Today’s Presenter

James R. Baker, Jr., MD
Food Allergy: The Unrecognized Epidemic

What are the causes?
The immune system is determined by environmental inputs; epigenetics!
## Understanding the Immune System

**Fundamental Forces Changing Human Immunity Over the Past 62 Years**

<table>
<thead>
<tr>
<th>Medical Advancements</th>
<th>Environmental Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet &amp; Lifestyle Factors</td>
<td>Genetic Factors</td>
</tr>
</tbody>
</table>
Epidemiological evidence for current hypotheses in the rise in food allergy

Parents' country of birth (Asian infants at increased risk)
- Koplin et al. Allergy 2012 – egg allergy
- Martin et al. CEA 2013 – eczema
- Koplin et al. Allergy 2014 – food allergy

Maternal diet during pregnancy (consumption of egg)
- Koplin et al. JACI 2010

Cesarean section delivery
- Koplin et al. Allergy 2012
- Koplin et al. PAI 2008

Infant dietary factors
- Later introduction of allergenic foods
  - Du toit et al. JACI 2008
  - Poole et al. Pediatrics 2006
  - Szeffler et al. JACI 2008
  - Koplin et al. JACI 2010
- Duration of breastfeeding
- Maternal consumption of egg during breastfeeding
- Age at first introduction of solids
  - Koplin et al. JACI 2010

Family history of allergy
- Koplin et al. IJERPH 2013

Prenatal

Genetic factors – FLG null mutation
- Brown et al. JACI 2010 (food allergy)
- Tan et al. JACI 2012 (food sensitisation alone)

Fetal epigenetic modification
- Through maternal exposure
  - Elevated maternal folate
    - Dunstan et al. Allergy 2012

Factors associated with the “hygiene hypothesis”
- Presence of siblings
- Early childcare attendance
- Cat exposure
- Dog exposure
- Use of antibiotics
  - Koplin et al. Allergy 2012

Postnatal

Environmental factors
- Cutaneous exposure to food allergens
  - FoxAT et al. JACI 2009
  - Brough HA, Santos AF et al. JACI

Vitamin D insufficiency
- Allen et al. JACI 2013

Blue = no association
Green = possibly protective
Red = possible risk factor

G Lack and KJ Allen 2015
Can food allergies be prevented?
In response to the food allergy epidemic, pediatricians began to withhold food from “at risk” infants.

Rates of food allergy began to rise more rapidly due to “skin sensitization?”

In Israel (where infants were fed peanut) allergy was much lower than in England where peanut was not fed to infants.

This prompted a 6-year controlled trial of feeding vs. withholding peanut.

NEJM 372;9  Feb. 26, 2015
Randomized Trial of Peanut Consumption in Infants At Risk for Peanut Allergy: LEAP Study

A Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
</tr>
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<tbody>
<tr>
<td>SPT-Negative Cohort (N=530)</td>
<td>13.7%</td>
<td>1.9%</td>
</tr>
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<td>SPT-Positive Cohort (N=98)</td>
<td>35.3%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Both Cohorts (N=628)</td>
<td>17.2%</td>
<td>3.2%</td>
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B Per-Protocol Analysis

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<tr>
<td>SPT-Negative Cohort (N=500)</td>
<td>13.9%</td>
<td>0.4%</td>
</tr>
<tr>
<td>SPT-Positive Cohort (N=89)</td>
<td>34.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Both Cohorts (N=589)</td>
<td>17.3%</td>
<td>0.3%</td>
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C Intention-to-Treat Analysis (worst-case imputation)

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<tr>
<td>Both Cohorts (N=640)</td>
<td>16.8%</td>
<td>4.7%</td>
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NEJM 372;9   Feb. 26, 2015
What are the current treatments for food allergies?
Epinephrine is the first-line treatment for anaphylaxis, a serious allergic reaction that is rapid in onset and may cause death.

Individuals who are prescribed epinephrine should carry two epinephrine auto-injectors with them at all times.

