Dr. Lee Frick Lecture:
Food Allergy

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Faculty Disclosure

Hugh A. Sampson, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from:
• Genentech, Novartis

Consulted for:
• Allertein Therapeutics, LLC, Food Allergy Initiative, University of Nebraska

Held Common Stock in:
• None

Research, clinical trial, or drug study funds received from:
• Food Allergy Initiative, National Institutes of Health

I will not be discussing products that are investigational or not labeled for use under discussion.
Knowledge Gaps:
1) basic mechanisms of oral tolerance
2) basic immunopathogenic mechanisms of IgE- & non-IgE-mediated disorders
3) optimal diagnostics & therapeutic strategies
   - utilizing approaches used >100 yrs ago
   - Allergy tests [prick skin tests]
   - Elimination diets
   - Oral immunotherapy
4) properties of foods that make them allergenic
5) effects of cooking, additives/preservatives & processing on allergenic properties of foods
6) genetic & epigenetic factors \(\Rightarrow\) food allergy
Food Allergy is a Global Issue

A limited number of foods are responsible for the majority of food-induced allergic reactions in children world-wide.

USA & Canada:
- Milk
- Egg
- Peanuts
- Tree nuts
- Seafood

USA & Canada:
- Milk
- Egg
- Peanuts
- Tree nuts
- Seafood

France:
- Egg
- Milk
- Peanuts
- Mustard

Australia:
- Milk
- Egg
- Peanuts
- Sesame seeds

New Zealand:
- Milk
- Egg
- Peanuts

UK:
- Milk
- Egg
- Peanuts
- Tree nuts

Israel:
- Egg
- Milk
- Sesame seeds

Japan:
- Egg
- Milk
- Wheat
- Buckwheat
- Fish
- Fruit

But major regional differences
Increasing Prevalence of Peanut Allergy in the United States

Peanut or Tree Nut Allergy < age 18 yrs

Sicherer SH et al. JACI 2010; 125(6):1322-1326
CDC Brief on Food Allergy in US

- 3 million or ~4% of children <18 yrs have food allergy
  - 18% increase between 1997 and 2007

Figure 4. Average number of hospital discharges per year among children under age 18 years with any diagnosis related to food allergy: United States, 1998–2006

3.5 fold increase in hospital discharges over 8 yr period

<table>
<thead>
<tr>
<th>Years</th>
<th>Average number of discharges per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998–2000</td>
<td>2,615</td>
</tr>
<tr>
<td>2001–2003</td>
<td>4,135</td>
</tr>
<tr>
<td>2004–2006</td>
<td>19,537</td>
</tr>
</tbody>
</table>

*Statistically significant trend.
SOURCE: CDC/NCHS, National Health Interview Survey.
Food Allergy and Anaphylaxis

- Olmstead County Survey: 50% ↑ in food-induced anaphylaxis in past decade  
  \[\sim 50,000 \text{ cases / yr in US}\]
  
  Decker et al. *JACI* 2008; 122:1161-1165

- FDA NEISS [34 EDs; 2 mo period]: ED visits / year in US
  - food allergy: \(~ 125,000\)
  - hospitalizations: \(~ 3,100\)
  - anaphylaxis: \(~ 14,000\)

  Ross et al. *JACI* 2008; 121:166-171

- Fatal reactions in US: \(?\)  
  \[\text{estimates of } \sim 100 \text{ / yr}\]
  - \(~ 10\% \) of food-allergic reactions are life-threatening
  - virtually all fatal reactions are preceded by relatively mild reactions – What changed?  How to predict?
Earlier “Dogma”

- Strict avoidance of food allergens until an infant’s immune system becomes more mature will prevent the development of food allergy.
  - Contamination & environmental exposure make strict avoidance virtually impossible.
  - High levels of environmental exposure to peanut during infancy promote sensitization (Fox AT et al. JACI 2009;123:417-23).
  - Early oral exposure may actually promote tolerance.

