Oral and Sublingual Immunotherapy for Food Allergy

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UNC
SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRICS

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
Allertein	Minority Stockholder
Dannon Co. Probiotics	Advisory Board
ExploraMed	Consultant
Intellijject	Consultant
Mast Cell, Inc.	Minority Stockholder
McNeil Nutritionals	Consultant
Merck & Co.	Consultant
Novartis	Consultant
Pfizer	Consultant
Portola Pharmaceuticals, Inc.	Consultant
Schering-Plough	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
Food Allergy Initiative	Grantee
National Peanut Board	Grantee
Wallace Foundation	Grantee

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

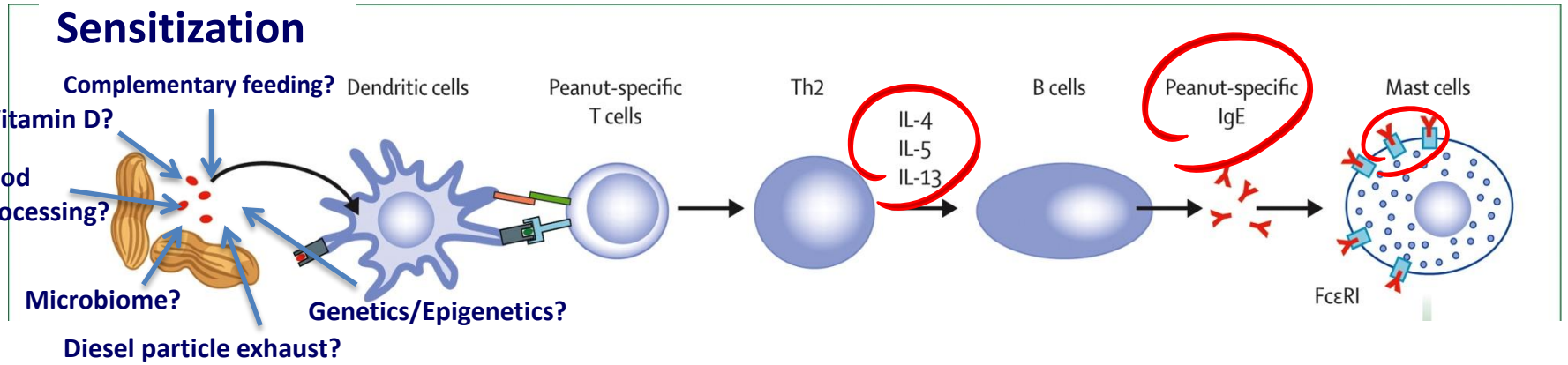
- **Peanut allergy**
  - Prevalence ~1%
  - Most common cause of anaphylaxis in children presenting to the ED
  - Most common cause of fatal food anaphylaxis
- **Standard of care**
  - Avoidance of only foods appropriately diagnosed
  - Self-injectable epinephrine/antihistamines
- **No proactive therapy available**

Fleischer 2007 Curr.Allergy Asthma Rep.
Skripak 2007 J Allergy Clin. Immunol.

Life-long?

Transient?

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



Burks AW. Lancet 2008

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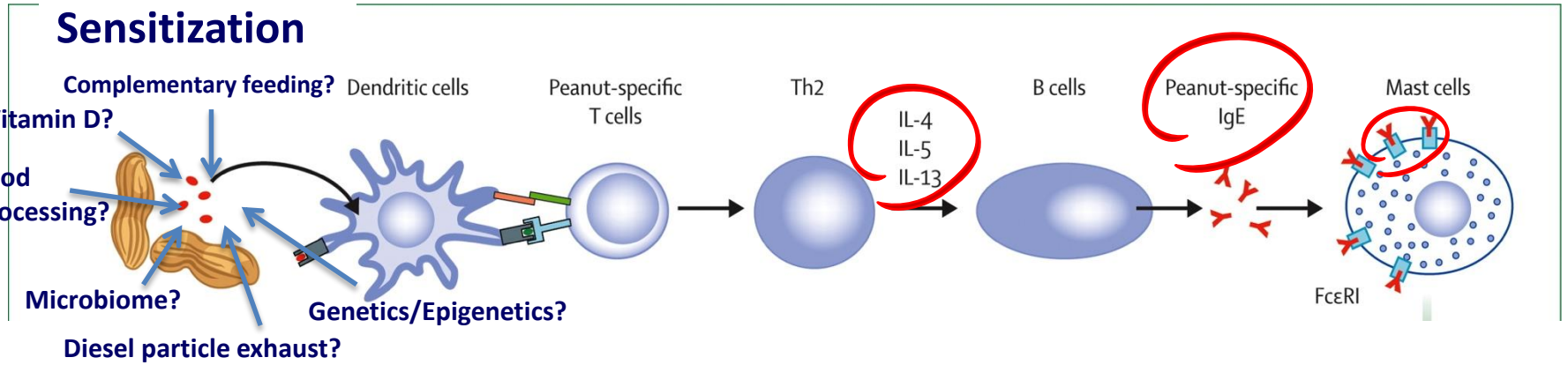

When – in utero?, epicutaneous?, oral?

