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Oral Immunotherapy for Food Allergy

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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.

Name of Organization	Nature of Relationship
AAAAI	Board Member
Abbott Laboratories	Speaker
Allertein	Minority Stockholder
Food Allergy Initiative	Chairman
Dow AgroSciences	Consultant
McNeill Nutritionals	Consultant
Merck	Consultant
Mylan Specialty	Speaker
Novartis Pharma AG	Consultant
Orange Ridge Associated Universities	Participant
Unilever	Consultant

- **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.

Name of Organization	Nature of Relationship
National Institutes of Health	Grantee
FAAN	Grantee
FAI	Grantee
National Peanut Board	Grantee
Wallace Foundation	Grantee

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Food Allergy Background

- Egg, milk and peanuts account for ~80% of food allergic reactions among children in the United States

Sampson, et al. J Allergy Clin Immunol 2003

- Peanut allergy affects ~1% of U.S. population
  - *~12 million Americans have food allergy, ~ 4% of children*
  - *Most common cause of fatal food anaphylaxis*

Branum et al. 2009 Pediatrics

- Severe reactions with low threshold
  - *~ 70 mg of peanut (1/5 of a peanut)*

Burks et al. JACI 2011

Food Allergy Background

- Subcutaneous IT for peanut allergy attempted but significant side-effects

Nelson et al. JACI 1993

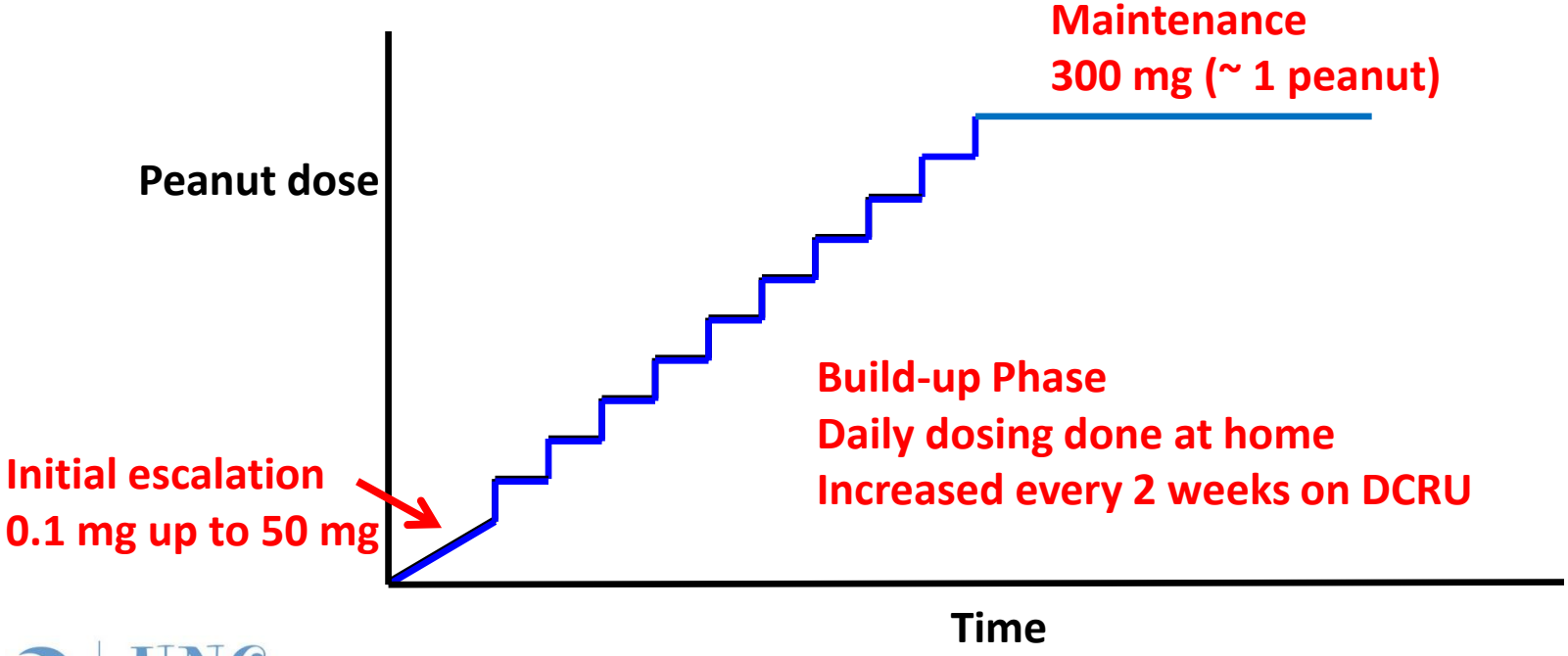
- Anecdotal evidence that oral administration of food allergens would allow for desensitization