- Peanut allergy 1/10th prevalence compared to UK (du Toit JACI 2008; 122:984).
- Milk allergy in Israel followed ~13,000 infants; 381 (2.9%) developed CMA (Katz Y et al. JACI 2010; 126:77-82).
Earlier “Dogma”

• All IgE-mediated food allergy is the same; i.e. single phenotype
• Strict elimination of a food allergen will promote the development of tolerance; eliminates “boosting” and loss of memory cells
  - children with food allergy + atopic dermatitis who had no accidental ingestions became tolerant whereas those having frequent accidents developed more severe and persistent food allergy (reverse causation)
  - parents often unknowingly gave children milk & egg in baked products; our efforts at stringent diets may have contributed to delay in tolerance induction
Natural Course of Food Allergy

- Following standard of care: strict food allergen avoidance

Percent with clinical food allergy

Birth | 2 | 4 | 6 | 8 | Years

80% at 16 yrs

Milk & Egg
Ovomucoid: IgE Epitopes

IgE-binding Sites

Persistent egg allergy

Transient egg allergy

Effect of Cooking on Sequential & Conformational Epitopes of Food Proteins

Hypothesis: Children who “outgrow” milk allergy (Pt #2) will tolerate baked-milk products
“Heat-Denatured Milk” Study

100 milk-allergic pediatric subjects enrolled
- Mean age: 6.7 yrs; range: 2.6 – 17.3 yrs

Challenged sequentially to baked muffin, waffle & uncooked milk (~ 1.3 g milk protein / baked product)

Milk challenges:
- 9 (~10%) “outgrown” – tolerated all challenges
- 68 [77%] HCM tolerant – baked-milk products only
- 23 [23%] Allergic – could not tolerate milk in any form

No difference between groups: age, family history, exclusive breast feeding, age of 1st reaction

Allergic patients had larger PSTs, > milk-specific IgEs and > basophil activation than HCM tolerant patients

Nowak et al. JACI 2008; 122:342-347
Basophil Activation in CMA

• Change is CD63 expression on basophils:
  - whole blood stimulated with varying milk protein
  - basophils identified as CD123⁺, HLA-DR⁻, CD41a⁻, CD203⁺

Wanich N et al
Milk-specific IgE Epitope Binding

Standard protocol

Failed all

Pass baked/all

αS1 Casein

αS2 Casein

β Casein

βlac

κ Casein

Competition

Failed all

Pass baked/all

Wang J et al. JACI 2010; 125:695-702
Changes in Milk-specific PST, IgE & IgG₄ in HCM-Tolerant Subjects

Baked-milk products added to the diets of HM-tolerant children

- Median Skin Prick Test (wheal diameter, mm) in HCM-tolerant Group over Time
  - P = <0.001

- Median Casein-Specific IgG₄ (μg/L) in HCM-tolerant Group over Time
  - P = 0.001

- Median Milk-Specific IgE (kU/L) in HCM-tolerant Group over Time
  - P = 0.183

- Median B Lactoglobulin-Specific IgG₄ (μg/L) in Baked Milk Group over Time
  - P = 0.592
“Heat-denatured Milk” Study
Long-term Follow-up

• 89 children (median age: 6.5 yrs; IQR: 5.1- 8.5) followed for a median of 34 months (IQR: 18 – 49 mos.)

• 60 children (median age: 5.4 yrs; IQR: 4.1- 8.7) followed for a median of 40 months (IQR: 31 – 46 mos.)

• Of 66 H-M tolerant children (Group A), 43 (65%) tolerated regular milk (UHM), 14 (21%) continued on H-M products, and 9 (14%) chose to eliminate all milk products

• Of 23 H-M reactive children (Group B), 2 (8%) tolerated UHM, 3 (13%) tolerated H-M products, and 18 (79%) remained reactive to all forms of milk
Development of Tolerance

HM vs. UHM tolerant

HM-tolerant 28 times more likely to develop full tolerance compared to UHM tolerant; p = 0.0004

N = 60
N = 57

Treated vs. Controls

HM-tolerant treated 16 times more likely to develop full tolerance compared to control; p < 0.0001

N = 66
N = 23
N = 57
N = 60
Diagnostic Approaches

- from allergen source to components

Traditional diagnostics

CRD helps distinguish sensitization to allergenic protein from cross-reactivity
Allergen Component Protein & Peptide Microarray Assays

