Hope for a Safer Future:

A Special Report on Food Allergy Therapies
It can be an overlooked ingredient, a cross-contact mistake – any food that was thought to be safe, but wasn’t. For individuals and families managing food allergies, exposure to the wrong food might result in mild symptoms or a dangerous medical emergency known as anaphylaxis, a severe allergic reaction that affects multiple organ systems and can shut down breathing and blood flow.

Food allergies are increasingly common. A FARE-supported report by FAIR Health, an independent nonprofit organization dedicated to transparency in health care costs and health insurance information, found that treatment for anaphylactic reactions to food rose nearly 400 percent over the past decade. More than two million U.S. children have had at least one severe or life-threatening food allergy reaction. Food allergies are an ever-present source of anxiety, and for many in the food allergy community, protection from life-threatening reactions is the top research priority.
Food allergy is a disease in which a patient’s antibodies – immune defenses that normally attack invading organisms – instead target harmless food proteins. When these food-specific IgE antibodies encounter the food protein and bind to it, they trigger the release of histamine and other molecules that cause allergy symptoms. A severe reaction is like an uncontrolled storm of immune responses that overwhelms the body.

The Current State of Food Allergy Treatment
To date, the U.S. Food and Drug Administration (FDA) has not approved a treatment to prevent food allergy reactions or dampen their severity. This leaves food allergy patients and families with limited choices. Current recommendations are to avoid even trace amounts of problem foods and carry epinephrine auto-injectors, which can halt anaphylaxis symptoms and buy time for emergency care, but can’t prevent reactions from occurring.

Food is central to our lives, so strict avoidance of common foods can be challenging, and often has social implications. Patients and their families face years – often a lifetime – of constant vigilance, paying close attention to every mouthful, every day. FARE-funded research indicates that U.S. families of children with food allergies shoulder about $25 billion per year in direct and indirect costs.

Still, when compared to strict avoidance, no intervention to treat food allergies has been conclusively shown to have benefits that outweigh its risks. Identifying safe, effective therapies that meet this standard is the goal that drives food allergy treatment research forward.

Fortunately, that goal is now closer than ever before thanks to recent progress in clinical trials, controlled research studies that are key steps in the approval process for new therapies. At this writing, there are more than 50 clinical trials for food allergy nationwide, with nearly 15,000 participants, although eligibility requirements, exclusion criteria (such as severe asthma), limited study sites and personal reasons prevent some patients from joining. Well-designed trials are usually blinded at the start, with participants and researchers not knowing who is receiving the study’s active treatment, although in many trials, all participants are eventually offered active treatment.

Possible treatments to prevent food allergy reactions are being developed and tested by food allergy centers, academic institutions and pharmaceutical companies. Currently, the best-studied treatments are different approaches to allergen immunotherapy, sometimes called desensitization, in which controlled exposure to an allergen trains the patient’s immune system to be less reactive.

Desensitization therapies attempt to raise the reaction threshold, the dose of food that results in a reaction. If patients can tolerate small amounts of their allergens, the proteins that cause their allergic reactions, accidental exposures become less dangerous, allowing food allergy patients and their families to live safer, less stressful lives.

Bryan Bunning, a food allergy patient and researcher who is the brother of clinical trial participant, explained it this way: “Once you’ve had a life-threatening reaction, that anxiety stays with you. Being part of a study can take away some of the burden of food allergies, both for you and your family. You still need to carry epinephrine and read labels, but if immunotherapy is successful there’s less fear of having a deadly reaction from a bite of the wrong food or cross-contact. You and your entire family can live life more freely, with less worry.”

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Clinical trials are the lifeblood of treatment research, and everyone who benefits from a new treatment owes a debt to the pioneers who tested it first. Hugh Sampson, MD, of the Icahn School of Medicine at Mount Sinai calls these volunteers “the real heroes of this whole movement. They are going through a lot in order to help us understand whether or not a treatment works, and I think that anybody who does that really deserves a huge pat on the back.”