Patriarca et al.

- Oral immunotherapy (OIT) trials:
  - *Peanut – Duke, Arkansas, Germany, others underway*
  - *Milk – Johns Hopkins, Duke, Stanford*
  - *Egg – CoFAR: Mt. Sinai, Hopkins, Nat'l Jewish, Arkansas, Duke*

Pilot Peanut OIT Study

- Objective: Determine safety and efficacy
- Design: open-label



Jones, JACI 2009

Safety Assessment

- 28 subjects studied
- Mean age at enrollment
  - *4.8 years (range: 1.1-9.4 years)*
- Initial escalation day (0.1 – 50 mg)
  - *26/28 (93%) experienced allergic symptoms*
  - *Generally mild*
  - *4/28 (14%) subjects required epinephrine*

Hofmann, JACI 2009

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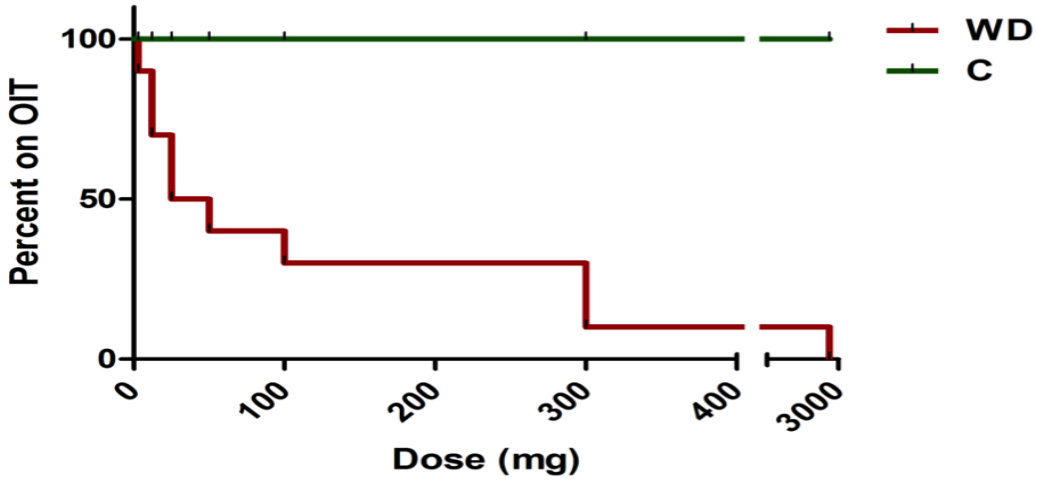
Safety of Food OIT

- Risk factors for unanticipated reactions:
  - *Fever, viral infections, exercise, menses* (Varshney JACI 2009)
- Symptoms occur with ~15-25% of doses
  - *Predominantly mild and oropharyngeal*
  - *<1% of doses – moderate-severe symptoms*
- Epinephrine use
  - *<1% of doses*
- Gastrointestinal symptoms are early and limiting
  - Drop-out rate ~10-20%



