Update on CoFAR (Consortium for Food Allergy Research)

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Johns Hopkins University School of Medicine
President, American Academy of Allergy, Asthma and Immunology

AAAAI FOUNDATION

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

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AAAAI FOUNDATION FACULTY DEVELOPMENT AWARD

Lori Broderick, MD, PhD
UC San Diego
Project: "Molecular Mechanisms of Immunodysregulatory Disorders"
$240,000 paid over 3 years

Sarah E. Henrickson, MD, PhD
Children's Hospital of Philadelphia
Project: "Defining Exhaustion and Immunometabolic Alterations in Primary Immunodeficiency"
$240,000 paid over 3 years

Adora A. Lin, MD, PhD
Children's National Medical Center
Project: "Elucidation of the Role of B Cells in Food Allergy, Sensitization, and Tolerance"
$240,000 paid over 3 years

2018 Grant Impact Study Results

$ = ROI
$$$$
$$$$$
$$$$$$$

$4.7 million granted as major awards since 1993
$66 million more granted to our awardees after Foundation provided initial support.

That's a 1,300% return on investment

Thank you donors and congratulations awardees!

Your donation in 2018 will fund more research in 2019.

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Thank you for your support.

Thank You!

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

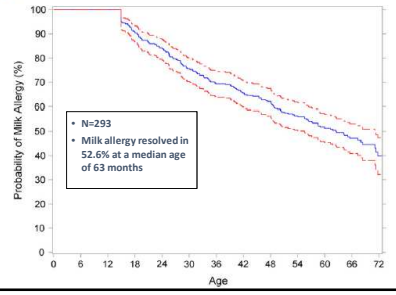
CoFAR Observational Studies

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

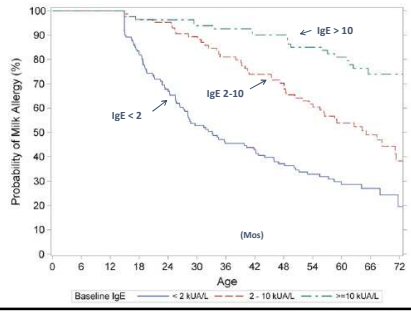
- In 2005 – 2006 enrolled 512 infants with milk and / or egg allergy
- 3 – 15 months of age at enrollment
  - 293 with milk allergy
  - 213 with egg allergy
  - 77.7% sensitized to milk, 88.7% to egg, and 68.8% to peanut.
  - Although exclusions were in place to reduce the number of infants enrolled with peanut allergy, 26.6% had a serum peanut-specific IgE >5 kU_A/L
- Main objectives to to investigate immunologic, genetic and environmental factors that determine the natural course of egg and milk allergy and the development of peanut allergy

The natural history of milk allergy in an observational cohort

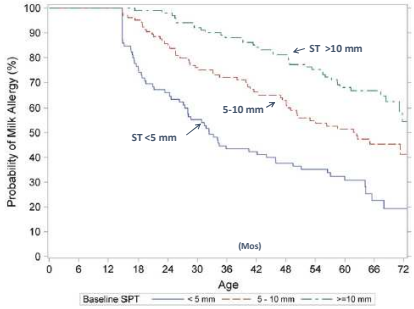
Robert A. Wood, MD,[a,*] Scott H. Sicherer, MD,[b,*] Brian P. Vickery, MD,[c] Stacie M. Jones, MD,[d] Andrew H. Liu, MD,[e] David M. Fleischer, MD,[e] Alice K. Henning, MS,[f] Lloyd Mayer, MD,[g] A. Wesley Burks, MD,[c] Alexander Grishin, PhD,[b] Donald Stablein, PhD,[d] and Hugh A. Sampson, MD[b] *Baltimore and Rockville, Md, New York, NY, Chapel Hill, NC, Little Rock, Ark, and Denver, Colo*
JACI 2104



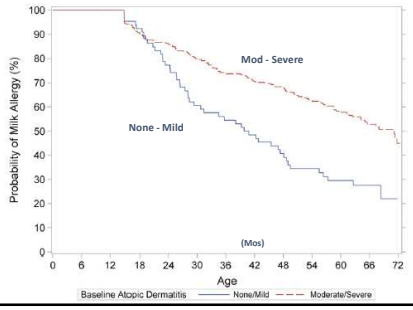
CoFAR Natural History of Milk Allergy: Relationship to Baseline IgE