Outside of clinical trials, some allergists in private practices or academic centers offer immunotherapy to their food allergy patients. Because these treatment approaches vary among care providers, the benefits and risks of immunotherapy outside the clinical trial setting can be harder to assess. FARE believes that discussions between a patient and a physician relating to immunotherapy should mirror the informed consent procedures in a clinical trial setting.
Three types of immunotherapy to treat food allergy have made significant progress in human clinical trials: oral immunotherapy, in which allergen is eaten; sublingual immunotherapy, in which allergen is placed under the tongue; and epicutaneous immunotherapy, in which allergen in a dermal patch is applied to the skin. Regardless of the approach being tested, in most clinical trials an oral food challenge precedes food allergen immunotherapy. Increasing doses of the problem food are eaten until reaction symptoms result. The lowest dose that causes symptoms is the patient’s baseline reaction threshold. This initial oral food challenge also confirms the patient’s food allergy diagnosis.
One immunotherapy that is commonly used to treat non-food allergies has made less progress in clinical trials for food allergy. **Subcutaneous** ("under the skin") immunotherapy, or SCIT, uses injections ("allergy shots") to desensitize patients to allergens including pollen, mold, pet dander and insect venom. Early food allergy research on SCIT raised safety concerns. In a 1992 clinical trial, a study participant died from anaphylaxis after accidentally being given an injection that contained peanut. Further research found that peanut SCIT injections frequently caused systemic allergic reactions requiring epinephrine, and SCIT was largely abandoned as a food allergy treatment. More recently, new efforts are underway to develop safer SCIT methods.

**Oral Immunotherapy**

A food allergy patient taking **oral immunotherapy (OIT)** eats increasing doses of their allergen in an attempt to become desensitized to the problem food. OIT has a long history – one account of using OIT to treat egg allergy was published in 1908.

A typical course of OIT begins with an initial day of escalating doses under medical supervision, starting with tiny amounts of food protein and doubling repeatedly to a small, tolerated dose. Next, at home over a period of months, this daily dose is increased each week or two until a maintenance dose is reached. The maintenance dose is consumed every day for months or years. Typical OIT doses are measured in milligrams or grams.

Oral food challenges during the maintenance period test how much food allergen the patient can eat without reaction following treatment. A desensitized patient can tolerate an oral food challenge while their program of daily maintenance dosing continues. Immunotherapy results in **sustained unresponsiveness** when a patient can discontinue the maintenance dose for a period of weeks and still pass an oral food challenge. Introduced in 2012, the term sustained unresponsiveness reflects that we do not know how long the immunological changes resulting from immunotherapy will persist.

The food allergies treated with OIT in clinical trials are egg, milk, wheat, soy, peanut, tree nut and sesame, as well as baked milk and baked egg. Published success rates for OIT vary widely, with the reported percentage of treated patients that achieve desensitization ranging from 30 percent to more than 90 percent. In studies that retest patients after maintenance dosing is discontinued, a smaller fraction of patients achieve sustained unresponsiveness. Many of the studies have been small, and the methods used have often been inconsistent.

Reactions are common during OIT. Most involve localized symptoms, such as itchy mouth or upset stomach, although severe, systemic reactions sometimes occur. Factors that can increase the likelihood of a systemic reaction include infection, exercise and non-steroidal anti-inflammatory drugs like ibuprofen. A significant fraction of patients, 10-30 percent, drop out of treatment because they can’t tolerate the reactions caused by OIT, especially symptoms that affect the gut.

During or after OIT, a minority of patients (3-15 percent) develop eosinophilic esophagitis (EoE). This allergic condition damages the tube that carries food from the mouth to the stomach. EoE can also occur in children who have spontaneously outgrown a food allergy without OIT, making it difficult to know whether OIT has directly caused a subsequent case of EoE or simply uncovered it.

Quality of life is an important factor in weighing the benefits and risks of immunotherapy. Food allergy parent...
Jill Mindlin puts it this way: “The decision to participate in a study is a very personal one to be made, after careful consideration, by each family. There are many pros and cons to participating: frequent trips to the research center, the day to day work of complying, and a number of food challenges, which can be frightening. However, knowing that our daughter would be protected from an accidental ingestion brings a tremendous sense of peace. Every added protection we can give her before she leaves for college brings us comfort.” Jill’s daughter, Maya, a clinical trial veteran, recognized the downsides and possible rewards of study participation at an early age: “I would rather get an EpiPen from the doctor in the hospital in a controlled setting now, than to have to get one from a stranger on the street 10 years from now.”