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Efficacy in Open-Label Peanut OIT

- 29 subjects completed the protocol
- 27/29 (93%) consumed 3.9 g protein during DBPCFC
  - *Equivalent to ~ 13 peanuts*
- Greatly increased threshold from initial dosing day when 93% subjects reacted to < 50 mg

Jones, JACI 2009

Immunologic Changes with PN OIT

- Suppression of effector cells
  - *Mast cell responses decreased in SPT*
  - *Basophil responses decreased in ex vivo assay*

- Peanut-specific serum antibodies
  - *IgE initially increased, then decreased after 18 mo*
  - *IgG4 increases by 3 mo and stays elevated*

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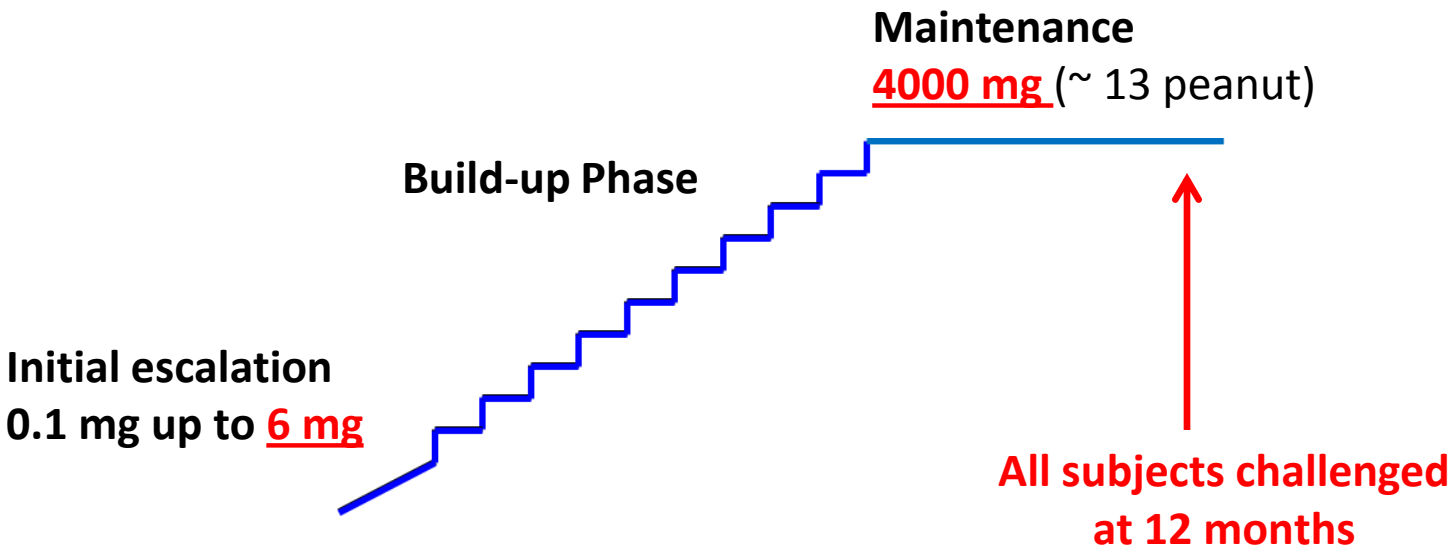
Double-Blind Placebo-Controlled Follow-up Study

- **Objective:** Placebo-controlled trial to demonstrate desensitization caused by OIT



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Varshney, JACI 2011

Subjects in Double-Blind Placebo Study

- 28 subjects enrolled
- Median age at enrollment 69 months
  - *(range: 28-126 months)*
- Randomization: 2:1 scheme
  - *OIT: 19*
  - *Placebo: 9*
- Median baseline Peanut-IgE
  - *OIT: 104 kU/L*
  - *Placebo: 57 kU/L*