- Ordered array of overlapping peptides (20/18)
- 6 major milk proteins: $\alpha_s1$, $\alpha_s2$-,$\beta$- & $\kappa$-caseins, $\beta$-lactoglobulin & $\alpha$-lactalbumin
- Microliters of serum
- Labeled with Cy3
# Component Resolved Diagnostics in Food Allergy

## Pollen Cross-Reactive Components

<table>
<thead>
<tr>
<th>Food</th>
<th>Pollen cross-reactive components*</th>
<th>LTP</th>
<th>Pollen non-cross-reactive components**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h 8</td>
<td></td>
<td>Ara h 9</td>
</tr>
<tr>
<td></td>
<td>Ara h 5</td>
<td></td>
<td>Ara h 1; Ara h 2; Ara h 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ara h 4; Ara h 6; Ara h 7</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 1</td>
<td></td>
<td>Cor a 8</td>
</tr>
<tr>
<td></td>
<td>Cor a 2</td>
<td></td>
<td>Cor a 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cor a 11</td>
</tr>
<tr>
<td>Soybean</td>
<td>Gly m 4</td>
<td></td>
<td>Gly m 1</td>
</tr>
<tr>
<td></td>
<td>Gly m 3</td>
<td></td>
<td>Gly m 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gly m 6</td>
</tr>
<tr>
<td>Wheat</td>
<td>Tri a 12</td>
<td></td>
<td>Tri a 19 (ω-5 gliadin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tri a 21 - αlfa gliadin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tri a 26 - HMW glutenin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tri a 28 - AAI dimer 0.19</td>
</tr>
</tbody>
</table>

* Birch tree pollen, Timothy grass pollen for wheat
** Storage seed proteins, albumins and globulins

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**Ana risk**

PRP-10 Profilin

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Component Resolved Diagnostics in Food Allergy

- Ara h 2 > 1.63 kU/L → 123/123 positive challenge
  - Ara h 2 < 1.63 kU/L → 52/82 positive challenge
  - Ara h 2 level does not predict threshold dose
    Bindslev-Jensen C. et al. (in press)

- Poor correlation between fruit & hazelnut IgE & clinical reaction
- Sensitization to Bet v 1 homologues, Pru av 1 / Mal d 1 / Cor a 1, is a risk factor for OAS
- Sensitization to LTPs, Pru av 3 / Mal d 3 / Cor a 8 / Jug r 3, is a risk factor for systemic reactions to cherry / apple / hazelnut / walnut (30% - 50%)
  - sensitization to Cor a 9 is a risk factor for systemic reaction, especially in children
Epitope Diversity & Reactivity

- Greater epitope diversity = more peanut-specific IgE molecules present on mast cells ➔ greater releasibility

- Greater epitope diversity = more severe reactions

- BUT other factors must be contributing to clinical reactivity; e.g. permeability, effector cell activation

Shreffler et al. *JACI* 2004; 113:776-782
Immunotherapeutic Approaches

• Allergen-specific Immunotherapy
  - Feeding “heat-denatured” protein
  - Oral Immunotherapy [OIT]
  - OIT+ omalizumab
  - Sublingual Immunotherapy [SLIT]
  - Epicutaneous Immunotherapy
  - Engineered recombinant protein [EMP-123]

• Allergen non-specific immunotherapy
  - Anti-IgE immunotherapy
  - Chinese Herbal medications
Oral Immunotherapy

- Published OIT studies:
  - Schofield (egg) 1908
  - Staden (milk) 2007*
  - Skripak (milk) 2007*
  - Longo (milk) 2008
  - Buchanan (egg) 2008*
  - Jones (peanut) 2009
  - Varshney (peanut) 2011
  - Anagnostou (peanut) 2011
  - Rodriguez (egg) 2011
  - Martorel (milk) 2011
  - Keet (milk) 2012
  - Varshney et al. J Allergy Clin Immunol 2011

