FARE
Food Allergy Research & Education

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A Vision and Plan for Food Allergy Research

Food allergy is a major medical and public health issue with rising prevalence, no preventive treatments, and little knowledge of the underlying causes. Food Allergy Research & Education (FARE), the leading nonprofit organization working on food allergies, seeks to transform the prevention and treatment of food allergy by investing in research, education, advocacy and awareness. This paper lays out a roadmap for the future of food allergy research, building on discussions at an April 2013 Research Retreat.

The Problem

Up to 15 million Americans have food allergies. Food allergy reactions can range from mild to severe, but the severity of past reactions does not predict the severity of future reactions, so even someone who has previously only had mild reactions must be prepared for the next reaction to be life-threatening. In the U.S., a food allergy reaction sends someone to the emergency room every three minutes.

Currently, the treatment for food allergy is limited to strict avoidance of the problem food(s) and treatment of reactions, when they occur, with self-injectable epinephrine and rapid transport to an emergency room. Despite this vigilance, strict food avoidance is difficult to carry out and accidental exposures to allergens are all too common. The day-to-day precautions required to avoid potentially deadly reactions put an enormous and real social and psychological burden on the affected individual and family. As a result, individuals with food allergies and their families have to make significant alterations to their lifestyles to remain safe. The societal and health care economic impact of food allergy on families is substantial, with the estimated annual cost of caring for a child with food allergy in the U.S. at $24.5 billion.

More concerning, the problem appears to be growing at a rapid rate. Numerous studies have supported the anecdotal view that food allergy is far more prevalent today than in the recent past. In May 2013, a CDC report found that the prevalence of food allergy among children increased 50 percent between 1997 and 2011.

The Opportunity

The time is ripe for a coordinated and well-resourced approach to accelerating progress in food allergy research.

While there is currently no approved treatment for preventing food allergy reactions, a number of potential therapies show promise. However, these investigational therapies are not being advanced to the clinic as quickly as they could be due to a number of challenges—organizational, financial and scientific—that require a coordinated effort to overcome. Finding a way to expedite these trials would accelerate understanding and allow more

families to have access to potentially beneficial therapies as soon as possible.

At the same time, most experts believe the therapies currently under study will not be effective for all patients, and that a rational approach to the ultimate prevention and cure for food allergy will require a deep understanding of the root causes of food allergy. Fortunately, there has never been a better time to conduct research into the causes of human disease. There have been dramatic advances in the technologies and tools for studying human biology, and for developing highly relevant laboratory models, but these methods have not yet been broadly applied to food allergy.

Finally, the merger in 2012 of the Food Allergy & Anaphylaxis Network and the Food Allergy Initiative created FARE, a single and highly effective nonprofit organization with the ability to focus attention, resources and effort on what is most needed to advance the field. FARE's mission is to ensure the safety and inclusion of individuals with food allergies while relentlessly seeking a cure. In addition to investing in world-class research, FARE provides evidence-based education and resources, undertakes advocacy at all levels of government, and increases awareness of food allergy as a serious public health issue.

Seizing the Opportunity: FARE Research Retreat, April 2013

Recognizing the need and the opportunity, FARE brought more than 50 leading researchers, senior government officials, industry representatives and food allergy advocates to a Research Retreat in Washington, D.C., on April 12-13, 2013. The dual goals of the Retreat were to lay out a short-term plan for advancing immunotherapy to the clinic and to develop an overall vision for the future of food allergy research.

The following vision statement was broadly endorsed at the start of the Retreat as the scientific community's goal for the future of food allergy research:

> *By 2023, we will be able to accurately diagnose food allergy and predict individual disease progression and response; we will be able to offer patients effective therapies beyond avoidance; we will do this informed by a deep biological understanding of food allergy and via a vibrant community of investigators.*

The following is a synopsis of the Retreat discussions, and the plan that follows builds on ideas discussed during the meeting.

Diagnosing the Problem: Retreat Summary

The state of clinical trials in food allergy

Immunotherapy offers great promise for food allergy, but it remains in the experimental stage and the patient community is eager for viable treatments to become available. To date, the results of more than a dozen clinical trials of oral immunotherapy (OIT) have been published. The studies suggest that about 75 percent to 80 percent of patients with food allergies can be desensitized for some period of time. However, consistent with the early-stage nature of OIT research, many of the trials to date have taken place at independent sites using different protocols—varying in the number of subjects and duration of the trial, the specific form of the allergen given, the escalation and maintenance dose schedule, the use of a "control" group for comparison, etc. While these early studies have increased our understanding, a more consistent and coordinated approach across investigative sites is needed to provide the type of information necessary to establish the safety and efficacy of immunotherapy in the treatment of food allergy.