Varshney, JACI 2011

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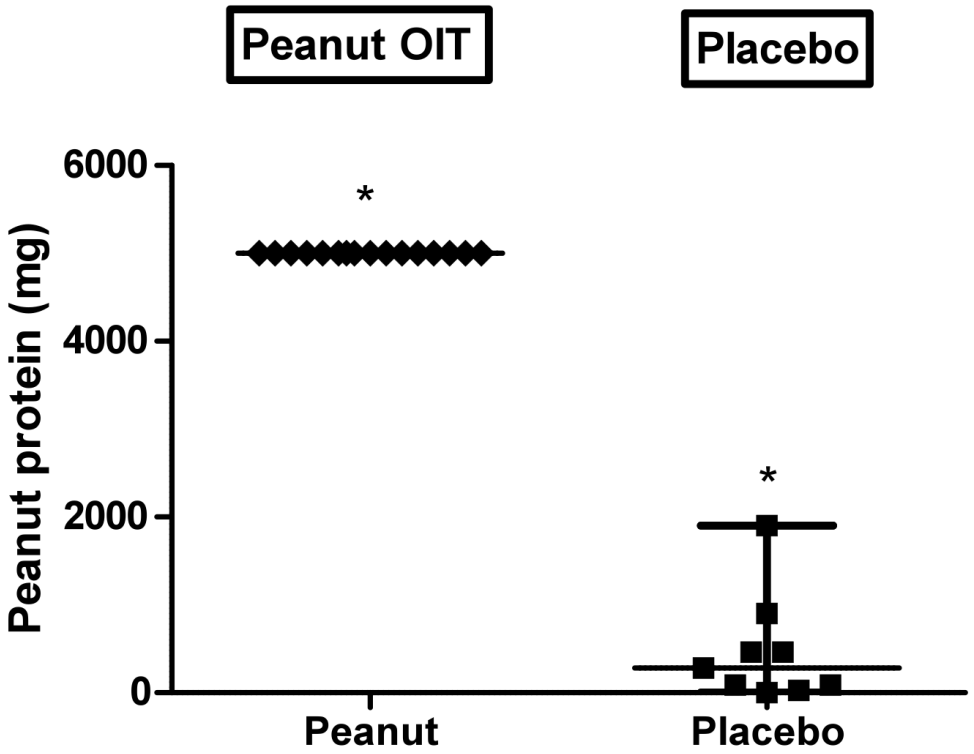
DBPCFC Outcomes Demonstrate Desensitization After 12 mo of OIT