* denotes DBPC

- NIAID-sponsored Consortium of Food Allergy Research
  - comprised of 5 sites: MSSM, Hopkins, Duke, Arkansas & NJH
- Investigate utility of OIT in egg-allergic patients
CoFAR 3: Egg OIT

- **Primary Objectives**
  - study the clinical effects, as well as the safety and immunologic effects, of an egg OIT protocol

- **Study Design**
  - multi-center randomized, double-blind, placebo-controlled, prospective study through 40 - 48 weeks

- **Enrollment criteria (target n = 55)**
  - Age 6 to 18 yrs
    - convincing clinical history of egg allergy
    - serum IgE [UniCAP™] to egg of >5 kUA/L [<12 mo]
  - OR Age 5 yrs
    - convincing clinical history of egg allergy
    - serum IgE [UniCAP™] to egg of >12 kUA/L [<12 mo]
Egg OIT - Study Phases

**Egg Challenge (5 gm DBPC)**
~44 wks

**Desensitization**

**Dose Build-up (max 2000 mg)**

**Home Maintenance (8 – 10 weeks)**

2000 mg

~ 12 – 14 months

“Maintenance”

4 – 6 wks off

**Egg Challenge (10 gm DBPC)**
~12 – 24 mo later

**Egg Challenge (10 gm DBPC)**

Tolerance

**Initial escalation day (max 50 mg)**
# Results of Oral Food Challenge

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=participants)</th>
<th>Egg OIT (n=participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 gm desensitization OFC (44 wks)*</td>
<td>0/15 (0%)</td>
<td>21/40 (52.5%)</td>
</tr>
<tr>
<td>10 gm desensitization OFC (2 yr)**</td>
<td>0/15 (0%) (n=1)</td>
<td>30/40 (75%) (n=34)</td>
</tr>
<tr>
<td>10 gm tolerance OFC (2 yr)*</td>
<td>0/15 (0%) (n=0)</td>
<td>11/40 (27.5%) (n=29)</td>
</tr>
</tbody>
</table>

*\(p < 0.001\)

**\(p = 0.025\)

- 25% of ~12,000 doses associate with AR; 95% mild
- 6 Egg OIT subjects stopped dosing prior to 2 yr OFC
- PST wheal size & egg-induced basophil activation ↓; egg-specific IgG4 increased in Egg OIT group

Supported by NIH-NIAID U19AI066738 and U0AI066560
Peanut Sublingual Immunotherapy

- 18 subjects (1.6 – 10.5 yrs) randomized 11:7 to peanut SLIT
  - 6 mo dose escalation to 2 mg & 6 mos maintenance
  - DBPCFC to 2.5 g
- Results:
  - 11.5% of active doses & 8.3% of placebo doses associated with ARs
  - DBPCFC (median):
    - Active – 1,710 mg
    - Placebo – 85 mg

20-fold more PN ingested by SLIT Grp vs Placebo; P=0.011

Kim et al. JACI 2011; 127:640-646
Peanut Sublingual Immunotherapy

Kim et al. JACI 2011; 127:640-646
Epicutaneous Immunotherapy

- Cow’s milk EPIT: double-blind placebo-controlled
  - 3 mos – 15 yrs with + OFC to < 10 ml of milk
- Applied patch for 48 hrs 3x’s/week
  - 1 mg milk powder on patch
  - 21 subjects screened; 19 randomized
  - median age: 3.82 yrs [10 mo – 7½ yr]
- Treated for 3 mo & then repeated OFC
  - 4 local adverse reactions (2 in placebo); no systemic
- OFC Outcome (per protocol):
  - Milk-EPIT (n=9): 1.77±2.98 ml → 23.61±28.61 ml; p=0.18
  - Placebo (n=7): 4.36±5.88 ml → 5.44±5.88 ml; p=NS
  
  Dupont et al. JACI 2010; 125:1165-67

- CoFAR – peanut EPIT in 60 6 – 15 y/o peanut allergics
“Engineered” Recombinant Proteins