The challenges of advancing OIT to the clinic underscore a greater challenge for clinical trials in food allergy. There are currently not enough sites or centers conducting high-quality clinical research in food allergy, and the research that is underway is being conducted independently or through partnerships between individual centers. There does not yet exist a coordinated, standardized approach to organizing and pursuing food allergy research across multiple centers that would hasten progress towards commercialization.

Beyond the current efforts in immunotherapy, immune modulation also shows promise (for example, with anti-

IgE), and yet it has been difficult to organize the trials, obtain funding and interest pharmaceutical partners. Indeed, there may be immunologic agents currently in use for other disorders that could prove efficacious for food allergy—but there is not yet an effective way to identify, prioritize and test such agents for food allergy.

In other fields, disease advocacy organizations have supported and organized networks of centers for conducting clinical research that have enabled multi-center trials, attracted industry interest and garnered results for their communities; prominent examples include the Cystic Fibrosis Foundation and the Multiple Myeloma Research Consortium.

The state of our understanding of the underlying causes

Relatively little is understood today about the underlying causes, mechanisms, and natural history of food allergy. Unanswered questions include: Why are food allergies more common today than in the past? What are the important prenatal and early life determinants of food allergies? Why are some people allergic to peanuts, others to eggs, and others to multiple allergens? Why are some food allergy reactions mild while others are severe or life-threatening?

The development and utilization of improved therapeutic options for food allergies is likely being hindered by this lack of knowledge, and yet, to date, the genetic and mechanistic science necessary to answer these questions has been limited. Additional work in both human and animal models is needed to identify mechanisms that will lead to improved biomarkers for therapeutic successes and to identify new therapeutic targets.

A major obstacle to conducting this research is the lack of shared tools and resources to facilitate it. The lack of a food allergy biorepository is a prominent case in point. Modern translational research is powerfully enabled by ready access to biospecimens and data from large numbers of well-characterized patients (those whose detailed health histories have been recorded). In the case of food allergy, some patient sample collections exist, but are not at the scale needed for progress, have not been characterized using the most modern tools, and have not been brought together or widely shared.

In other fields, there have been centrally organized efforts to build shared resources that are open and available for all to use, which has in turn spurred growth in research and led to discoveries. For example, T1D Exchange is an effort funded by the Leona M. and Harry B. Helmsley Charitable Trust that has enrolled 26,000 well-characterized type 1 diabetes patients to accelerate translational research in that field. The NIDDK Inflammatory Bowel Disease Genetics Consortium brought together an international effort to discover over 100 human genes contributing to that disorder. The Psychiatric Genomics Consortium has assembled over 50,000 samples for the study of schizophrenia. These diseases are less common than food allergy, and yet investigators have assembled and learned from large patient collections characterized in depth.

The state of the field

Compared to the scope of the problem and opportunity, there are simply not enough scientists working in the field of food allergy. The $31 million of National Institutes of Health (NIH) funding (FY 2012) in support of research on food allergy pales in comparison to other diseases, but NIH funding is constrained by the quantity of applications it receives. Currently, only 20 percent of extramural NIH funding for food allergy is unsolicited, suggesting that there is a relative lack of investigator-initiated research in the field.

But there is a significant hurdle for obtaining federal funding for investigator-initiated research—namely that grant applications typically require preliminary data showing the potential promise of the proposed line of research.[1] This poses a Catch-22 for young investigators

1 For example, R01 grants, NIH's gold-standard funding mechanism, require preliminary data. But the National Institute for Allergy and Infectious Diseases has noted that proposals for R21 grants, which are meant for exploratory research and do not explicitly require preliminary data, increasingly include preliminary data and that such data "correlates with funding success." *www.niaid.nih.gov/researchfunding/grant/strategy/Pages/r21decide.aspx#c.*

embarking on a career as well as established investigators interested in exploring a new field—it is difficult to generate preliminary data without funding, and it is difficult to get funded without preliminary data. This is of particular concern for the food allergy field, given the relative dearth of established, well-funded investigators.

