Oral and Sublingual Immunotherapy for Food Allergy

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Curnen Distinguished Professor
and Chair
Department of Pediatrics
University of North Carolina
Faculty disclosure

• **FINANCIAL INTERESTS**
I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount (including consulting fees, grants, honoraria, investments, etc.) or invest money which may create or be perceived as a conflict of interest.

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<th>Name of Organization</th>
<th>Nature of Relationship</th>
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<td>Allertein</td>
<td>Minority Stockholder</td>
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<td>Dannon Co. Probiotics</td>
<td>Advisory Board</td>
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<td>ExploraMed</td>
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<td>Intelliject</td>
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<td>Mast Cell, Inc.</td>
<td>Minority Stockholder</td>
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<td>McNeil Nutritionals</td>
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<td>Merck &amp; Co.</td>
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<td>Novartis</td>
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<td>Portola Pharmaceuticals, Inc.</td>
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<td>Schering-Plough</td>
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• **RESEARCH INTERESTS**
I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

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<tr>
<td>National Institutes of Health</td>
<td>Grantee</td>
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<tr>
<td>Food Allergy Initiative</td>
<td>Grantee</td>
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<tr>
<td>National Peanut Board</td>
<td>Grantee</td>
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<td>Wallace Foundation</td>
<td>Grantee</td>
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Background: Food allergy

- **Prevalence:**
  - 3 million school age children (3.9%)
  - 18% increase since 1997

  *Branum 2009 Pediatrics*

- “**evolved dependence**” – changes in commensals, subclinical infections, asymptomatic carriers
  
  *Rook – CEI – 2010*

- **Peanut allergy**
  - Prevalence ~1%
  - Most common cause of anaphylaxis in children presenting to the ED
  - Most common cause of fatal food anaphylaxis

- **Standard of care**
  - Avoidance of only foods appropriately diagnosed
  - Self-injectable epinephrine/antihistamines

- **No proactive therapy available**

What is the mechanism for the development of allergic disease and food allergy?

Sensitization

- Complementary feeding?
- Vitamin D?
- Food processing?
- Microbiome?
- Genetics/Epigenetics?
- Diesel particle exhaust?

Dendritic cells → Peanut-specific T cells → Th2

B cells → Peanut-specific IgE → Mast cells

IL-4, IL-5, IL-13

Burks AW. Lancet 2008
What is the mechanism for the development of allergic disease and food allergy?

Sensitization

Complementary feeding? Dendritic cells Peanut-specific T cells Th2 B cells Peanut-specific IgE Mast cells

Vitamin D? Food processing? Microbiome? Genetics/Epigenetics? Diesel particle exhaust?

When – in utero?, epicutaneous?, oral?

Burks AW. Lancet 2008
What is the mechanism for the development of allergic disease and food allergy?

**Sensitization**

- Dendritic cells
- Peanut-specific T cells
- Th2
  - IL-4
  - IL-5
  - IL-13
- B cells
- Peanut-specific IgE
- Mast cells

**Allergic reaction**

**Systemic symptoms**
- Airway obstruction
- Hives
- Low blood pressure
- Arrhythmia

**Local symptoms**
- Itching
- Swelling
- Nausea
- Vomiting
- Cramping
- Diarrhoea

**Peanut allergens**
- Histamines
- Leukotrienes
- Cytokines
- Prostaglandins

Burks AW. Lancet 2008
Can we produce long-term tolerance in allergic diseases?

• What is the ultimate goal for therapy?

• Desensitization
  • In the context of food allergy –
    • tolerate more food on a food challenge while on treatment
    • would this provide protection from accidental food ingestion?

• Tolerance
  • Discontinuation of the therapy –
    • sustained long-lasting therapeutic benefits

• Current paradigm
  • *Peripheral T cell tolerance* - crucial for such benefits
Can we produce long-term tolerance in allergic diseases?

• Clinical desensitization
  • Tolerate the ingestion of more food while on treatment
    • greater than pre treatment

• Oral immunotherapy - OIT
• Sublingual immunotherapy – SLIT
Can we produce long-term tolerance in allergic diseases?

- **Clinical desensitization**
  - Tolerate the ingestion of more food while on treatment
    - greater than pre treatment

- **Clinical findings in 3 studies of food allergy**
  - CoFAR egg OIT - Jones, Burks, Sampson et al. NEJM July 2012
  - Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011
  - CoFAR peanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
Paradigm of food immunotherapy – OIT/SLIT

Allergy → Tolerance

Build-up phase
- Initial modified dose escalation
- Weekly/bi-weekly dose escalation

Maintenance phase

Desensitization food challenge

Nowak-Wegrzyn JACI March 2011
Can we produce long-term tolerance in allergic diseases?