One 2017 study in which participants completed quality-of-life (QOL) surveys before and after treatment found overall QOL improvement for patients participating in OIT, compared to a control group that did not receive OIT. For patients with lower QOL scores before OIT, four months of immunotherapy tended to improve their reported QOL. However, some patients who started treatment with higher QOL scores had lower scores after four months of milk, egg or peanut OIT.

Biologic Drugs in OIT Clinical Trials

Small OIT trials have historically yielded varying results. By 2011, some investigators concluded that OIT could achieve more predictable outcomes and improve its safety profile only through larger research studies and more consistent OIT protocols. This drug development approach to OIT was adopted by Allergen Research Corp., now Aimmune Therapeutics, which produces AR101, a characterized peanut flour for OIT. AR101 differs in several respects from peanut OIT available through other clinical trials and through private practices. The AR101 dosing regime is standardized, starting at the same small amount and increasing on the same schedule to a final daily maintenance dose of 300 mg that, at roughly one peanut, is lower than most peanut OIT maintenance doses. Unlike the more variable food products for OIT available online or in grocery stores, AR101 is considered a biologic drug, with a defined protein content that eliminates another source of inconsistent dosing.

AR101 has successfully completed a Phase III clinical trial, a large study of safety and effectiveness that must be completed before a request is made for FDA approval. In the PALISADE trial, which evaluated highly peanut-allergic children, AR101 increased oral tolerance to peanut significantly compared to placebo. Half of the AR101-treated children ages 4-17 passed a one-gram oral peanut protein challenge after OIT. In contrast, only 2 percent of placebo-treated patients tolerated this dose. One in five AR101-treated patients left the trial. Twelve percent dropped out due to adverse reactions, including one patient who experienced severe anaphylaxis requiring epinephrine and one patient with eosinophilic esophagitis.

The next step for AR101 will be submission to the FDA for approval.

AR101 is not the only biologic drug that has recently been tested in OIT clinical trials. Phase II trials, small studies that examine safety and effectiveness, have combined OIT with omalizumab (Xolair), an injectable asthma medication that targets IgE antibodies. In a 2017 study, 83 percent of children receiving OIT plus Xolair were able to pass an oral food challenge after 28 weeks of multi-food OIT, compared to 33 percent of children receiving multi-food OIT plus placebo. The Xolair group also had fewer reactions during OIT. A 2015 FARE-funded study of milk OIT plus Xolair found that Xolair lowered the frequency and severity of reactions during OIT and allowed patients to desensitize more quickly, but did not significantly change the percentage of patients that become desensitized. In a 2016 study of peanut OIT plus Xolair, also funded by FARE, most placebo-treated patients were unable to tolerate the rapid desensitization and left the study prior to oral food challenge, while most Xolair-treated patients were able to continue treatment and eventually tolerated the challenge dose.

Sublingual Immunotherapy

In sublingual (“beneath the tongue”) immunotherapy, or SLIT, food allergen is dissolved in a small amount of liquid and held under the tongue for several minutes.
before being spat out or swallowed. This introduces undigested allergen to cells in the lining of the mouth that promote food tolerance. SLIT has been used to treat peanut, hazelnut, milk and peach allergies. While it resembles OIT in its dosing pattern – escalation followed by maintenance – SLIT uses smaller doses than OIT, because the volume of liquid that can fit under the tongue is limited. SLIT doses are typically measured in micrograms or milligrams.

Compared to OIT, few studies have investigated SLIT, and even fewer have compared the two approaches. Successful desensitization using either approach raises a patient’s reaction threshold, increasing the amount of problem food they can tolerate. On average, the amount of allergen tolerated following desensitization is greater with OIT, but SLIT is safer, with fewer systemic reactions and milder reaction symptoms. Like OIT, SLIT for food allergies is offered by some allergists, although private-practice SLIT is harder to find.

FARE is currently funding a Phase II clinical trial for peanut SLIT in very young children (ages 1-4 years) to evaluate effectiveness, safety and dosing. Investigators will also track various immune system components to gain insight into the immunological changes associated with desensitization and tolerance.