Other leading health advocacy foundations, recognizing the need to attract top talent to their causes, have sought to invest in promising scientists to improve the quality and fundability of their research, and to position them for long-term career success. The Cystic Fibrosis Foundation, Crohn's & Colitis Foundation of America, Melanoma Research Foundation and the National Multiple Sclerosis Society, among others, offer trainee awards for all stages of an academic career—for junior faculty, postdoctoral fellows, physicians seeking clinical research training, graduate students, and medical students. Many of these foundations also offer grants to attract established investigators to their fields.

The Solution: A Three-Pillar Approach to Achieve the Vision

The Retreat discussions have highlighted three important tracks for FARE to pursue in order to catalyze food allergy research.

1. Develop a strategy and infrastructure to test clinical hypotheses in man and advance clinical research rapidly

FARE's primary focus in the research realm is to advance therapies to the clinic as rapidly as possible so that they are widely available to patients. In order to do this, FARE will seek to 1) create a central organizing entity to standardize and coordinate clinical trial protocols, 2) build a clinical network of food allergy centers, and 3) organize the field to identify and prioritize clinical research opportunities.

Create a central organizing entity to standardize and coordinate clinical trial protocols

Drawing on the experience of other fields, and building on the success of the Consortium of Food Allergy Research funded by the National Institute of Allergy and Infectious Diseases, FARE seeks to establish a central entity to coordinate clinical development (the FARE Research Organization, also known as FARO), and a network of food allergy investigative sites for collaborative clinical research (the FARE Clinical Research Network).

FARO would serve as a hybrid between an academic research organization and the more traditional pharmaceutical industry development model. FARO would be responsible for designing, articulating and implementing product-specific clinical development strategies. In addition, FARO would coordinate the conduct of clinical trials within a network of food allergy research investigators, and would also be responsible for identifying and recruiting new investigator sites, developing efficiencies, hiring experienced staff, and developing systems for recruiting and enrolling subjects. FARO would assist the investigator sites to identify and train staff, who in turn would be able to interact with FARO for the purpose of facilitating the expert conduct of clinical trials sponsored/sanctioned by FARE. FARO would develop relationships with potential industry partners interested in funding the development of new therapies.

Key components of the vision for FARO include:

- A core staff, led by a Chief Medical Officer, that has relevant pharmaceutical/clinical research organization (CRO) expertise and is accountable to the Board of Directors of FARE;
- The identification and establishment of qualified investigative sites, envisioned as members of the FARE Clinical Research Network; and
- The building, development and validation of standardized systems for collection of consistently high-quality data that can be submitted to regulatory authorities in support of applications for marketing approvals.

This concept was reviewed and discussed at the Research Retreat, and received broad and enthusiastic support from the attendees.

Build a clinical research network

An essential part of advancing immunotherapy and other potential therapies to the clinic will be the establishment

of a network of high-quality clinical research centers that have agreed to collaborate on multi-center clinical trials, following consistent protocols and openly sharing data. To meet this need, FARE will establish the FARE Clinical Research Network, modeled on successful networks already established for other diseases.

The FARE Clinical Research Network would be coordinated and managed by FARO. In the initial startup phase, a limited number of food allergy centers will be selected to join the FARE Clinical Research Network as members. Member sites will be selected after a rigorous process to ensure that studies will be done in the highest-quality manner. Sites that are selected to participate in the Network will be able to note their status as a "FARE Clinical Research Network Member" for marketing purposes. New sites will be expected to participate in a comprehensive training program, including basic clinical trial research through food-allergy-specific procedures, and to abide by data-sharing protocols, as described below. The sites would be subject to regular audits by FARO.

The ultimate goal in creating the FARE Clinical Research Network is to expand the number of centers conducting high-quality clinical research in order to accelerate the availability of treatments. A well-functioning Network could be expected to attract the interest and engagement of industry, which could further accelerate progress towards new treatments.

Organize the field to identify and prioritize opportunities

There is an immediate need to coordinate current immunotherapy clinical trials to accelerate progress toward U.S. Food and Drug Administration approval. The discussion at the Retreat envisioned a joint effort coordinated across multiple centers focused on a short-term goal—preventing adverse reactions from accidental ingestion of an allergen—in the interest of making a form of immunotherapy available to the public as quickly as possible. The long-term goal would be to induce permanent tolerance.

Establishing common protocols is critical to the success of this effort, including the use of double-blind placebo-controlled food challenges (DBPCFC). In addition, the Retreat participants discussed the prioritization of allergens according to their prevalence and severity. While these ideas received general support at the Retreat, further discussion needs to take place to continue to refine the approach and plan its execution. Establishing the FARE Clinical Research Network infrastructure described above will also be critical to making rapid progress.