Antihistamines do not reverse the symptoms of anaphylaxis.
FARE believes this is a pivotal time for drug development for food allergy
How do we advance life-changing treatments?
Launched in June 2015, the FARE Clinical Network is a groundbreaking initiative that will elevate the quality of care for patients with food allergies and advance research.

The FARE Clinical Network allows for a coordinated approach to food allergy research, accelerating the development of life-changing food allergy therapeutics in ways that single researchers and centers cannot accomplish alone.

- Collaboration across 24 member centers of excellence
FARE Clinical Network

- FARE Clinical Network centers will change the face of food allergy research and care by:
  - Raising the quality of care for food allergy nationwide
  - Reducing discrepancies in among providers
  - Making comprehensive care accessible for all food allergy patients
  - Being lead sites for clinical trials of new therapeutics

- FARE Clinical Network centers will have the capability to
  - Provide sub-specialty food allergy services of the highest quality
    - >200 DBPC food challenges a year (baseline)
    - Prior experience with clinical trials
  - Rapidly apply new evidence-based knowledge as it becomes available
  - Help build national food allergy patient registry and bio-repositories
FARE Clinical Network
Expanding the Scientific/Medical Community

- Need new investigators in the field
- Broader clinical engagement and participation
- Provide specific awards to encourage leadership
  - Gittis Award (training career award)
  - FARE Investigator in Food Allergy Awards
    - 5 awards announced in 2015, representing a commitment of $2.5 million over 5 years
- Increase young and more diverse investigators on review and advisory boards
FARE Investigator Award Recipients – 2015

- **2 New Investigator Awards**
  - Jessica O’Konek, PhD, University of Michigan (Ann Arbor, MI)
  - Duane Wesemann, MD, PhD, Brigham and Women’s Hospital (Boston, MA)

- **3 Mid-Career Awards**
  - Simon Hogan, PhD, Cincinnati Children’s Hospital (Cincinnati, OH)
  - Michiko Oyoshi, PhD, Boston Children’s Hospital and HMS (Boston, MA)
  - Erik Wambre, PhD, Benaroya Research Institute (Seattle, WA)
FARE Research Advisory Board Members

- Dr. Daniel Adelman, Chief Medical Officer, Alvine Pharmaceuticals, Inc.
- Dr. David Artis, Professor of Immunology, Weill Cornell Medical College
- Dr. Pamela A. Guerrerio, Chief, Food Allergy Research Unit, NIAID-NIH
- Dr. Stacie Jones, Professor and Chief of Allergy & Immunology, University of Arkansas
- Dr. Nicholas W. Lukacs, Professor and Director of Research, Food Allergy Center, University of Michigan
- Dr. Cathryn R. Nagler, Bunning Professor, The University of Chicago
- Dr. Robert Schleimer, Chief, Division of Medicine-Allergy-Immunology, Northwestern University
- Dr. Jim Baker, CEO & Chief Medical Officer, FARE
Can we move away from food challenges in clinical trials?
Can we move away from food challenge?

• No; food challenge remains the gold standard
  ▪ End point that is *relevant*, but still has issues
    • Different factors affect reactions
    • Aimmune™ suggests placebo effect.
  ▪ However, no evidence that any other assay is viable
    • Prior suggestions of IgG4 levels
    • Treg production and hypo-methylation of Foxp3
    • Mt. Sinai and Kings’ publications hopeful for basophil assays
Some consensus around Basophil histamine release as a useful assay

This test is not straightforward and requires standardization

After large scale trials, if a therapeutic endpoint is achieved for a population approved drugs will not require challenge testing.
Food Allergy Therapies in Development
Example: Viaskin® Peanut Patch
Example: Viaskin® Peanut Patch

- Placed on skin and releases peanut antigen
- Delivered via dendritic cells to the immune system
- 100 subjects (70 with a non-severe and 30 with a severe allergy), were treated for two weeks with 20 µg to 500 µg
- The dose of 500 µg in adults and adolescents, and the dose of 250 µg of Viaskin® Peanut in children, were shown to be well-tolerated
- Suggests satisfactory safety of Viaskin® Peanut in patients allergic to peanuts.
Aimmune™ Oral Immunotherapy