Placebo - median 280 mg
Peanut OIT - 5000 mg

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Varshney, JACI 2011

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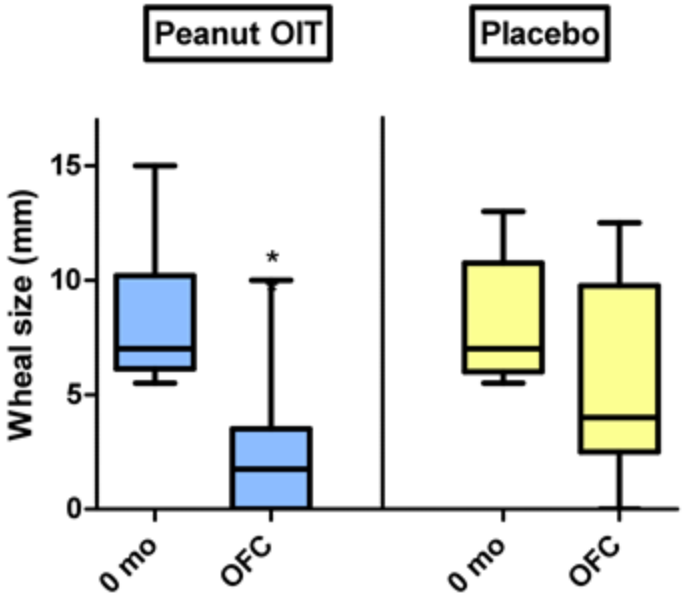
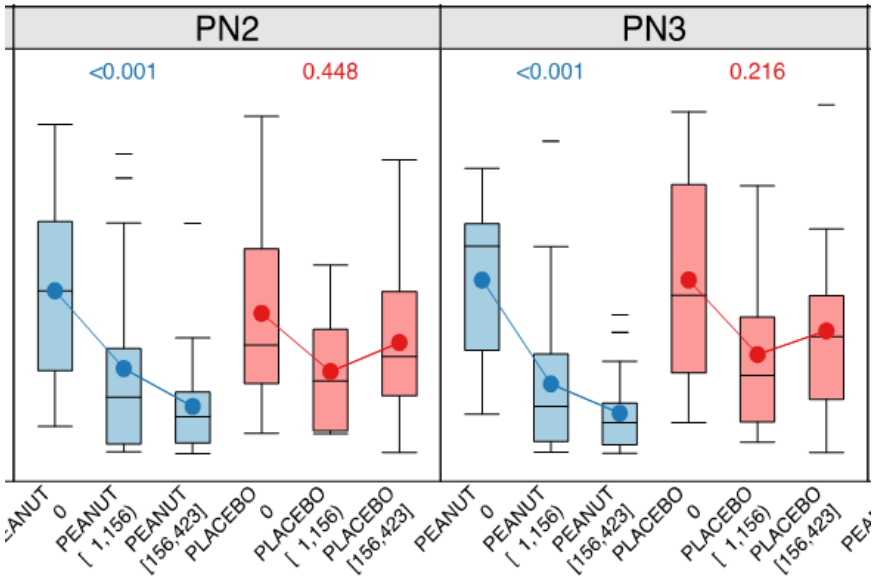
Effector Cell Suppression

Skin Prick Test



Basophil Activation Assay