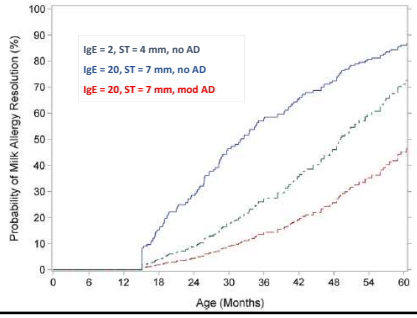
CoFAR Natural History of Milk Allergy: Relationship to Baseline Skin Test



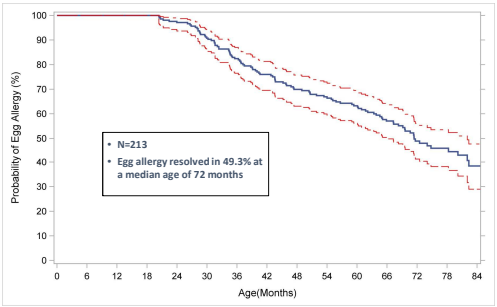
CoFAR Natural History of Milk Allergy: Relationship to Baseline Atopic Dermatitis



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

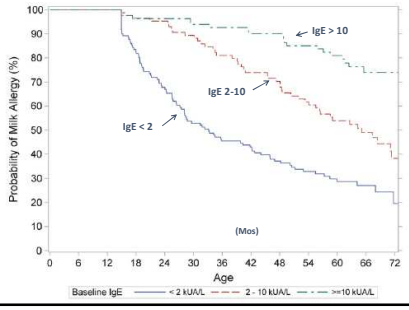


CoFAR Natural History of Egg Allergy

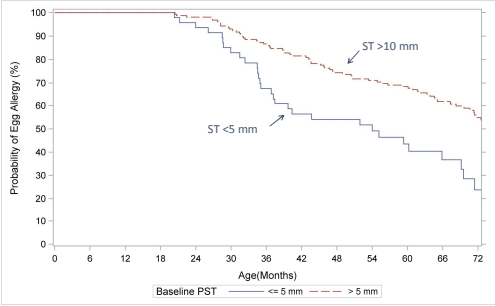


Sicherer, Wood et al JACI 2014

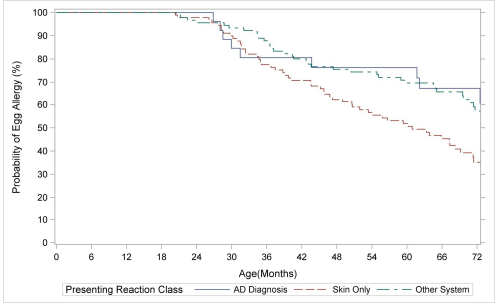
CoFAR Natural History of Egg Allergy: Relationship to Baseline IgE



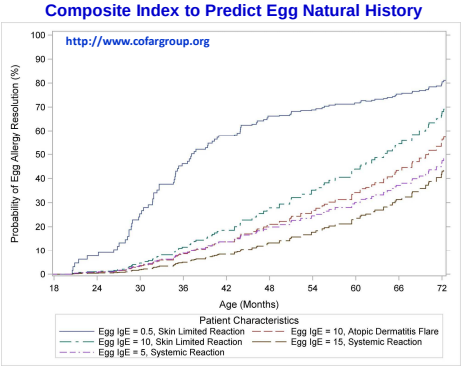
CoFAR Natural History of Egg Allergy: Relationship to Baseline Skin Test



CoFAR Natural History of Egg Allergy: Relationship to Initial Presentation



Composite Index to Predict Egg Natural History



CoFAR2: Development of Peanut Allergy

- **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**

Additional findings from CoFAR2

- **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 2102):**
  - **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 wit**h rectal delivery (compared to oral, SQ, IM, IP)**

CoFAR 1: EMP-123 Phase 1 Trial Results

(Wood et al Allergy 2013)

- **Conducted a Phase I 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

	Placebo	Egg OIT
5 gm desensitization OFC (Month 10)	0/15 (0%)	21/40 (52.5%)
10 gm desensitization OFC (Month 22)	0/15 (0%)	30/40 (75%)
10 gm tolerance OFC (Month 24)	0/15 (0%)	11/40 (27.5%)