**Epicutaneous Immunotherapy**

Like SLIT, epicutaneous (“on the skin”) immunotherapy, or EPIT, introduces food allergen directly to tolerance-promoting cells. However, unlike both OIT and SLIT, EPIT exposes patients to food allergens on the skin rather than through the digestive tract. A dermal patch that adheres to the skin is coated with a small (micrograms) dose of food allergen. The EPIT regimen also differs from OIT and SLIT during the two-week initiation period: the amount of food allergen in the patch remains constant, but the hours per day that the patch is worn increase, until each patch is worn 24 hours and replaced daily.

DBV Technologies is developing the Viaskin patches used for EPIT. Patches are being developed to treat peanut, milk and egg allergies. Testing is most advanced for Viaskin Peanut, which has completed a Phase III clinical trial. Phase II clinical trial results have been reported for the safety and effectiveness of Viaskin Milk. Viaskin Egg is in pre-clinical development.

Phase II trials of Viaskin Peanut found that the 250-µg peanut patch is more effective in children under age 12 than in older children and adults. The PEPITES Phase III clinical trial of Viaskin Peanut in children ages 4-11 demonstrated a significant response to the treatment but did not meet one of the statistical thresholds set prior to the trial. Thirty-five percent of the treatment group and 14 percent of the placebo group responded during the yearlong trial. Compared to placebo, Viaskin Peanut treatment significantly increased the average cumulative dose of peanut that patients tolerated. The FDA has agreed to consider an application for Viaskin Peanut approval.

Preliminary results from the Phase II MILES trial for Viaskin Milk have also been reported. Three different daily doses were tested in children (ages 2-11) and adolescents (ages 12-17). The highest response rate, 58 percent, was achieved using a 300-µg milk patch to treat children for one year. By comparison, the response rate to placebo patches among children in the same age group was 33 percent. Further trials for Viaskin Milk are planned.

Patients tolerate EPIT better than OIT, with a smaller fraction of patients leaving EPIT studies because of side effects. EPIT reactions are largely limited to the skin. Rashes at the patch sites are common, but systemic reactions requiring epinephrine have not been reported. Daily dosing adherence for EPIT is higher than for OIT, exceeding 95 percent in the PEPITES trial.
OIT, SLIT and EPIT have advanced farthest toward FDA approval, but they are not the only food allergen immunotherapies on the horizon. Additional treatment prospects are in earlier stages of development.
Some of these prospects involve modifications of the immunotherapies discussed above, while others are novel.

- A Phase II peanut OIT trial is planned to compare AR101 with AR101 plus dupilumab (Dupixent), a biologic drug that targets immune system pathways associated with allergy. Dupixent has already been approved as an effective treatment for moderate to severe eczema.

- More testing is also needed to show whether biologic drugs like Xolair or Dupixent can protect patients independent of OIT, by raising the threshold for reaction.

- Other possible therapeutic agents that are being studied in combination with immunotherapies include probiotics and Chinese herbal medicine formulations.

- Astellas Pharma Inc. is recruiting adults with peanut allergy to a clinical trial of ARA-LAMP-vax, a DNA-based vaccine that contains genes for peanut allergens rather than the allergens themselves. By activating immune defenses not linked to allergy, the vaccine may shift immune activity away from IgE responses.

- A new version of peanut SCIT developed by HAL Allergy is in Phase I safety testing. The peanut proteins have been modified to make them less allergenic and better tolerated.

- One investigation that received funding from FARE is developing intranasal vaccines that deliver food allergens in an emulsion of very fine oil-water droplets. Initial results in mice are encouraging.

At the same time, there has also been progress in building food allergy research infrastructure. Established in 2015, the FARE Clinical Network (FCN) now includes 30 centers of excellence nationwide. Through the FCN collaboration, top research and clinical care institutions across the country ensure that food allergy patients can access state-of-the-art diagnosis, disease management and research. In addition to hosting clinical trials, FCN member institutions will soon share with the FARE Patient Registry deidentified (anonymous) information from electronic medical records, expanding the pool of data available to fuel research. Amy M. Scurlock, MD, and Stacie M. Jones, MD of Arkansas Children’s Hospital, an FCN site with 18 active or recruiting food allergy clinical trials, recently voiced the optimism held by many in the research community: “The food allergy field is entering an exciting new era with potential for lasting impact on disease burden.”