At the same time as there is an effort to expedite immunotherapy trials, FARE will support efforts to identify and prioritize other promising approaches for clinical investigation (e.g., anti-IgE). This exercise could include scouring the immunologic agents currently in trials or approved and on the market to see which may have promise for the treatment of food allergy. A successful implementation of the FARE Clinical Research Network should lower the costs and barriers to undertaking clinical trials in food allergy so that promising immunomodulators can be readily tested.

2. Develop the scientific understanding, tools and resources necessary to facilitate research that will build a pipeline of future therapies

FARE is committed to building a foundation that will help advance therapies to the clinic as quickly as possible. To do this, it is critical that FARE invest in research that helps increase our understanding of the disease and in developing tools and resources that facilitate the advancement of clinical research.

Support basic research that can translate into therapeutic advances

At a time when federal funding for research is constrained, FARE is committed to supporting the basic research necessary to develop a deeper understanding of the causes and mechanisms underlying food allergy. By improving our understanding of the disease, scientists will be able to better determine targets for treatment.

Establish a patient registry and biorepository

A large (n>10,000 samples) food allergy patient registry and biorepository (with DNA, RNA, serum collected on each participant) could dramatically accelerate discovery

of genetic risk factors and environmental triggers of food allergy. If the participants are followed over time, it would be possible to describe the natural history of food allergy and to discover serum biomarkers, critical for the design of clinical trials and stratification of patients, respectively.

As food allergy is a complex genetic disease with multiple genetic risk factors and environmental triggers, large samples of patients (thousands per allergen) will likely be needed to enable robust discovery. Rather than obtain samples from patients allergic to each of many different allergens, it will likely be more productive to pilot the effort with larger collections for a couple of allergens. A pilot study of at least n=5,000 cases of peanut allergy was discussed as one high-priority example.

Samples for the biorepository could be obtained in at least four ways: existing biorepositories; traditional clinic and population-based collections; clinical trials conducted by FARE; and via newer social media and Web-based ascertainment. These are non-mutually exclusive, and each has advantages. Clinic-based collections provide high-quality phenotype data collected in a standardized manner; trial-based collections offer the possibility of regimented recruitment and response to therapy; and social-media- and Internet-based ascertainment has the greatest speed and efficiency. FARE will seek to pursue a blended strategy that captures the benefits of each.

Serum, DNA, RNA, clinical history, immune testing and (where available) oral food challenge data would be collected from patients at the FARE Clinical Research Network centers, or at a minimum for all FARE-sponsored studies. For patients participating in immunotherapy trials, long-term data and samples should be collected.

Samples should be uniformly characterized with genome-wide genotyping arrays and, as costs allow, exome sequencing and epigenetic analysis; analysis by experienced statistical geneticists should be performed. The immune system should be extensively characterized, both for potential biomarkers and for possible microbial triggers of allergy, and combined with genetic data; sequencing of the immune repertoire may also be informative.

Enable the development of tools and reagents

The availability of high-quality, standardized tools and reagents can accelerate progress and improve reproducibility of research findings. One particular need that should be a priority is the development of diagnostic tools, such as biomarkers, to provide firm evidence of desensitization and the induction of tolerance. Such tests would decrease the need for multiple DBPCFC during therapeutic trials, and would thus increase the safety of those trials. Such tests would also be immensely valuable for clinical practice.

Other examples of tools for food allergy research might include purified allergens (ideally, characterized at a molecular level), immunological reagents, predictive animal models, and cellular assays of allergic responses. FARE will establish a forum for food allergy researchers to identify key shared needs, provide a pool of funding to develop these tools, and disseminate the tools once available.

Establish data-sharing protocols (open access)

A Web-based food allergy research portal should be developed so that results of genetic and immunological studies, and any key standardized research tools, can be made available to all investigators in the field. Funding from FARE will be contingent on agreements to share data and results with other investigators rapidly and with limited embargo periods. Conditions for deposition of data should meet or exceed the NIH standards for deposition in the National Center for Biotechnology Information's database of Genotypes and Phenotypes (dbGaP) and other such databases.

3. Actively attract and develop outstanding investigators to the field of food allergy

FARE will draw on the successful experience of other organizations to design funding mechanisms that bring new investigators into the field—both promising young investigators and senior investigators who are focused on basic, translational and clinical research—and help them succeed by allowing them to pursue novel ideas and

generate the necessary preliminary data that will lead to larger extramural grants.

