

An uncontrolled, pilot phase I safety trial in 11 children, median age 8 years (range, 7-17 years), with milk allergy combined monoclonal anti-IgE antibody (omalizumab) with milk OIT during the escalation phase. Milk OIT had an excellent safety, with 9 treated children advancing to the full maintenance dose of 8g milk during the milk DBPCFC at 24 weeks. A multi-center randomized trial of anti-IgE throughout the course of milk oral immunotherapy in children and adults with milk allergy is ongoing and will provide more robust data regarding safety and efficacy of combined treatment.

Is food oral immunotherapy ready for clinical practice?

The studies of food OIT give hope that the cure for food allergy is within reach. Preliminary data on food-OIT and SLIT suggest a beneficial treatment effect, although significant adverse reactions to OIT are common. Four meta-analyses on immunotherapy for milk, egg, and peanut allergy pointed out significant limitations of the published studies [3,9,21,25]. The two most recent analyses, which strictly adhered to all Cochrane criteria, were published by the Cochrane Collaboration [21,30]. These meta-analyses included all randomized controlled, quasi-randomized controlled and case controlled trials of peanut and milk OIT published from 1990 through January, 2012. Among 746 papers addressing peanut OIT, only one study fulfilled the inclusion criteria [28]. Authors of the Cochrane Report concluded that based on the findings of one small trial, peanut OIT cannot be recommended as routine treatment for patients with peanut allergy. This conclusion echoed the statements made by the authors of the other meta-analyses. In the meta-analysis of milk OIT studies, slightly less rigorous criteria were used and 16 records representing 5 clinical trials were reviewed. In total there were 196 children (106 in the treatment group and 90 in the control) included in these studies. The authors considered the quality of these trials to be low and because no standardized protocols were used, guidelines and further studies are necessary prior to incorporating desensitization into clinical practice.

None of the studies included in the meta-analyses provided evidence that OIT can induce permanent “tolerance,” and none of the trials followed subjects for more than two years, thus the long-term protective effects.
of food OIT remain unknown. At this time, food OIT remains limited to the research setting [24]. Further research utilizing large, high-quality randomized controlled trials is necessary to evaluate the long-term efficacy, safety and cost-effectiveness of OIT.

**Epicutaneous immunotherapy (EPIT)**

An alternative route of allergen delivery is **via skin**. In the mouse models, T-cells purified from mesenteric lymph nodes (MLNs) of mice orally immunized with ovalbumin transferred allergic skin inflammation to naïve recipients that were challenged with ovalbumin via skin. These results indicated that cutaneous exposure to food antigens can reprogram gut-homing effector T cells in lymph nodes to express skin-homing receptors [23].

In a pilot study, 18 cow milk-allergic children (mean age 3.8 years, range 10 months to 7.7 years) were randomized 1:1 to receive active EPIT or placebo [5]. Cow milk allergy was confirmed by baseline milk oral challenge and the threshold dose of milk was established. Children applied 1 mg skim milk powder or 1 mg glucose as placebo on the skin under patch for 48 hours three times per week for three months. EPIT-treated children had a trend toward increased milk threshold doses at the follow-up milk oral challenge from a mean of 1.8 mL at baseline to 23.6 mL at three months, whereas there was no change in the placebo-group. There were no significant changes in milk-specific IgE levels from baseline to 3 months in either group. The most common side effects were local pruritus and eczema at the site of EPIT application. There were no severe systemic reactions; however, one child had repeated episodes of diarhrea following EPIT. Based on these findings, EPIT warrants further evaluation for food allergy.

**Baked Milk and Egg Diet - an Alternative Approach to Oral Immunotherapy**

Children with transient egg and milk allergy generate IgE antibodies directed primarily against conformational allergenic epitopes that undergo degradation during extensive heating or food processing. In addition to the degradation of conformational epitopes by high temperature, heated egg white proteins undergo enhanced gastric digestion while ovomucoid bound to grain matrices in baked products form insoluble complexes of decreased allergenicity [15]. Two large clinical trials investigated the tolerance to extensively heated (baked into wheat muffins and waffles) milk and egg in children [13, 19]. In both studies, tolerance to baked milk and egg was determined in the majority (approximately 75%) of children during a physician-supervised OFC. Additional studies confirmed that baked milk and egg are tolerated by the majority of milk and egg allergic children.

Compared to the children who continued strict dietary avoidance according to the current standard of care, children ingesting baked milk or egg developed tolerance to unheated milk and egg at an accelerated rate [12]. These findings suggest that for the majority of egg and milk allergic children, strict avoidance of baked products is unnecessary and may account for delayed acquisition of tolerance. The results of these baked milk and egg trials are changing the