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

Stacie M. Jones, MD,[a] A. Wesley Burks, MD,[b] Corinne Keet, MD,[c] Brian P. Vickery, MD,[b] Amy M. Scurlock, MD,[a] Robert A. Wood, MD,[c] Andrew H. Liu, MD,[d] Scott H. Sicherer, MD,[e] Alice K. Henning, MS,[f] Robert W. Lindblad, MD,[f] Peter Dawson, PhD,[f] Cecilia Berin, PhD,[e] David M. Fleischer, MD,[d] Donald Y. M. Leung, MD,[g] Marshall Plaut, MD,[h] and Hugh A. Sampson, MD,[e] for the Consortium of Food Allergy Research (CoFAR) *Little Rock, Ark, Chapel Hill, NC, Baltimore, Rockville, and Bethesda, Md, Denver, Colo, and New York, NY*

JACI April 2016

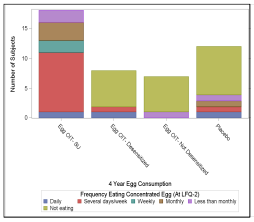
Table 1. Food Challenge Defined Clinical Outcomes with Long-term Egg OIT

Time from Egg OIT Initiation	Desensitization	Sustained Unresponsiveness
24 months	30/40 (75%)	11/40 (27.5%)
36 months	32/40 (80%)	19/40 (47.5%)
48 months	32/40 (80%)	21/40 (52.5%)

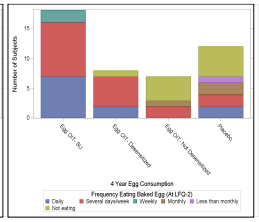
In the 22 subjects still dosing in years 3 and 4, 54.5% still reported reactions with dosing

Egg Consumption at Follow-Up (Year 4)

Concentrated Egg



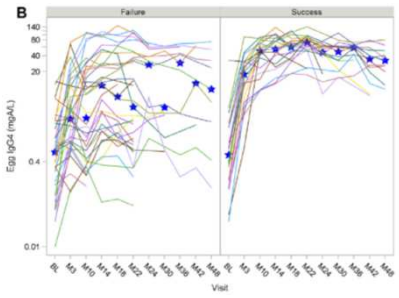
Baked Egg



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<.001)

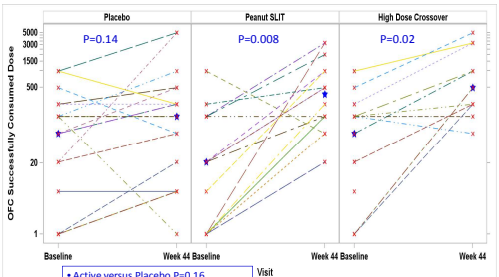


CoFAR4: Peanut SLIT Study

(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)**

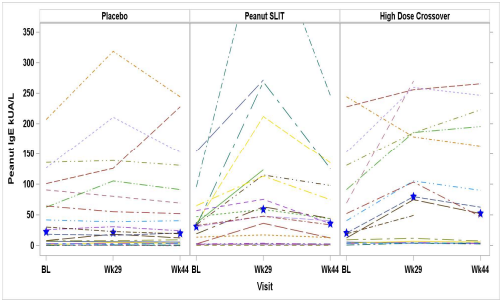
Peanut SLIT: Oral Food Challenge Baseline to Week 44



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

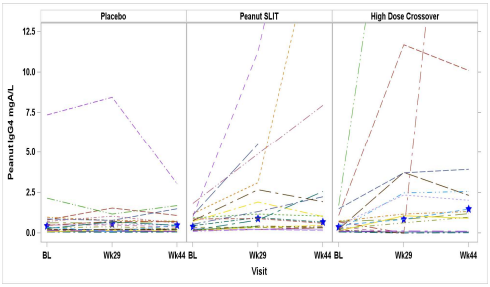
Responders defined as tolerating 1 gram OFC or 10-fold increase in threshold over baseline

Change in Peanut-Specific IgE During SLIT



Fleischer et al JACI 2013;131:119

Change in Peanut-Specific IgG4 During SLIT



Fleischer et al JACI 2013;131:119

CoFAR Peanut SLIT Study: Safety and Study Conclusions

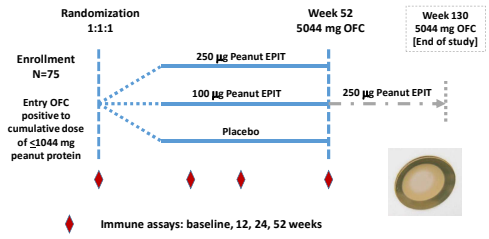
(Fleischer et al JACI 2013;131:119)

- 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 oral-pharyngeal 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



Jones et al JACI 2016

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"

