Update on CoFAR (Consortium for Food Allergy Research)

Robert A. Wood, MD
Professor of Pediatrics and International Health
Director, Pediatric Clinical Research Unit
Johns Hopkins University School of Medicine
President, American Academy of Allergy, Asthma and Immunology

AAAII FOUNDATION
Funding research that leads to the prevention and cure of asthma and allergic and immunologic disease

2018 RECIPIENTS:

Lori Broderick, MD, PhD
Project: "Neonatal Immune Function and Health in Preterm Infants with SGA Birth Weight"

Sarah L. Hendrickson, MD, PhD
Project: "Stem Cell and Tissue Engineering Approaches to Treat Asthma"

Adora A. Uls, MD, PhD
Project: "Translation of the Role of CD44 in Asthma, Dust Mite, and Allergen Dermal and Airway Tissue"
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$4.7 million granted as major awards since 1993
$44 million more granted to our awardees after
Foundation provided initial support.
That’s a 1,300% return on investment

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For Your Many Contributions That Advance Our Specialty
CoFAR History and Acknowledgements

2005 – 2015 (two 5 year awards)
• PI: Hugh Sampson
• Study sites / site PIs
  - Arkansas Children's Hospital: Stacie Jones
  - Duke → UNC: Wesley Burks
  - Johns Hopkins: Robert Wood
  - Mt. Sinai: Hugh Sampson / Scott Sicherer
  - National Jewish: Donald Leung
• NIAID / DAIT Project Officer: Marshall Plaut
• Coordinating Center: EMMES
• 42 abstracts presented at various international meetings and 30 manuscripts to date, including JACI, NEJM, Nature Genetics, and Nature Communications

2017 – 2024
• PI: Hugh Sampson
• Study sites / site PIs
  - Arkansas Children's Hospital: Stacie Jones
  - Duke → UNC: Wesley Burks
  - Johns Hopkins: Robert Wood
  - Massachusetts General: Wayne Shreffler
  - Mt. Sinai: Hugh Sampson / Scott Sicherer
  - National Jewish: Donald Leung
  - Stanford: Sharon Chinthrajah
• NIAID / DAIT Project Officer: Marshall Plaut
• Coordinating Center: Rho

CoFAR Observational Studies

In 2005 – 2006 enrolled 512 infants with milk and / or egg allergy
• 3 – 15 months of age at enrollment
  - 293 with milk allergy
  - 219 with egg allergy
  - 77.7% sensitized to milk, 88.7% to egg, and 68.8% to peanut.
  - Although exclusions were in place to reduce the number of infants enrolled with peanut allergy, 26.6% had a serum peanut-specific IgE > 5 kU/L

Main objectives to investigate immunologic, genetic and environmental factors that determine the natural course of egg and milk allergy and the development of peanut allergy

CoFAR2: The Natural History of Milk, Egg, and Peanut Allergy

• In 2005 – 2006 enrolled 512 infants with milk and / or egg allergy
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  - 219 with egg allergy
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Main objectives to investigate immunologic, genetic and environmental factors that determine the natural course of egg and milk allergy and the development of peanut allergy
Milk allergy resolved in 52.6% at a median age of 63 months.
CoFAR Natural History of Milk Allergy: Relationship to Baseline Atopic Dermatitis

Composite Index to Predict Milk Natural History (http://www.cofargroup.org)

CoFAR Natural History of Egg Allergy
CoFAR Natural History of Egg Allergy: Relationship to Baseline IgE

- IgE < 2
- IgE 2-10
- IgE > 10

CoFAR Natural History of Egg Allergy: Relationship to Baseline Skin Test

- ST < 5 mm
- ST > 10 mm

CoFAR Natural History of Egg Allergy: Relationship to Initial Presentation

- Presenting Reaction Cases
- All Diagnoses
- Skin Only
- Other System
Over the course of the study with follow up to a median age of 8 years, 40% of the cohort had a diagnosis of peanut allergy. Important baseline factors associated with peanut allergy included peanut sensitization status and breastfeeding (which was protective).