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Varshney, JACI 2011

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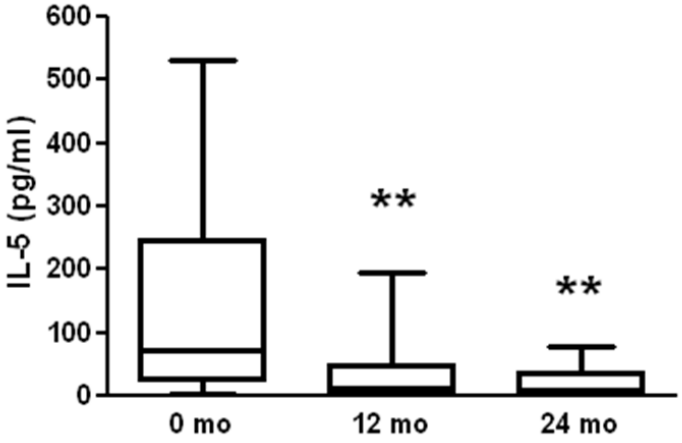
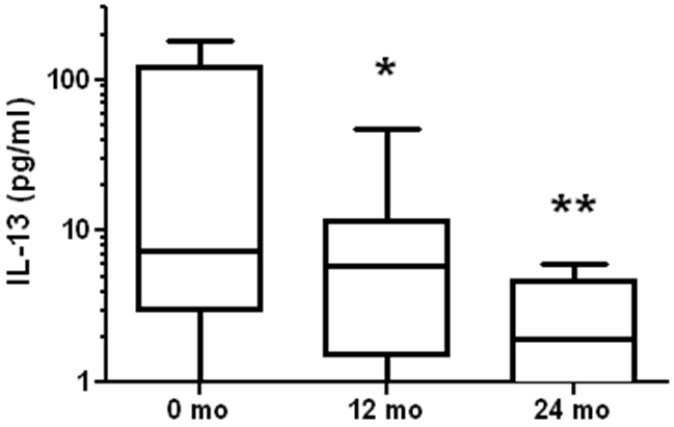
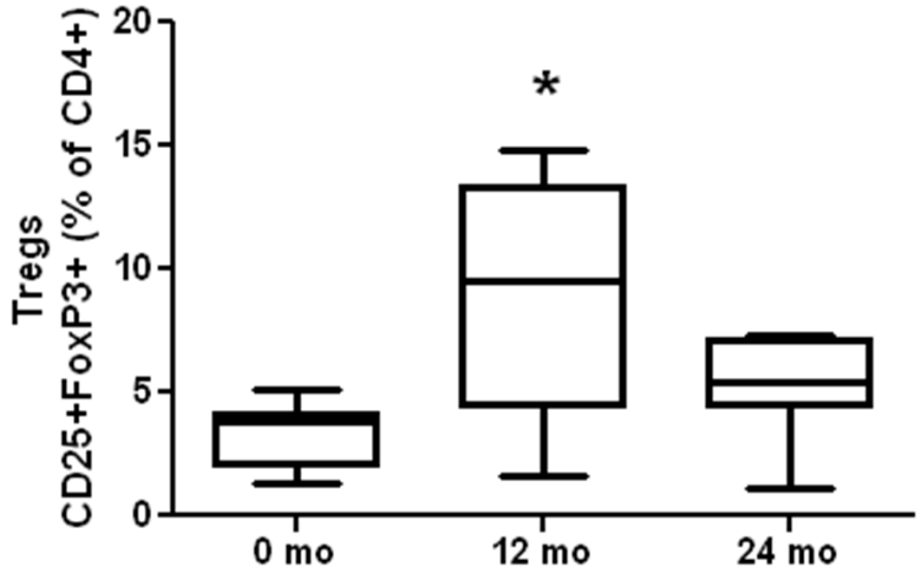
Th2 Responses are Decreased with a Transient Rise in Tregs