---

**Table III**

<table>
<thead>
<tr>
<th>Allergen-non-specific therapy for food allergy.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alergenowo-nieswoista terapia alergii pokarmowej.</td>
<td>---</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Effects</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal anti-IgE</strong></td>
<td>Binds to circulating IgE, prevents IgE deposition on mast cells, blocks degranulation; interferes with the IgE-facilitated antigen presentation by B- and dendritic cells.</td>
<td>Improves symptoms of asthma and allergic rhinitis, protection against peanut anaphylaxis in 75% of treated patients (highest dose-group).</td>
<td>Subcutaneous at monthly or 2 week intervals, unknown long-term consequences of IgE depletion; may be combined with specific-food –OIT [16]</td>
</tr>
<tr>
<td><strong>Chinese herbs FAHF-2</strong></td>
<td>Up-regulation of Th1 cytokines: IFN-γ, IL-12 Down-regulation of Th2 cytokines: IL-4, IL-5, IL-13, decreased allergen-IgE and T cell proliferation to peanut</td>
<td>Reverses allergic inflammation in the airways, protects mice from peanut-induced anaphylaxis for prolonged periods of time</td>
<td>Oral, generally safe and well tolerated, 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</td>
</tr>
<tr>
<td><strong>Probiotics and prebiotics</strong></td>
<td>Increased IgA and IL-10, suppression of TNF-α, reduced casein-induced T-cell activation and circulating soluble-CD4, and Toll-like receptor 4 signaling.</td>
<td>Prenatal maternal and postnatal infant supplementation for 6 months decreased AD-prevalence at 2 and 7 years of age. In 830 healthy term infants at low risk for atopy cumulative prevalence of AD at 1 year of age was 5.7% in infants fed with the cow milk-based formula with prebiotic compared to 9.7% infants in the control group not fed prebiotic (P=0.04).</td>
<td>Generally safe, well-tolerated and cost-effective.</td>
</tr>
<tr>
<td><strong>Trichuris suis ova therapy</strong></td>
<td>Stimulation of IL-10 synthesis</td>
<td>In a mouse model of food allergy protection against food IgE-sensitization and anaphylaxis.</td>
<td>Safe and afforded clinical improvement in Crohn’s disease and ulcerative colitis; no beneficial effect in adults with allergic rhinitis. High prevalence of GI side effects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-clinical (murine models)</th>
<th>---</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactococcus lactis transduced with IL-10</strong></td>
<td>Decreased serum IgE and IgG1; increased gut IgA, increased gut and serum IL-10</td>
</tr>
<tr>
<td><strong>Lactococcus lactis transduced with IL-12 and β-lactoglobulin</strong></td>
<td>Decreased IgG1 in serum and BAL, decreased IL-4 and increased IFN-γ production by β-lactoglobulin stimulated splenocytes</td>
</tr>
<tr>
<td><strong>Toll-like receptor 9 agonist</strong></td>
<td>Induction of mucosal and systemic Th1 responses; decreased peanut-specific IgE and IgG2</td>
</tr>
</tbody>
</table>

paradigm of the current management of milk and egg allergy, allowing for a more perso-
nalized approach based on the reactivity to baked milk and egg. It is critical, that the introduction of baked milk and egg must be done under physician supervision during an oral food challenge. The introduction of ba-
ked egg and milk adds layers of complexity compared to strict allergen avoidance, but markedly improves patient lifestyle. A large clinical trial is ongoing to further explore the effects of introducing progressively hi-
ger doses of less-extensively heated milk protein on the development of tolerance to unheated milk.

Other antigen-specific approaches

A number of additional approaches to food allergy have been evaluated in animal studies, as outlined in Table III, including im-
munotherapy with modified peanut vaccine, peptide immunotherapy, immunization with pDNA, CpG immunotherapy, and human immu-
noglobulin Fc-Fc fusion proteins. These approaches are promising but remain in the very early stages of development and are far
removed from clinical application.

Allergen non-specific therapy

A number of novel therapies that are not
directed at individual allergens have been eval-
uated in clinical studies including Chi-
inese herbal therapy (FAHF-2), anti-IgE the-
rapy, probiotics, and Trichuris suis therapy.
Additional pre-clinical approaches include probiotic bacteria transfected with IL-10 and IL-12 and toll-like receptors (Table III).

Conclusions

In the past two decades, food allergy has emerged as an important public health issue in countries with a western life-style. Current management of food allergy relies on dietary avoidance and there is no therapy proven to restore permanent oral tolerance to food. Among the novel approaches, oral immunotherapy alone or in combination with anti-IgE antibody and Chinese herbal formula FAHF-2 are likely to advance into clinical practice in the more immediate future. However, these approaches have to be further validated in large clinical trials before advancing into clinical practice. Diets containing extensively heated (baked) milk and egg for the majority of milk- and egg-
allergic patients represent a safer alternative approach to food oral immunotherapy and are already changing the paradigm of strict dietary avoidance for milk and egg-allergic children.

References
5. Dupont C., Kalach N., Soulaines P. et al.: Cow’s milk-epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivi-
6. Enrique E., Malek T., Pineda F. et al.: Sublingual immunotherapy for hazelnut food allergy: a follo-

7. Enrique E., Pineda F., Malek T. et al.: Sublingual immunotherapy for hazelnut food allergy: a rando-
10. Fleischer D.M., Burks A.W., Vickery B.P. et al.: Consortium of Food Allergy. Sublingual immunothe-
11. Keet C.A., Frischmeyer-Guerrerio P.A., Thyaga-
17. Nairsety S.D., Skripak J.M., Steele P. et al.: Open-
20. Nowak-Wegrzyn A., Sampson H.A.: Future ther-
23. Oyoshi M.K., Ekhal A., Scott J.E. et al.: Epicutan-
27. Skripak J.M., Nash S.D., Rowley H. et al.: A rando-
28. Varshney P., Jones S.M., Scurlock A.M. et al.: A random-
zized controlled study of peanut oral immu-