In an initial study that did not include analysis of environmental exposure to peanut in the home, frequent maternal ingestion of peanut during pregnancy - twice per week or more - was a significant predictor (odds ratio 2.9) of peanut allergy, along with male gender and elevated egg and milk IgE levels. A subsequent study evaluated the amount of peanut in the household dust and found a dose-response relationship between the amount of environmental peanut and peanut allergy, and the relationship was augmented by increasing severity of atopic dermatitis.

Studies of the gut microbiome revealed milk allergy resolution was associated with enrichment of Clostridia and Firmicutes (Bunyananich et al JACI 2016).

Accidental or OFC exposure with reaction to egg, milk or peanut did not boost IgE sensitization (Sicherer et al JACI: IP 2017).

In a study of accidental reactions in preschool age children (Fleischer et al Pediatrics 2017):
- About 2 of 3 accidental ingestions resulting in reactions were due to lack of vigilance
- About half of reactions occurred when not under parental supervision
- Purposeful trying of avoided foods accounted for 11% of reactions
- Epinephrine was not given for 30% of severe reactions
CoFAR 5: Eosinophilic Esophagitis Registry

- Registry of 705 patients with biopsy proven EoE (Chehade et al, JACI: IP 2108)
- Clinical findings included:
  - Delays in diagnosis were common
  - Comorbidities were common (allergic disease (91%), infectious and immune disorders (44%), and neurodevelopmental disorders (30%)
  - The rate of EoE in parents was 3% and siblings 4.5%.
- Genetic studies were conducted in collaboration with the Cincinnati Children’s Hospital identified a number of putative susceptibility loci for EoE and elucidated a likely role of CAPN14 (encodes calpain 14, a calcium-activated cysteine protease) in the tissue-specificity and allergic-disease-linked aspects of the disorder (Kottyan et al Nat Genet 2014; Kottyan et al Genes Immun 2018.

CoFAR Interventional Studies
Development of a Recombinant Peanut Vaccine (EMP-123)

- Selection of the 3 major peanut allergens Ara h 1, Ara h 2, and Ara h 3 as the antigens
- Modification of the proteins to disrupt sequential IgE binding epitopes
- Encapsulation of the modified proteins in heat/phenol-killed *E. coli*
- EMP-123 = Encapsulated, Recombinant Modified Peanut Proteins Ara h 1, Ara h 2, and Ara h 3
- Safe and effective in mouse models, most effective with rectal delivery (compared to oral, SQ, IM, IP)

CoFAR 1: EMP-123 Phase 1 Trial Results
(Wood et al Allergy 2013)

- Conducted a Phase 1 safety study to investigate the safety of EMP-123 therapy
- Gave increasing doses weekly over 8 weeks, then 3 maintenance doses given every 2 weeks
- Top dose 7 cc per rectum containing 3063 mcg of the modified proteins (similar to SLIT doses)
- Of 10 peanut allergic subjects, 5 were unable to complete dosing due to adverse reactions and 2 experienced grade 3 anaphylaxis
- No current plans to further develop this product (but other approaches using modified allergens still of great interest)

CoFAR3: Egg OIT Trial
(Burks et al, N Engl J Med July 2012)

- Randomized, placebo controlled, multicenter
- 10 month escalation to 2000 mg maintenance, then OFC to 5 grams of egg protein ("desensitization challenge")
- Un-blinding, 12-36 additional months of daily maintenance, repeat 10 gram OFC annually
- If OFC successful: stop dosing for 8 weeks and repeat OFC ("tolerance" / SU challenge)
- Primary endpoint: Sustained Unresponsiveness after the avoidance period (month 24)
Egg OIT: Oral Food Challenge Results Summary

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Egg OIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 gm desensitization OFC (Month 10)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>10 gm desensitization OFC (Month 22)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>10 gm tolerance OFC (Month 24)</td>
<td>0/15 (0%)</td>
</tr>
</tbody>
</table>

Key Results:
- 75% were desensitized after 22 months of OIT
- 19 out of 30 who were desensitized at 22 months lost protection after avoiding egg for 8 weeks

Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy

Table 1. Food Challenge Defined Clinical Outcomes with Long-term Egg OIT

<table>
<thead>
<tr>
<th>Time from Egg OIT Initiation</th>
<th>Desensitization</th>
<th>Sustained Unresponsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months</td>
<td>30/40 (75%)</td>
<td>11/40 (27.5%)</td>
</tr>
<tr>
<td>36 months</td>
<td>32/40 (80%)</td>
<td>19/40 (47.5%)</td>
</tr>
<tr>
<td>48 months</td>
<td>32/40 (80%)</td>
<td>21/40 (52.5%)</td>
</tr>
</tbody>
</table>

In the 22 subjects still dosing in years 3 and 4, 54.5% still reported reactions with dosing.

Egg Consumption at Follow-Up (Year 4)

Legend:
- Daily
- Several times a week
- Weekly
- Monthly
- Less than monthly
- Strict avoidance
When compared with subjects not achieving SU, subjects achieving SU had higher IgG4 values (P<0.001)

CoFAR4: Peanut SLIT Study
(Fleischer et al JACI 2013;131:119)

- Design summary:
  - Randomized, placebo controlled, N = 40
  - 2 gram peanut OFC at baseline
  - 10 months escalation to 1.3 mcg, then OFC ("desensitization challenge")
  - Un-blinding, placebo subjects offered escalation to "high dose" SLIT (3.7 mcg)
  - 12 – 24 additional months with daily maintenance, repeat OFC annually
  - If OFC successful: stop dosing for 6 weeks, repeat OFC ("tolerance" challenge)

Peanut SLIT: Oral Food Challenge Baseline to Week 44

- Active versus Placebo: P=0.16
- 70% on peanut SLIT were responders compared with 15% on placebo (P < .001)

Responders defined as tolerating 1 gram OFC or a 10-fold increase in threshold over baseline.
• No significant changes were seen between the active and placebo groups
• Significant within group changes from baseline were seen with active SLIT for OFC response as well as changes in peanut IgE and IgG4
• Safety overall reassuring:
  • Of 10,855 peanut doses, 63.1% were symptom free; excluding oropharyngeal symptoms, 95.2% were symptom free
• Conclusion: Peanut SLIT safely induced a modest level of desensitization in a majority of subjects
CoFAR4 Follow-up Study
(Burks et al JACI 2015;131:119)

- Assessed response rates at 2 and 3 years as well as SU in those who were fully desensitized
- Data were somewhat limited by the fact that over 50% discontinued therapy
- By study’s end, 4 (10.8%) of 37 SLIT treated participants were fully desensitized and all 4 achieved SU
- Approximately 98% of the over 18,000 doses that were administered were tolerated without adverse reactions beyond the oropharynx, with no severe symptoms or use of epinephrine
- We again concluded that peanut SLIT induced a modest level of desensitization and had an excellent long-term safety profile
- The low rate of SU was not surprising but we were struck by the high discontinuation rate, especially in view of the excellent safety profile.

CoFAR6: EPIT for Peanut Allergy

Randomization
1:1:1

Enrollment
N=75
Entry OFC positive to cumulative dose of <10^44 mg peanut protein

Placebo
250 µg Peanut EPIT

5044 mg OFC

Week 52
5044 mg OFC

Placebo
250 µg Peanut EPIT

Week 130
5044 mg OFC [End of study]

Immune assays: baseline, 12, 24, 52 weeks

CoFAR6: Defined Endpoints

Primary endpoint
- The proportion of subjects with a treatment success following 52 weeks of blinded treatment
- Treatment success defined as:
  - Passing a 5044 mg OFC at week 52
  - OR
  - by a >10-fold increase in the successfully consumed dose (SCD) of peanut protein at week 52 compared to baseline OFC (Same as the VIPES trial)
**Peanut EPIT: Treatment Success**

75 subjects randomized: 25 placebo, 24 100 µg, 25 250 µg (1 withdrew post-randomization)

6 withdrawals: 3 placebo, 3 100 µg – all “treatment failures”