• Clinical desensitization
  • Tolerate the ingestion of more food while on treatment
    • greater than pre treatment

• Clinical findings in 3 studies of food allergy

  – CoFAR egg OIT – Jones, Burks, Sampson et al NEJM July 2012
    – 55 subjects (> 5 yrs) – 40-egg OIT, 15-placebo
      – multicenter, blinded treatment, thru 48 weeks

  – Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011

  – CoFAR eanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
Can we produce long-term tolerance in allergic diseases?

**CoFAR3 - egg OIT trial - Objectives and study design**

### Clinical desensitization

<table>
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<tr>
<td>5 gm desensitization OFC (10 Month)*</td>
<td>0/15 (0%)</td>
<td>22/40 (55%)</td>
</tr>
<tr>
<td>Continue OIT 12 months</td>
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<tr>
<td>10 gm desensitization OFC (22 Month)*</td>
<td>0/15 (0%)(n=1)</td>
<td>30/40 (75%)(n=34)</td>
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* P < .001

Jones, Burks, Sampson et al. NEJM July 2012
Can we produce long-term tolerance in allergic diseases?

- Clinical desensitization
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  - CoFAR egg OIT - Jones, Burks, Sampson et al. NEJM July 2012
  - Peanut OIT - Varshney, Jones, Burks et al. JACI March 2011
    - 25 subjects – 16 - active treatment; 9 – placebo (3 withdrew)
  - CoFAR peanut SLIT - Fleischer, Burks, Sampson et al. JACI January 2013
Can we produce long-term tolerance in allergic diseases?  
Peanut OIT – UNC/Arkansas studies

Peanut OFC – 12 months of treatment

![Graph showing peanut protein levels for Peanut OIT and Placebo groups]

*P<.001
Can we produce long-term tolerance in allergic diseases?

• Clinical desensitization
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• Clinical findings in 3 studies of food allergy
  – CoFAR egg OIT - Jones, Burks, Sampson et al NEJM July 2012
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  – CoFAR peanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
    – 40 subjects – adolescents and young adults, peanut SLIT
Can we produce long-term tolerance in allergic diseases?  
CoFAR – Peanut SLIT

40 subjects – adolescents and young adults, peanut SLIT or placebo

Week 68 - compared to Week 44 (P = .05)
Week 68 – compared to Baseline (P = .009)

OFC  
Successfully Consumed Dose

Fleischer et al. JACI January 2013
Can we produce long-term tolerance in allergic diseases?

Desensitization begins clinically and immunologically
• Initial step in development of long-lasting tolerance?

Mechanism(s) of desensitization?
• Old paradigm versus new understanding of desensitization
  • What causes lack of response?
    • Not
      • controlled release of mediators
    • Recent work - antigen-IgE FcεRI complex endocytosed
• Suggestion of alterations in early signaling events
  • Also histamine 2 receptor changes
Can we produce long-term tolerance in allergic diseases?

Effector cell suppression

**Skin prick test-mast cell**

Peanut OIT | Placebo
---|---
| | *

**Basophil activation assay**

CD 63+

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<tr>
<th></th>
<th>PN2</th>
<th>PN3</th>
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<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.448</td>
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Varshney, JACI 2011
Paradigm of food immunotherapy – OIT/SLIT

Allergy → Tolerance

Build-up phase
- Initial modified dose escalation
- Weekly/bi-weekly dose escalation

Maintenance phase

Discontinuation Tx.
- Elimination diet

Desensitization food challenge

Nowak-Wegrzyn JACI March 2011
Paradigm of food immunotherapy – OIT/SLIT

- **Allergy**
  - Build-up phase
    - Initial modified dose escalation
    - Weekly/bi-weekly dose escalation
- **Desensitization food challenge**
- **Tolerance**
  - Maintenance phase
  - Discontinuation Tx.
    - elimination diet
  - Tolerance food challenge

Nowak-Wegrzyn JACI March 2011
Can we produce long-term tolerance in allergic diseases?

• Clinical tolerance (sustained unresponsiveness)
  • Tolerate the ingestion of food off treatment
    • how long is enough though? – 1 month, 4 months, 12 months?
Can we produce long-term tolerance in allergic diseases?

- **Clinical tolerance (sustained unresponsiveness)**
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- **Clinical findings in 2 studies of food allergy**
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  - Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011
Can we produce long-term tolerance in allergic diseases?