- Feeding small, progressively larger doses of food to an individual to desensitize them (*not* tolerant)

- Dose of food must be well documented

- Significant side effects

- Only documented efficacy known for treating food allergy
Phase II Trial Design

**Screen/Rand**
- Inclusion criterion: fail DBPCFC at 100mg or less

**Double-Blind OIT Up-Dosing**
- Primary Endpoint: pass DBPCFC at 300mg

**Up-dosing is done in the clinic**
**Maintenance dosing at home**

**Initial Escalation**
- 1 day
- 2 weeks

**Possible dose reductions and re-escalations**

Week 18-20

Week 22-24
Phase II Trial Results

PLACEBO GROUP
Symptom severity in exit DBPCFC

AR101 GROUP
Symptom severity in exit DBPCFC

Maximal symptom severity
- Black: Severe
- Gray: Moderate
- Light Gray: Mild
- White: None

Intent to Treat (ITT) Analysis
Percent of all Subjects Tolerating Dose at 22 weeks

Completer Analysis
Percent of all Completers Tolerating Dose at 22 weeks
Future Treatments for Food Allergies
The Immune Synapse
Summary of the 4 CD4 T Helper Cells

Jinfang Zhu, and William E. Paul
Blood 2008;112:1557-1569

©2008 by American Society of Hematology
Fajt ML, Wenzel SE.
### TABLE I. Summary of DBPC trials using biologic medications in patients with T_{h}2/type 2-high asthma

<table>
<thead>
<tr>
<th>Target</th>
<th>Biologic therapies used</th>
<th>Type of study</th>
<th>Major outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Anti-IgE mAb (rhuMAb-E25, omalizumab)</td>
<td>Allergen challenge: mild-to-moderate allergic asthma</td>
<td>↓ Early and late asthmatic response, ↓ serum free IgE</td>
<td>30-33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic moderate-to-severe allergic asthma</td>
<td>↓ Asthma exacerbations, ↓ serum free IgE</td>
<td>34-42, 44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic severe allergic asthma</td>
<td>↓ Asthma exacerbations greater when subanalyzed by type 2-high phenotypes (↑ FeNO levels, blood eosinophil counts, or serum periostin levels)</td>
<td>43</td>
</tr>
<tr>
<td>IL-4 and IL-13 Mutant IL-4 (pitrakinra); IL-13 antibody (IMA-638)</td>
<td>Allergen challenge: mild allergic asthma</td>
<td>↓ Late asthmatic response</td>
<td>48, 49</td>
<td></td>
</tr>
<tr>
<td>IL-4Rα mAb (AMG 317); mutant IL-4 (pitrakinra)</td>
<td>Chronic moderate-to-severe asthma</td>
<td>No effect on prespecified clinical asthma outcomes in “all comers,” + SNPs of IL-4Rα gene associated with clinical response (pitrakinra)</td>
<td>50, 84</td>
<td></td>
</tr>
<tr>
<td>IL-13 mAb (lebrikizumab, tralokinumab)</td>
<td>Chronic moderate-to-severe asthma</td>
<td>↑ FEV₁; greatest clinical benefit when subanalyzed by type 2-high phenotypes (↑ peristin and sputum IL-13⁺)</td>
<td>29, 83</td>
<td></td>
</tr>
<tr>
<td>IL-13 mAb (GSK679586)</td>
<td>Very severe asthma</td>
<td>No effect on prespecified clinical asthma outcomes</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>IL-4Rα mAb (dupilumab)</td>
<td>Chronic moderate-to-severe asthma with type 2-high phenotype (blood eosinophils ≥300 cells/µL or sputum eosinophils ≥3%)</td>
<td>↓ Asthma exacerbations, ↓ FeNO, ↓ β-agonist use, ↑ FEV₁</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>IL-5</td>
<td>Anti–IL-5 (SB-240563)</td>
<td>Allergen challenge: mild allergic asthma</td>
<td>No effect on clinical asthma outcomes despite ↓ in blood and sputum eosinophil counts</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Anti–IL-5 (mepolizumab)</td>
<td>Mild-to-moderate allergic asthma</td>
<td>No effect on clinical asthma outcomes despite ↓ in blood, sputum, bone marrow, and airway eosinophil counts</td>
<td>19, 26</td>
</tr>
<tr>
<td></td>
<td>Anti–IL-5 (mepolizumab; reslizumab)</td>
<td>Chronic, refractory, severe asthma with type 2-high phenotype (sputum eosinophils ≥3%, or ↑ blood eosinophil counts or FeNO levels)</td>
<td>↓ Asthma exacerbations, ↓ blood/sputum eosinophils, ↑ FEV₁</td>
<td>20, 21, 27, 54, 89, 90</td>
</tr>
<tr>
<td></td>
<td>Anti–IL-5Rα (benralizumab)</td>
<td>Chronic eosinophilic asthma with type 2-high phenotype (sputum eosinophils ≥2.5%)</td>
<td>↓ Eosinophils in airway mucosa/submucosa, sputum, bone marrow, and blood; clinical measures not evaluated</td>
<td>91</td>
</tr>
<tr>
<td>TSLP</td>
<td>Anti-TSLP mAb (AMG 157)</td>
<td>Allergen challenge: mild allergic asthma</td>
<td>↓ Late asthmatic response, ↓ in blood/sputum eosinophil counts, ↓ FeNO levels</td>
<td>97</td>
</tr>
</tbody>
</table>