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Kulis, AAAAI 2011

Tolerance Induction in Open Peanut OIT Study

- Desensitization
  - *Ability to safely ingest large amount of peanut while on OIT*
- Tolerance
  - *Ability to ingest peanut following OIT with a period of avoidance of peanut for weeks to months*
- Design
  - *19 subjects on OIT for 33-70 months*
  - *Stopped OIT for 4 weeks*
  - *Median peanut consumed: 5000 mg*

Burks, AAAAI 2012

Clinical Results

- At Baseline:
  - *Median PST **8 mm** (range 5 – 21)*
  - *Median peanut-specific IgE **84.1 kU_A/L** (range 9.11 – 401)*
  - *19/19 (100%) developed symptoms < 50 mg on Day 1*

- After a range of 33-70 months of OIT, the rates of successful tolerance induction were:
  - *Per Protocol Analysis: 11/19 (58%)*
  - *Intention-to-Treat Analysis: 11/27 (41%)*

- These 11 subjects now eat peanut *ad lib* without symptoms

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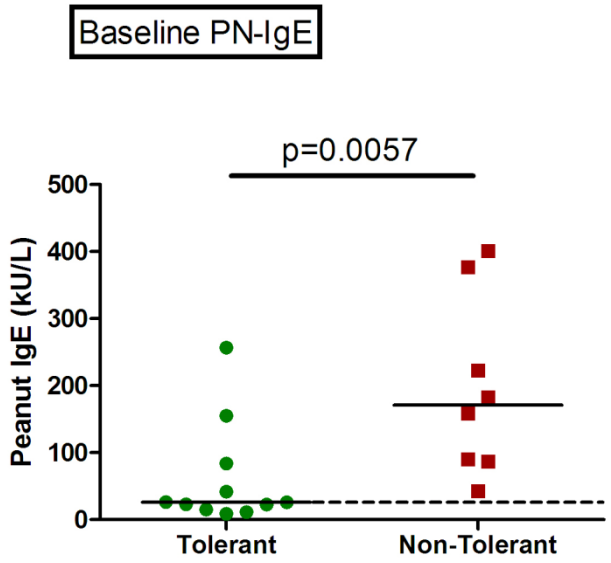
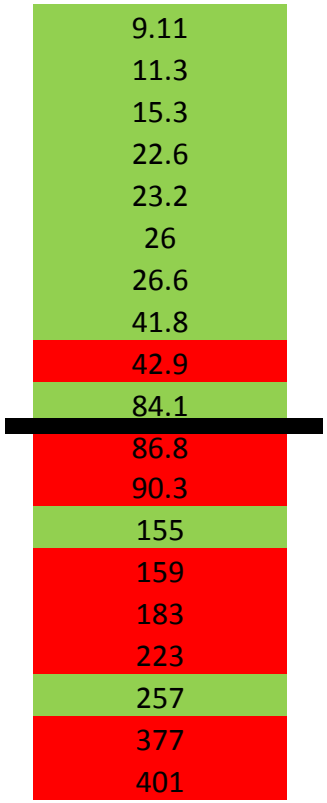
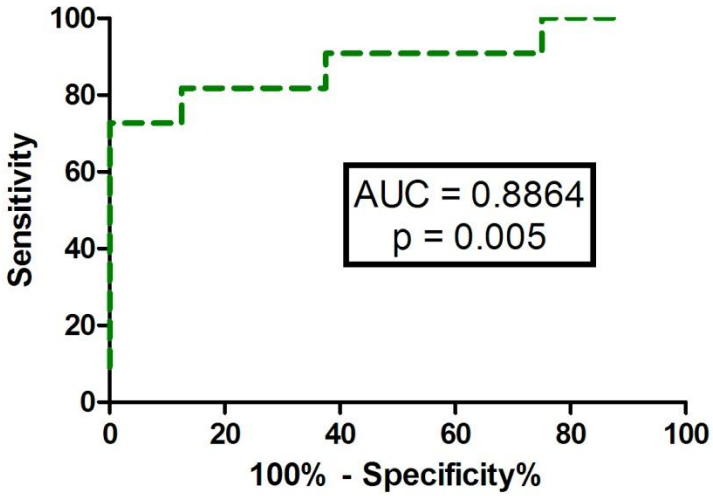
Lower Peanut-specific IgE Levels at Baseline are Associated with Tolerance







Baseline peanut IgE	Sensitivity (95%CI)	Specificity (95%CI)
< 85.45 kU_A/L	81.8 % (48.2 - 97.8)	87.5% (47.4 – 100)

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Milk OIT Study

- Trial conducted at Johns Hopkins and Duke
- Objective: Determine safety and efficacy of milk OIT
- Design:
  - *Entry DBPCFC*
  - *Randomized – 2:1 Milk OIT vs Placebo*
  - *OIT for 5-6 mo (500 mg maintenance dose)*
  - *Final DBPCFC*

Skripak, JACI 2008

Milk OIT Study

- 19 subjects aged 6-17 years (median 9.5)
  - *12 Milk OIT; median IgE: 34.8 kU/L (range 5-314)*
  - *7 Placebo: median IgE: 14.6 kU/L (range 1-133)*

- Median threshold doses on DBPCFC:
  - *Entry (n=19 subjects) – 40 mg*
  - *Final for Milk OIT – 5140 mg (range 2540-8140)*
  - *Final for Placebo – 40 mg*

Skripak, JACI 2008

Milk OIT vs SLIT

- Objective: Compare OIT vs SLIT for milk allergy
- Design:
  - *Entry DBPCFC*
  - *n=30 subjects randomized*
    - SLIT alone (7 mg maintenance)
    - SLIT then OIT (1000 mg)
    - SLIT then OIT (2000 mg)
  - *On therapy for ~18 mo*
  - *Final DBPCFC with 8 g of milk protein*

