NIAID Support for Food Allergy Research

The National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) is committed to supporting research to help everyone better understand, prevent, and manage food allergy. Within NIH, NIAID is the lead institute for research in food allergy. NIAID has significantly increased its support of food allergy research over the last 5 years, from $1.2 million in fiscal year (FY) 2003 to $19.2 million in FY 2008. This funding supports the spectrum of research from basic research in allergy and immunology to food allergy clinical trials. Examples of the major NIAID-supported programs in this area are the Exploratory Investigations in Food Allergy program, the Immune Tolerance Network (ITN), and the Consortium of Food Allergy Research (CoFAR).

Through major solicited grants and contracts and intramural research, as well as through investigator-initiated research, NIAID supports basic research in allergy and immunology that provides an increasingly better understanding of the immune system and how, in certain people, foods elicit an allergic reaction that can sometimes be severe. NIAID also conducts clinical trials that are attempting to alter the body's immune response so that it no longer triggers allergic reactions to food. Through these research efforts, NIAID-supported scientists and clinicians are making significant progress in combating food allergies that affect millions of children and adults worldwide.

Current Food Allergy Research Within Major Solicited Programs

The **Asthma and Allergic Diseases Cooperative Research Centers** (**AADCRC**) program is the main component of the NIAID asthma and allergy research portfolio that focuses on the biological mechanisms of allergy. Established in 1971, the program is now in its fourth decade of continuous funding. Fifteen centers, located throughout the United States, conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases, including food allergy and anaphylaxis, a severe allergic reaction that can be life-threatening. AADCRC projects include

- A clinical trial to determine whether extensively heated milk in baked products, in which milk proteins are denatured, can be tolerated by milk-allergic individuals, and if so, whether regular feeding of baked milk products can reduce the severity of milk allergy
- A clinical trial to determine whether oral immunotherapy with milk extract, when combined with regular injections of anti-immunoglobulin E (IgE), the primary antibody associated with allergic reactions, can reduce the severity of milk allergy
- Studies of the pathogenesis of eosinophilic esophagitis (EE), which may be associated with food allergy, and the capacity of anti-IgE to prevent allergic reactions to food

The **Inner City Asthma Consortium** (**ICAC**), which was recompeted in FY 2002, is an NIAID-supported research network that aims to improve the treatment of children living in environments where the prevalence and severity of asthma is particularly high. ICAC is conducting an observational study to assess antibodies to milk, egg white, and peanut in infants at risk for developing asthma to determine if there is a correlation between food allergies and the onset of asthma later in life.

The **Exploratory Investigations in Food Allergy** initiative, co-sponsored by NIAID, the Food Allergy and Anaphylaxis Network (FAAN), the former Food Allergy Project, now part of the Food Allergy Initiative, and the U.S. Environmental Protection Agency (EPA), supports innovative pilot studies and developmental research on the mechanisms of food allergy, with a goal of attracting additional investigators who are new to the field of food allergy research. In June 2008, NIAID announced 12 two-year grants, totaling approximately $2.5 million, to investigators to lead high-impact, innovative studies of food allergy. The EPA issued an additional four awards under this research initiative.

The NIAID-supported projects will address key questions aimed at improving treatment and preventing food allergy, including studies to predict which food proteins are likely to cause allergic reactions; studies to identify the factors that trigger severe responses, including

anaphylaxis; and studies to examine the contribution of other immune disorders to food allergy. Other NIAID projects will help define the genetics of human food allergy and the role of interactions between genes and the environment in food allergy pathogenesis.

The **Immune Tolerance Network (ITN)** is an international consortium of researchers dedicated to the development and evaluation of novel, tolerance-inducing therapies for immune-mediated disorders, including allergic diseases. Co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International, the ITN, which was established in 1999, is conducting two clinical trials designed to uncover the basic biological mechanisms of early-life allergen exposure and its effect on the development of allergic diseases, including food allergy. The first trial will determine whether early (beginning at ages 4 to 10 months) and regular consumption of a peanut snack by children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In the second trial, oral mucosal immunotherapy with house dust mite, cat, and Timothy grass will be given for a year to children between the ages of 18 and 30 months to determine if the therapy reduces the development of allergy to these allergens; allergy to other allergens, including food allergens; and asthma. Additional information on the ITN research activities can be found at www.immunetolerance.org.

The **Consortium of Food Allergy Research (CoFAR)** was established in FY 2005 to conduct basic and epidemiological studies on food allergy; to support clinical trials and animal studies to evaluate new therapeutic approaches and potential mechanisms underlying therapeutic strategies for food allergy and anaphylaxis; and to develop educational programs aimed at parents, children, and health care providers. CoFAR is conducting an observational study on the natural history of food allergy, including the correlation between environmental influences and both the development of food allergies to peanuts and the loss of allergy to eggs and milk in high-risk infants. In addition, the Consortium is enrolling participants in two clinical trials

- To assess whether gradual ingestion of egg powder will improve the amount of egg that egg-allergic children can tolerate, and whether it will also induce oral tolerance to egg
- To examine the effectiveness of using an extract of modified peanut, given under the tongue, as a therapy for peanut allergy

A third project, not yet started, will examine the effectiveness of genetically modified peanut allergens, encapsulated within heat-killed *E. coli* bacteria and given in the rectum, as a therapy for peanut allergy. Additional information on CoFAR can be found at web.emmes.com/study/cofar.