- Vaccines for peanut allergy – affects >1.6 million
- Identified *Ara h1* - 3 as major allergenic proteins, isolated, sequenced & cloned full-length cDNAs
- Identified IgE-binding epitopes on *Ara h1* - 3
- Substituted single amino acid within epitope using PCR mutagenesis;
  - e.g. *Ara h2* – a.a. 27-36 - *D RRC QSQL ER*
  - eliminates or markedly reduced IgE binding
  - T cell proliferative response unchanged
  - recombinant protein produced in *E. coli*
"Engineered" Recombinant Protein

Ara h1

Single amino acid substitution

Ara h2

% IgE binding

Immunoblot

T-cell Epitope Specificity

## Desensitization with HKE-Ara h1-3 (EMP-123) Suppository: Protocol

<table>
<thead>
<tr>
<th>Sensitization</th>
<th>Desensitization</th>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.g.</td>
<td>p.r</td>
<td>I.g.</td>
</tr>
</tbody>
</table>

- **Sensitization:**
  - 6 groups
  - N=12/group

- **Desensitization**
  - Sham
  - EMP123, 0.9µg
  - EMP123, 9µg
  - EMP123, 90µg
  - HKE-vector
  - Naive

- **Challenge**
  - 1st
    - n=12
    - sac. 4
    - SP culture
  - 2nd
    - n=8
    - sac. 4
  - 3rd
    - n=4
    - sac. 4

### Symptom Score
- Body temperature
- Plasma histamine level

Li XM et al. *JACI* 2003; 112:159-67
Desensitization with HKE-Ara h1-3 (EMP-123) Suppository: W22 Challenge

** p<0.01 vs Sham

Li XM et al. *JACI* 2003; 112:159-67
Desensitization with HKE-Ara h1-3 (EMP-123) Suppository: W22 Challenge

Plasma Histamine, nM

<table>
<thead>
<tr>
<th>Group</th>
<th>Methyl Cellulose</th>
<th>0.9 μg</th>
<th>9 μg</th>
<th>90 μg</th>
<th>Vector</th>
<th>90 μg</th>
<th>Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HKE-mAra h1-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9 μg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 μg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 μg</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Inverse response with body temperature

*p < 0.05 vs Sham
EMP-123 Desensitization
Peanut-specific IgE Levels

PN-Specific IgE, ng/ml

Sham
EMP-123, 0.9
EMP-123, 9
EMP-123, 90
HKE-vector
Naïve

*, p<0.05; ***, p<0.001 vs Sham
EMP-123-Induced Decrease in Th2 Cytokine Production

**IL-4**

- **IL-4, pg/ml**
  - Sham
  - 0.9 µg
  - 9 µg
  - 90 µg
  - vector
  - Naive

**IL-5**

- **IL-5, pg/ml**
  - Sham
  - 0.9 µg
  - 9 µg
  - 90 µg
  - vector
  - Naive

- PN (yellow bars)
- Medium (blue bars)

- **Significance Levels**:
  - *: p < 0.05
  - **: p < 0.01
  - ***: p < 0.001
“Engineered” Recombinant Proteins

- In the murine model of peanut anaphylaxis, treatment with EMP-123 prevented allergic reactions following peanut challenge as demonstrated by the following:
  - lack of allergic symptoms or ↑ plasma histamine
  - ↓ peanut-specific IgE and ↑ IgG2a
  - ↓ Th2 cytokines, IL-4, -5, & 13 & ↑ IFN-γ and TGF-β from peanut-stimulated splenocytes in vitro
- CoFAR Study: Phase 1 Safety Study (EMP-123):
  - 10 peanut-allergic adults given 10 μg – 3060 μg over 10 wks + 3 biweekly doses
  - 3 with mild-mod & 2 with severe reactions; failed to complete dosing
  - PST titration significantly reduced (p =0.02)
  - no change in PN-specific IgE or IgG₄
Treatment of Food Allergies

• Avoidance & emergency treatment

• Allergen-specific Immunotherapy
  - Feeding “heat-denatured” protein
  - Oral Immunotherapy [OIT] + anti-IgE
  - Sublingual Immunotherapy [SLIT]
  - Epicutaneous Immunotherapy
  - Engineered recombinant protein