Keet, JACI 2012

Milk OIT vs SLIT

- Successfully desensitized following therapy:
  - *SLIT alone: n=1/10 passed Final DBPCFC*
  - *SLIT then 1000 mg OIT: n=6/10*
  - *SLIT then 2000 mg OIT: n=8/10*

- OIT improves efficacy over SLIT alone
- OIT associated with higher percentage of allergic side-effects per dose

Keet, JACI 2012

Milk OIT Combined with Omalizumab

- Hypothesis: pre-treatment with Xolair may allow for safer and faster OIT protocols
- n=11 subjects; median age 8 years
- Design:
  - *9 weeks Xolair*
  - *Rush OIT - 0.1 mg initial, max dose 1000 mg*
  - *OIT continued for 7-11 weeks*
  - *Xolair stopped*
  - *Continue OIT for 8 weeks*
  - *DPBCFC*

Nadeau, JACI 2011

Milk OIT Combined with Omalizumab

- n=9/10 subjects reached 1000 mg dose during rush desensitization day 1
- Higher dose than other studies escalation day
  - *Typically < 50 mg dose*
- n=9/10 subjects passed the DBPCFC
  - *Cumulative dose of 7250 mg*
- Xolair pre-treatment may allow for more rapid oral desensitization in milk allergic patients

Nadeau, JACI 2011

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Egg OIT CoFAR

- Primary Objectives
  - *study the clinical effects, safety and immunologic effects, of an egg OIT protocol*
    - *Primary endpoint: attainment of clinical tolerance after 2 yrs*
- Study Design
  - *multi-center randomized, double-blind, placebo-controlled, prospective study through 10 months; open-label extension through 48 months*
- Enrollment criteria (target n=55)
  - *Age 6 to 18 yrs, either sex, any race, any ethnicity with:*
    - convincing clinical history of egg allergy
    - serum IgE [UniCAP™] to egg of >5 kUA/L [<12 mo]; OR
  - *Age 5 yrs, either sex, any race, any ethnicity with:*
    - convincing clinical history of egg allergy
    - serum IgE [UniCAP™] to egg of ≥12 kUA/L [<12 mo]

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Results
Oral Food Challenge Success Rates

	OFC Performed		Response Rates	
	Placebo	Egg OIT	Placebo	Egg OIT
5 gm desensitization OFC (10 mo.)	13	35	0/15 (0%)* (n=13)	22/40 (55%)* (n=35)
10 gm desensitization OFC (22 mo.)	1***	34	0/15 (0%)* (n=1)	30/40 (75%)* (n=34)
10 gm tolerance OFC + open egg (24 mo.)	0***	29	0/15 (0%)** (n=0)	11/40 (27.5%)** (n=29)
10 gm tolerance OFC + open egg (~36 mo.)	N/A	13	N/A	18/40 (45%)# (n=13)

*p<.001; **p=.025; p<.01;***OFC performed w/ criteria met

1 subject in the 2 yr tolerant group had reaction ~1 yr after OFC upon eating a fried egg; continues ad libitum egg diet

Burks, Jones et al NEJM July 2012

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Critical knowledge gaps in food OIT research

Summary - consistent results

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

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

3. Mechanistic studies – results differ depending on length of study

4. Tolerance not shown in blinded studies

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Team

- Physicians - Joe Roberts, Brian Vickery, Stacie Jones (AR), Hugh Sampson (Mt. Sinai), Wayne Shreffler (Harvard), Edwin Kim (UNC)
- Study coordinators - Pam Steele, Jan Kamilaris, Michele Cox
- Fellows - Amy Scurlock, Arianna Buchanan, Todd Green, Scott Nash, Pooja Varshney, Ananth Thyagarajan, and Drew Bird
- Laboratory - Xiaoping Zhong, MD/PhD; Laurent Pons, PhD; Mike Kulis, PhD; and Herman Staats, PhD

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