*SNP, Single nucleotide polymorphism.*

Blocking IL4 and IL13 Signaling: Dupilumab

- Sanofi-Regeneron biologic in phase II/III
  - Binds to the common alpha chain of the IL4 and IL13 receptor
  - Highly effective in treating asthma and atopic dermatitis
  - Also evidence of efficacy against nasal polyps

- Blocks “atopic march”

- Approval within a year for atopic dermatitis
How do we improve quality of life and health through research?
FARE initiated, organized and is the lead sponsor of an Institute of Medicine study, “Food Allergies: Global Burden, Causes, Treatment, Prevention and Public Policy.”

This study seeks to document the burden of food allergy on American life and its role as a public health issue, and address key questions about food allergies.

A comprehensive report on the state of food allergy in the U.S. is due in 2016.

Findings will provide essential information guiding future research, education and public policy efforts.
FARE: Our Mission

Life
- Living safe, productive lives with the respect of others

Health
- Enhance access to state of the art healthcare

Hope
- Research that provides new therapies
Identified Deaths from Food Allergy 2014-2015

- Viryt Kelmendi, age 14
- Simon Katz, age 16
- Morgan Crutchfield, age 17
- Rachel Cole, age 18
- Cody Kimball-Godfrey, age 17
- Ricky Goins, age 23
- Brandon Dixon, age 14
- Sergio Lopez, age 24
- Scott Johnson, age 16
- Derek “Landon” Wood, age 11
- Clayton Buckholtz, age 11
- Joseph DeNicola, age 7
- Jaime Mendoza, age 16
- Chandler Swink, age 19
- Edward Horan, age 24
- Annie LeGere, age 13
Key FARE Website Links

- Homepage: www.foodallergy.org
- Food Allergy Basics: www.foodallergy.org/about-food-allergies
- Food Allergy Facts & Statistics: www.foodallergy.org/facts-and-stats
- Tips for Managing Food Allergies in Different Environments: www.foodallergy.org/managing-food-allergies
- Resources for Different Audiences: www.foodallergy.org/resources-for
- FARE Research Overview & Current Grants: www.foodallergy.org/research
- Most Popular Resources: www.foodallergy.org/most-popular-resources
Our Next Webinar

Adult Onset Food Allergy

Gwen Smith
Editor and Co-owner
Allergic Living Magazine

Wednesday, January 20
1:00 – 2:00 PM ET

Member registration: Friday, December 18
General registration: Monday, January 4

Sponsored by:

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www.foodallergy.org