• Allergen non-specific immunotherapy
  - Anti-IgE immunotherapy (omalizumab)
  - Chinese Herbal medications
3D HPLC fingerprint of FAHF-2
JACI 2009
Persistent Effects of FAHF-2

Sensitization & Boosting
- Week 0 to 8
- Sensitization and Boosting: 10 & 50 mg PN + CT, ig
- FAHF-2 treatment: 64mg/day, ig

Challenge
- Week 14 to 66
- Challenge: 200mg PN + CT, ig

Sham

Early Treatment (w3-w9)

Late Treatment (w8-w14)

Naive

5 wk old C3H/HeJ mice

Srivastava K et al. JACI 2009; 123:443-451
Persistent effects of FAHF-2: Symptom Scores

Symptom Score

W14, W18, W22, W28

Early Treatment

Late Treatment

W34, W40, W50, W66

***, P<0.001 vs Sham
Persistent Effects of FAHF-2: Cytokines (Wk 50 Post-therapy)

Mesenteric lymph node cells

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Sham</th>
<th>FAHF-2</th>
<th>Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>0</td>
<td>**</td>
<td>0</td>
</tr>
<tr>
<td>IL-5</td>
<td>100</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>IL-13</td>
<td>1500</td>
<td>1400</td>
<td>0</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>2500</td>
<td>3000</td>
<td>200</td>
</tr>
<tr>
<td>IL-10</td>
<td>1800</td>
<td>2200</td>
<td>0</td>
</tr>
<tr>
<td>TGF-β</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
</tbody>
</table>

* Significant differences

P values

P < 0.05
Clinical Trial of FAHF-2

• Study Subjects:
  - 12 – 45 years of age
  - Documented peanut, tree nut, fish &/or shellfish allergy

• Study phases:
  - Acute phase I: 1 wk, DBPC, dose escalation (18 patients)
    - completed; no significant adverse effects
  - Extended phase I: 6 months open label (18 patients)
    - completed; no significant adverse effects
    - Monitor immunological changes
      - decreased basophil activation (p<0.05)
      - trend to decreased peripheral eosinophils (p=0.058)

• Phase II efficacy trial ongoing
Future Treatment of Food Allergies

• Avoidance & emergency treatment
• Allergen-specific Immunotherapy
  - Feeding “heat-denatured” protein
  - Oral Immunotherapy [OIT] + anti-IgE
  - Sublingual Immunotherapy [SLIT]
  - Epicutaneous Immunotherapy
  - Engineered recombinant protein

• Allergen non-specific immunotherapy
  - Anti-IgE immunotherapy (omalizumab)
  - Chinese Herbal medications
Therapeutics in the Pipeline

- Nanoparticles containing T-cell epitopes
  - T-cell epitopes of Ara h1, 2, 3 & 6
  - use in SLIT/OIT or subcutaneous formulations
- Ara h 2-FcγRI chimeric protein
- *Lactobacillus* transfected with IL-12 & β-lac
- Engineered recombinant proteins
  - multiple mutations of IgE-binding sites
- Nanoparticles containing peanut + LPS for SLIT
- Peanut-containing polymer film for oral application
  - overcomes low doses in standard SLIT
Future in Food Allergy

What we know here is very little, but what we are ignorant of is immense.

-- Pierre Simon Laplace 1749-1827

- Need for critical reassessment and strict adherence to the scientific method
- Need to understand basic immunology of tolerance and immunopathogenic mechanisms in man
- Need to understand the structural properties of allergens & effects of processing & additives
- Need to understand genetic & epigenetic factors ➔ FA
- Need for innovative diagnostic & therapeutic approaches
Future Directions in Food Allergy

• Food allergy is an ideal model to investigate allergic mechanisms – we can control allergen exposure
• Global epidemiologic initiatives are vital to help explain the increasing prevalence of food allergy
• Exploration of the microbiome & its effects on tolerance induction is critical
• Refinement of component- & epitope-based diagnostics will improve our ability to diagnose FA, but…
• Refinement of OIT and SLIT will provide relief to many food allergic patients, but they are not the final answer
• Genetic & epigenetic studies are critical & will uncover clues as to other mechanisms & pathways not yet appreciated in symptomatic food allergy