CoFAR3 egg OIT – sustained unresponsiveness (permanent tolerance?)

5 gm desensitization OFC (10 Month)*

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10 gm desensitization OFC (22 Month)*

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<td>0/15 (0%)(n=1)</td>
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Off OIT 4 weeks

10 gm tolerance OFC (23 Month)**

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<td>0/15 (0%)(n=0)</td>
<td>11/40 (27.5%)(n=29)</td>
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Continue OIT 12 months

10 gm tolerance OFC (~36 Month)

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<tr>
<td>N/A</td>
<td>18/40 (45%)(n=13)</td>
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* p<.001

** p=.025

Jones, Burks, Sampson et al. NEJM July 2012
Can we produce long-term tolerance in allergic diseases?

- Clinical tolerance (sustained unresponsiveness)
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Can we produce long-term tolerance in allergic diseases?

Clinical results - UNC and Arkansas studies

- 19 subjects with peanut allergy completed an OIT protocol
  - Oral food challenge (OFC) 4 weeks after stopping OIT
    - evaluate clinical tolerance (sustained unresponsiveness)
  - Peanut OIT - range of 33-70 months
    - Rates of successful tolerance induction?
  - 11 subjects now eat peanut *ad lib* without symptoms
    - Intention-to-Treat Analysis: 11/27 (41%)
    - Per Protocol Analysis: 11/19 (58%)

Vickery, Jones, Burks et al
Can we produce long-term tolerance in allergic diseases?

**Peanut IgE results**

Baseline – PN-IgE

![Graph showing PN-IgE levels at baseline with tolerant and not-tolerant groups.](Image)

- **p=0.0057**

**PN-IgE**

- Tolerant
- Not-tolerant

Both lower at end of study

Mechanistic results - UNC and Arkansas peanut OIT studies

Vickery, Jones, Kulis, Burks et al 2013
Peanut OIT changes antigen-specific T regs and suppresses the $T_H^2$ response to peanut

Mechanistic results - UNC and Arkansas peanut OIT studies
Critical knowledge gaps in food OIT/SLIT research

Summary - consistent results

1. **Desensitization** - begins within a few days/months of treatment
   – threshold goes up

1. **Allergic side effects** - primarily GI at the beginning
   - viral infections, exercise

1. **Mechanistic studies** - mast cell, basophil, B-cell and T-cell changes

2. **Tolerance** – suggestions but not shown in long-term blinded studies

Patriarca et al. Aliment Pharmacol Ther 2003;17:459-65
Meglio P, et al., Allergy 2004;59:980-7

Blumchen K et al. J Allergy Clin Immunol 2010;126:83-91
Jones SJ, Burks AW, Sampson HA et al – CoFAR 2011
What do we do next?

**DEVL**

Determining Efficacy and Value of Immunotherapy on the Likelihood of tolerance induction

- **Peanut allergic children** - 50 children - 9 – 36 months

- Randomized - 300 or 3000 mg peanut OIT within 6 mo of diagnosis

- **Primary endpoint:** tolerance
  - Novel mechanistic assays - antigen-specific T & B cell enumeration & function

- **DEVIL subjects** - half as likely as older OIT subjects to have an allergic side effect – \( p<0.0001 \)

- Study termination
  - 3/26 (11.5%) - older OIT cohorts
  - 1/50 (2%) – DEVIL cohort

- Significant early clinical and immunologic changes

**In peanut allergic children - peanut IgE goes up with age**
What do we do next?

Upcoming multicenter study

- **Peanut allergic children** - 144 children aged 1 – 4 years
- Randomized - 2000 mg of peanut OIT or placebo for 4 years
- Endpoints: full or partial desensitization, tolerance
  - Novel mechanistic assays (Burks, Jones - UNC, AR, Hopkins, Mount Sinai, Stanford)
Thank you

**UNC** - Brian Vickery, Mike Kulis, Edwin Kim, Pam Steele, Jan Kamilaris, UNC Fellows, Caitlin Burk

**Arkansas Children’s/UAMS** - Stacie Jones, Amy Scurlock

**CoFAR** – Hugh Sampson, Scott Sicherer, Stacie Jones, Bob Wood, David Fleischer, Andy Liu, Cecilia Berin

**Duke** – Joe Roberts, Herman Staats, Soman Abraham, Xiaoping Zhong, Duke Fellows

**NIAID** – Marshall Plaut

**EMMES** – Bob Lindblad, Don Stablein  
**ITN** – Audrey Plough, Peter Sayre, Mike Adamkiewicz

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