Senior research awards

Senior research awards will provide senior investigators who have a track record of research success outside of food allergy, ideally in a related field, the funding needed to explore new avenues. Drawing on the lessons from other disease foundations, FARE will seek to design a mechanism that will attract leading scientists to conduct research in food allergy.

Trainee and career development awards

In conjunction with the American Academy of Allergy, Asthma & Immunology (AAAAI), FARE offers an annual award, the Howard Gittis Memorial Research Award, to an individual entering the third or fourth year of fellowship training, or the first or second year of a junior faculty appointment. FARE seeks to augment the Gittis Award with a broader array of trainee and career awards to encourage the development of outstanding young scientists with an interest in food allergy.

Other career development opportunities

Other ideas discussed at the Research Retreat included having FARE sponsor a meeting for all investigators interested in food allergy during the AAAAI annual meeting, and establishing a Food Allergy Research School, built on the successful model of the Clinical Immunology Society Immunodeficiency School, which would enable senior investigators to mentor junior investigators. Both of these ideas will be explored.

What It Will Take to Succeed

FARE organization and governance

The plan above represents a more strategic engagement by FARE in the research realm. Successful execution will require the appropriate management expertise and capacity. The leading disease foundations described above include senior medical and scientific staff as part of their leadership teams; FARE seeks to follow this model. At a minimum, FARE will appoint a Chief Medical Officer to oversee the development of FARO and the FARE Clinical Research Network. As the plans for each of the pillars above come into greater focus, it may make sense to consider recruiting other senior scientific staff.

At the same time, a review of FARE's advisory board structure and function is warranted. Currently, FARE has a Medical Advisory Board that focuses on clinical care issues and a Research Advisory Board that serves primarily as a peer-review board for grant proposals. The recommendations above, if implemented, may require a rethinking of the functions and makeup of these Boards.

Funding

To succeed, this strategic plan will require a strong partnership between government, industry and FARE that is characterized by a substantial increase in investment from all parties in food allergy research. Exclusive of the significant investment that will be required by government and industry, a preliminary analysis suggests that FARE's investment in the proposed three-pronged strategy will exceed $100 million in two five-year phases. This would represent an incremental $10 million per year in fundraising.

In Phase I, FARE will seek to raise $50 million over the next five years to establish FARO, increase the number of clinical trials sites in the FARE Clinical Trials Network, and accelerate therapies already under study to FDA approval.

In the following five years—Phase II—FARE will seek to raise more than $50 million in additional funds to continue the work begun in Phase I and advance treatments for patients whose allergies are non-responsive to initial therapies.

Across these phases, FARE's investments will be allocated, roughly, as follows:

- 70 percent will go to establishing FARO and the FARE Clinical Research Network, with approximately two-thirds of this funding going toward sponsoring and conducting various trials and studies
- 20 percent will go to establishing and characterizing the biorepository, making available fundamental tools, and establishing the online food allergy research portal

- 10 percent will go to supporting promising basic, translational and clinical investigators interested in building a career in food allergy research

FARE is developing a major giving initiative to help fund this strategic plan. The plan should appeal to donors who see the value of investing in a proactive, long-term strategy that will lead to effective treatments. Via FARO and the FARE Clinical Research Network, FARE will actively monitor and communicate progress about research investments to donors.

Regular, ongoing communication with and engagement of the scientific community

This plan emerged from a series of discussions with scientific and clinical leaders in food allergy, culminating in the April 2013 Research Retreat. For the plan to succeed, the field needs to remain engaged and supportive.

Going forward, FARE will ensure a high level of two-way communication.

As part of this effort to ensure the ongoing engagement of the scientific community, FARE will establish working groups and charge them with refining the three pillars of the research strategy, including developing more detailed business plans. The anticipated completion date for these plans is early 2014.

Conclusion

Food allergy continues to grow as a public health issue—one in need of effective treatments that can prevent life-threatening reactions, and ultimately a cure. It is critical to seize this moment in the timeline of food allergy research to greatly accelerate progress in the field. A number of promising treatments are already under investigation, and there is a tremendous opportunity to apply new scientific approaches to understand and address the root causes of food allergy.

Realizing this promise will take a concerted, collaborative effort among individuals and families affected by food allergies, researchers, clinicians, research institutions, government agencies, industry and others. FARE is committed to leading this effort and to creating a future without life-threatening food allergies.

FARE
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