The **Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases** program was developed in response to a 2005 NIAID-sponsored workshop on the future of immunotherapy. This program supports basic research to identify and characterize novel allergens. In FY 2007, NIAID awarded two contracts through this program, one of which is for a study examining food allergens. The findings of these research projects will be used to develop a defined set of reagents that will be available to the research community for the study of allergic diseases.

NIAID Intramural Research

The NIAID **Laboratory of Allergic Diseases (LAD)** supports basic, translational, and clinical research on anaphylaxis. Researchers in LAD seek to better understand the various immune system components that are involved in anaphylaxis; identify molecular-level events that precipitate and characterize anaphylactic reactions in order to understand their triggers; and discover diagnostic markers or reveal targets for new immunotherapies.

LAD investigators have developed highly sensitive techniques to measure T-cell responses to food allergens. These techniques are being used to investigate how abnormal immune responses to foods cause clinical disease, specifically two food allergy-associated diseases, classic anaphylactic food allergy and eosinophil-associated gastrointestinal disorders, including EE and eosinophilic gastroenteritis (EG). NIAID investigators are studying molecules, called cytokines, that are released by T cells in response to food allergens, and how such cytokines may differentially promote anaphylaxis versus eosinophilic inflammation, resulting in different clinical diseases. Future research will include the further analysis of the T cells that may differentially promote anaphylactic versus eosinophilic forms of food allergy, including microarray analysis of pathogenic food allergen-specific T cells.

Additional Activities

NIAID supports other activities to improve the lives of those affected by food allergy.

Expert Panels

NIAID convened Expert Panels on Food Allergy Research in 1996, 2003, and 2006 to review current basic and clinical research efforts related to food allergies.

The 2006 Expert Panel was required to make recommendations to the Secretary of Health and Human Services to enhance and coordinate research activities concerning food allergies. The key recommendations were

- To investigate the natural history of food allergy in young children who have risk factors predisposing them to develop food allergy
- To resolve impediments to clinical trials design and conduct
- To perform clinical trials using food allergens, given orally or sublingually, to treat existing food allergy
- To conduct clinical trials to prevent the development of food allergy by giving oral high doses of food allergens to high-risk infants

The full report can be found at www.niaid.nih.gov/topics/foodAllergy/research/ReportFoodAllergy.

Food Allergy Clinical Trial Design Workshop

In response to the recommendations issued by the March 2006 NIH Expert Panel on Food Allergy Research, NIAID and the Food and Drug Administration convened the "Food Allergy Clinical Trial Design" workshop in FY 2008. The complexity and inherent risks of these clinical trials present many difficult questions related to the development, implementation, and oversight of study design and outcome measures. During the workshop, participants discussed these issues as well as possible methods to best satisfy ethical, safety, and regulatory requirements of clinical studies. A summary of the workshop will be published in FY 2009.

Food Allergy Clinical Guidelines

In FY 2007, NIAID, the American Academy of Allergy, Asthma and Immunology, and FAAN convened the "Guidelines for the Diagnosis and Management of Food Allergy" workshop to discuss the potential value of clinical guidelines for the diagnosis and treatment of patients with food allergies and diseases related to food allergy, such as atopic dermatitis, asthma, and EE.

In September 2008, NIAID solicited a contract to perform an evidence-based review of the literature on food allergy and establish a Clinical Practice Guidelines and Food Allergy Web site (www.niaid.nih.gov/topics/foodAllergy/clinical).

In addition, NIAID held the first meeting of the Food Allergy Clinical Guidelines Coordinating Committee, which was established to oversee the guidelines development process. The Committee members are representatives from professional organizations, advocacy groups, and other Federal agencies. The Committee has approved the nominations of the expert panelists to draft the guidelines and has discussed a plan for dissemination of the final guidelines. Information about the clinical practice guidelines process can be found at www.niaid.nih.gov/topics/foodAllergy/clinical/process. The final guidelines are expected to be published in 2010.

Future Plans

NIAID will recompete the CoFAR and Exploratory Investigations in Food Allergy in FY 2010. The goals for CoFAR will include study of interventions to prevent and treat food allergy, including Phase II clinical trials; long-term follow-up of the current observational study; observational studies to include food allergy-associated anaphylaxis; studies to evaluate the educational needs of, and create educational materials for, parents of food allergic children and health care providers; and basic science studies relevant to clinical research.

The Exploratory Investigations in Food Allergy initiative will continue to encourage new investigators to join the field of food allergy research and support research on the mechanisms of, and risk factors associated with, IgE-mediated food allergy/co-morbid conditions; pathogenesis, biomarkers, genetic components of food allergy, and severe food allergy; molecular characteristics of food allergens and their epitopes; and mechanisms of desensitization and tolerance to food allergens.

For more information on food allergy research, please visit the NIAID Food Allergy Web site at www.niaid.nih.gov/topics/foodAllergy or contact NIAID at ocpostoffice@niaid.nih.gov.

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