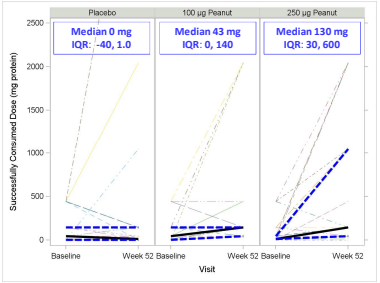
	Placebo N (%)	100 mg N (%)	250 mg N (%)	Total* N (%)
Primary Outcome*	3 (12)	11 (45.8)	12 (48)	25 (35)
SCD >1044 mg protein**	2 (12)	3 (12.5)	7 (28)	13 (17.6)
SCD >1044 mg protein + 10-fold increase***	2 (8)	2 (8.3)	4 (16)	8 (10.8)

***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*



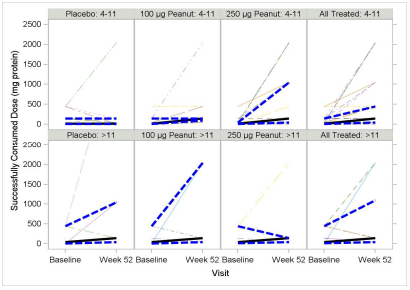
Placebo v 100µg P=0.014

Placebo v 250µg P=0.003

100 µg v 250 µg P=0.48

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

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



Age by treatment interaction P=0.03

P=0.006, age by treatment interaction with age as dichotomous variable

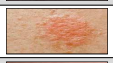
Safety of Peanut EPIT: *Dosing Reactions*

	Placebo (%)	100 mg (%)	250 mg (%)
Any Reaction (% per dose)	14.4	79.8	79.8
Patch Site* (Median % doses/subject)	1.6	92.8	96.1
Patch Site (Grade 2)	1.6	18.7	23.4
Patch Site (Extension beyond site)	1.6	8.9	16.2
Non-patch Site	0.2	0.2	0.1

*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

Grade	Skin Reaction Description	Skin Reaction Example Image
Grade 1A	Redness only	
Grade 1B	Redness and hard or stiff skin	
Grade 2	Redness and a few bumps	
Grade 3	Redness with many bumps or spreading bumps	
Grade 4	Redness with blisters	

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:

1. Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. *The Journal of allergy and clinical immunology.* 2013;131(3):805-812.
2. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *The Journal of allergy and clinical immunology.* 2014;133(2):492-499 e498.
3. Wright BL, Kulis M, Orgel KA, et al. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness. *Allergy.* 2016;71(11):1552-1560.
4. Berin MC, Grishin A, Masilamani M, et al. Egg-specific IgE and basophil activation but not egg-specific T-cell counts correlate with phenotypes of clinical egg allergy. *The Journal of allergy and clinical immunology.* 2018;142(1):149-158 e148.
5. Sackesen C, Suarez-Farinas M, Sillva R, et al. A new luminex-based peptide assay to identify reactivity to baked, fermented and whole milk. *Allergy.* 2018.
6. Suprun M, Grishina G, Henning A, et al. Peanut epitope-specific IgE binding can predict clinical peanut allergy. *Allergy.* 2018;73(s105):116.
7. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *The New England journal of medicine.* 2012;367:233-243.
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9. Jones SM, Sicherer SH, Burks AW, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *The Journal of allergy and clinical immunology.* 2017;139(4):1242-1252 e1249.

CoFAR References / Mechanistic Studies:

10. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *The New England journal of medicine.* 2012;367(3):233-243.
11. Kulis M, Saba K, Kim EH, et al. Increased peanut-specific IgA levels in saliva correlate with food challenge outcomes after peanut sublingual immunotherapy. *The Journal of allergy and clinical immunology.* 2012;129(4):1159-1162.
11. Sicherer SH, Wood RA, Stablein D, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy. *The Journal of allergy and clinical immunology.* 2010;125(5):1077-1083 e1078.
12. Caubet JC, Masilamani M, Rivers NA, Mayer L, Sampson HA. Potential non-T cells source of interleukin-4 in food allergy. *Pediatr Allergy Immunol.* 2014;25(3):243-249.
13. Chiang D, Chen X, Jones SM, et al. Single-cell profiling of peanut-responsive T cells in patients with peanut allergy reveals heterogeneous effector TH2 subsets. *The Journal of allergy and clinical immunology.* 2018;141(6):2107-2120.
14. Kosoy R, Agashe C, Grishin A, et al. Transcriptional Profiling of Egg Allergy and Relationship to Disease Phenotype. *PloS one.* 2016;11(10):e0163831.

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**
- **OUtMATCH: 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**