**Advances in immunology, cell biology and molecular biology have generated remarkable new tools to investigate how treatments change immune responses to food allergens.**

FARE has also brought together food allergy patients and researchers to ensure that research programs are informed by patient perspectives. Established in 2016 through a two-year Eugene Washington Engagement Award from the Patient-Centered Outcomes Research Institute (PCORI), FARE’s Outcomes Research Advisory Board (ORAB) includes patient representatives, researchers and stakeholders with diverse expertise. The 44 ORAB members have identified patient priorities for research, including the prevention of deadly reactions and inclusion of psychosocial support services in clinical trials. Members have shared these priorities with the research community through publications and conference presentations.

While immunotherapy for food allergy has existed for more than a century, progress has been slow. Fortunately, advances in immunology, cell biology and molecular biology have generated remarkable new tools to investigate how treatments change immune responses to food allergens. These innovations hold great potential to shed light on why a treatment succeeds for some patients and fails for others, so that we can identify which food allergy treatments might best protect individual patients. Prospects for safe, effective treatments to prevent food allergy reactions have never been brighter, and the field of food allergy research – in which FARE has invested more than $90 million – is poised to deliver on its promise.

Funded Research: the FARE Investigator in Food Allergy Awards

FARE is the world’s largest private funder of food allergy research, having invested more than $90 million to study the disease and find life-changing treatments.

To accelerate the pace of innovation and discovery, FARE’s multi-million dollar, multi-year Investigator in Food Allergy Awards brings new talent to the field of food allergy research. Exciting and potentially life-saving projects funded by FARE are led by the following innovative scientists:

**Edda Fiebiger, PhD, Boston Children’s Hospital and Harvard Medical School** – Fiebiger, recipient of the 2017 New Investigator Award, is evaluating whether inhibiting enzymes active during allergic reactions might lead to better outcomes for oral immunotherapy.

**Robert Anthony, PhD, Massachusetts General Hospital and Harvard Medical School** – Anthony, recipient of a 2017 Mid-Career Investigator Award, is examining the role of IgE glycosylation – the addition of sugar molecules to allergic proteins – in promoting or limiting allergic reactions.

**Stephanie Eisenbarth, MD, PhD, Yale School of Medicine** – Eisenbarth, recipient of a 2017 Mid-Career Investigator Award, is studying a unique, inherited predisposition to food allergens to understand the development of food allergies in the general population.

**Jessica O’Konek, PhD, University of Michigan (Ann Arbor)** – O’Konek, recipient of a 2015 New Investigator Award, researched the modulation of food allergy responses with nanoemulsion-based allergy vaccines, exploring the possibility of providing protection against anaphylaxis with intranasal administration of nanoemulsion combined with egg or peanut antigens.

**Duane Wesemann, MD, PhD, Brigham and Women’s Hospital (Boston)** – Wesemann, recipient of a 2015 New Investigator Award, sought to identify the extent to which primary Ig repertoires can be influenced by microbial and dietary exposures early in life and examine how modification of these exposures can reduce allergic response to food.

**Simon Hogan, PhD, University of Michigan (Ann Arbor)** – Hogan’s work focuses on identifying the key proteins and cells that cause the blood vessel fluid leak leading to severe anaphylaxis triggered by foods. He is the recipient of a 2015 Mid-Career Investigator Award.

**Michiko Oyoshi, PhD, Boston Children’s Hospital and Harvard Medical School** – Oyoshi is examining the role of maternal antibodies transferred to babies through breast milk in inducing oral tolerance in children. She is the recipient of a 2015 Mid-Career Investigator Award.

**Erik Wambre, PhD, Benaroya Research Institute (Seattle)** – Wambre is investigating the specific T cell responses to peanut allergic components to determine the cellular and molecular mechanism associated with peanut sensitization. He is the recipient of a 2015 Mid-Career Investigator Award.

**New Investigator Awards** support the development of an academic research career by providing $75,000 per year for salary support and laboratory expenses for two years for research conducted by individuals (MD, PhD, MD/PhD or DO) who have completed at least two years of research training and who do not have independent research funding.

**Mid-Career Investigator Awards** ($150,000 annually for up to five years) focus on established investigators holding the academic rank of Assistant Professor or Associate Professor, or the equivalent in non-academic research settings.