<table>
<thead>
<tr>
<th></th>
<th>Placebo N (%)</th>
<th>100 µg N (%)</th>
<th>250 µg N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome*</td>
<td>3 (12)</td>
<td>11 (46.6)</td>
<td>12 (48)</td>
<td>25 (35)</td>
</tr>
<tr>
<td>SCD &gt;1044 mg protein**</td>
<td>2 (12)</td>
<td>3 (12.5)</td>
<td>7 (28)</td>
<td>13 (17.6)</td>
</tr>
<tr>
<td>SCD &gt;1044 mg protein + 10-fold increase**</td>
<td>2 (8)</td>
<td>2 (8.3)</td>
<td>4 (16)</td>
<td>8 (10.8)</td>
</tr>
</tbody>
</table>

*P=0.005 Placebo vs 100 µg, P=0.003 Placebo vs 250 µg, P=0.48 100 µg vs 250 µg

**P=0.54 Placebo vs 100 µg, P=0.12 Placebo vs 250 µg, P=0.12 100 µg vs 250 µg

***P=0.55 Placebo vs 100 µg, P=0.26 Placebo vs 250 µg, P=0.27 100 µg vs 250 µg

**Change in Successfully Consumed Dose: Baseline to Week 52 by Treatment Group**

Solid lines represent median values
Hatched lines represent the upper and lower interquartile range

**Change in Successfully Consumed Dose: Baseline to Week 52 by Treatment Group**

**Treatment Response may be Greater in Younger Children (4-11 yrs)**

*P=0.03, age by treatment interaction with age as dichotomous variable*
Safety of Peanut EPIT: Dosing Reactions

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%)</th>
<th>100 µg (%)</th>
<th>250 µg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Reaction (% per dose)</td>
<td>14.4</td>
<td>79.8</td>
<td>79.8</td>
</tr>
<tr>
<td>Patch Site* (Median % doses/subject)</td>
<td>1.6</td>
<td>92.8</td>
<td>96.1</td>
</tr>
<tr>
<td>Patch Site (Grade 2)</td>
<td>1.6</td>
<td>18.7</td>
<td>23.4</td>
</tr>
<tr>
<td>Patch Site (Extension beyond site)</td>
<td>1.6</td>
<td>8.9</td>
<td>16.2</td>
</tr>
<tr>
<td>Non-patch Site</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*P<0.01, placebo vs. active EPIT; P=NS, 100 µg vs. 250 µg
**1 subject on 100 µg with systemic hives, treated with oral antihistamines

- Adherence was high ~ 97%
- No study-related SAEs reported
- No epinephrine use with dosing symptoms
- 1 withdrawal per protocol for grade 3 and 4 patch site reactions

CoFAR6: Patch Site Reaction Scoring

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin Reaction Description</th>
<th>Skin Reaction Example Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>Redness only</td>
<td></td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Redness and hard or stiff skin</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Redness and a few bumps</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Redness with many bumps or spreading bumps</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Redness with blisters</td>
<td></td>
</tr>
</tbody>
</table>

CoFAR EPIT Conclusions

- Peanut EPIT is associated with modest but significant change in consumed peanut protein (43-130 mg) when compared to placebo after 52 weeks of blinded EPIT
- Greater impact in younger children (4-11 yo)
- Adherence to EPIT and trial retention was high (97%)
- Peanut EPIT is safe with mild-moderate patch site reactions predominating
- Results of open-label extension to week 130 now being analyzed
- VIPES study (N = 221) showed similar results except the 100 mg patch was not superior to placebo (JAMA 2018)
CoFAR 7: Comparison of egg OIT to ingestion of baked egg in egg allergic children able to tolerate baked egg

- Study complete, analysis underway

CoFAR Mechanistic Studies:


CoFAR Mechanistic Studies:

The New CoFAR (funded 3/1/17)

Three protocols in late stages of development:

- PICNIC: Peanut Immunotherapy in Infants and Children
  - DBPC trial comparing two doses of peanut OIT to placebo in 6 – 17 month olds

- QUIMATCH: Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children
  - Study of omalizumab in 2 – 17 years olds, as monotherapy and as adjunct to OIT

- BEACON: Biomarkers of Early Atopy in Childhood Outcomes Network
  - Birth cohort study focused on food allergy and AD