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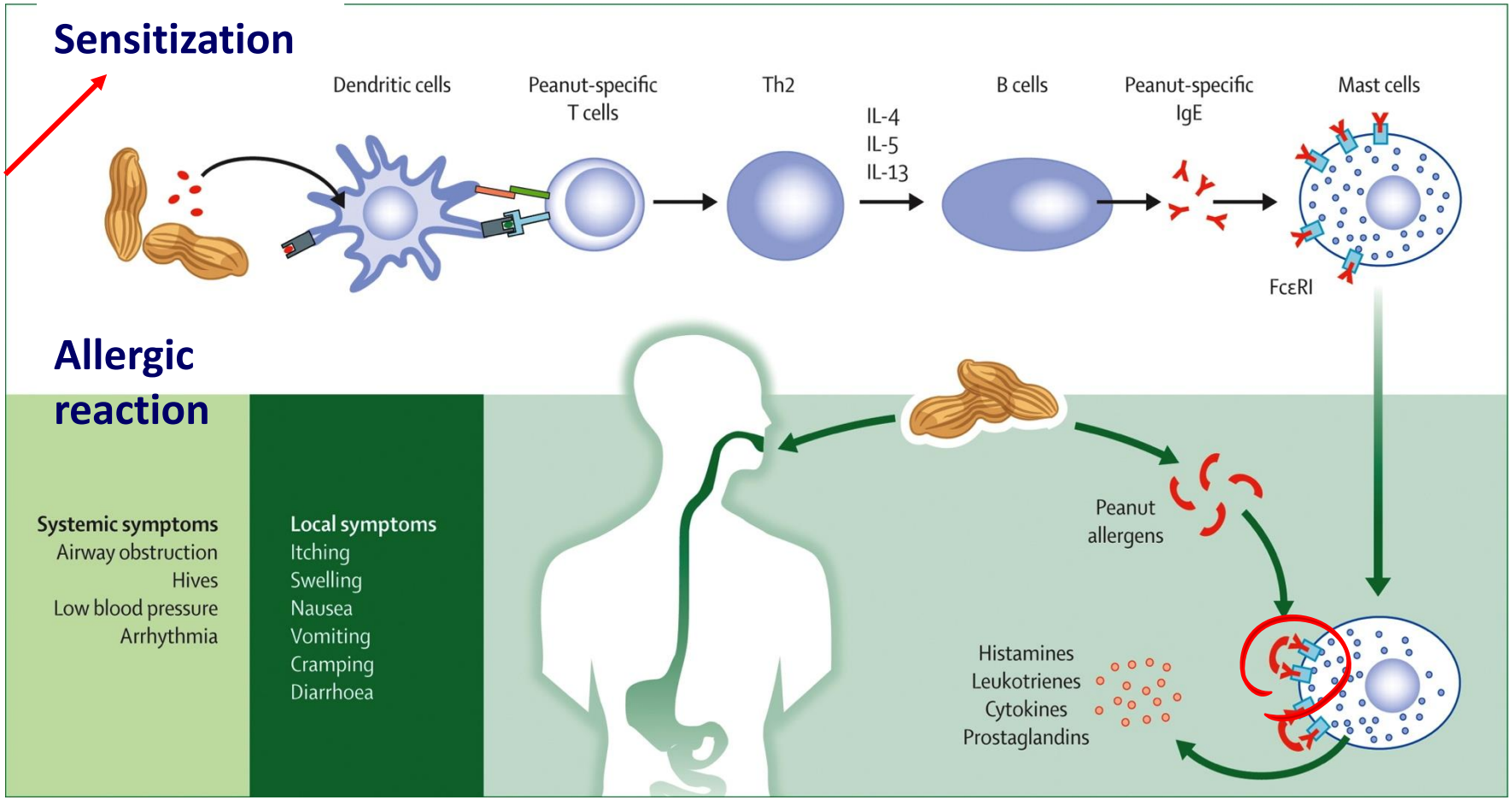

Burks AW. Lancet 2008

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

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- **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

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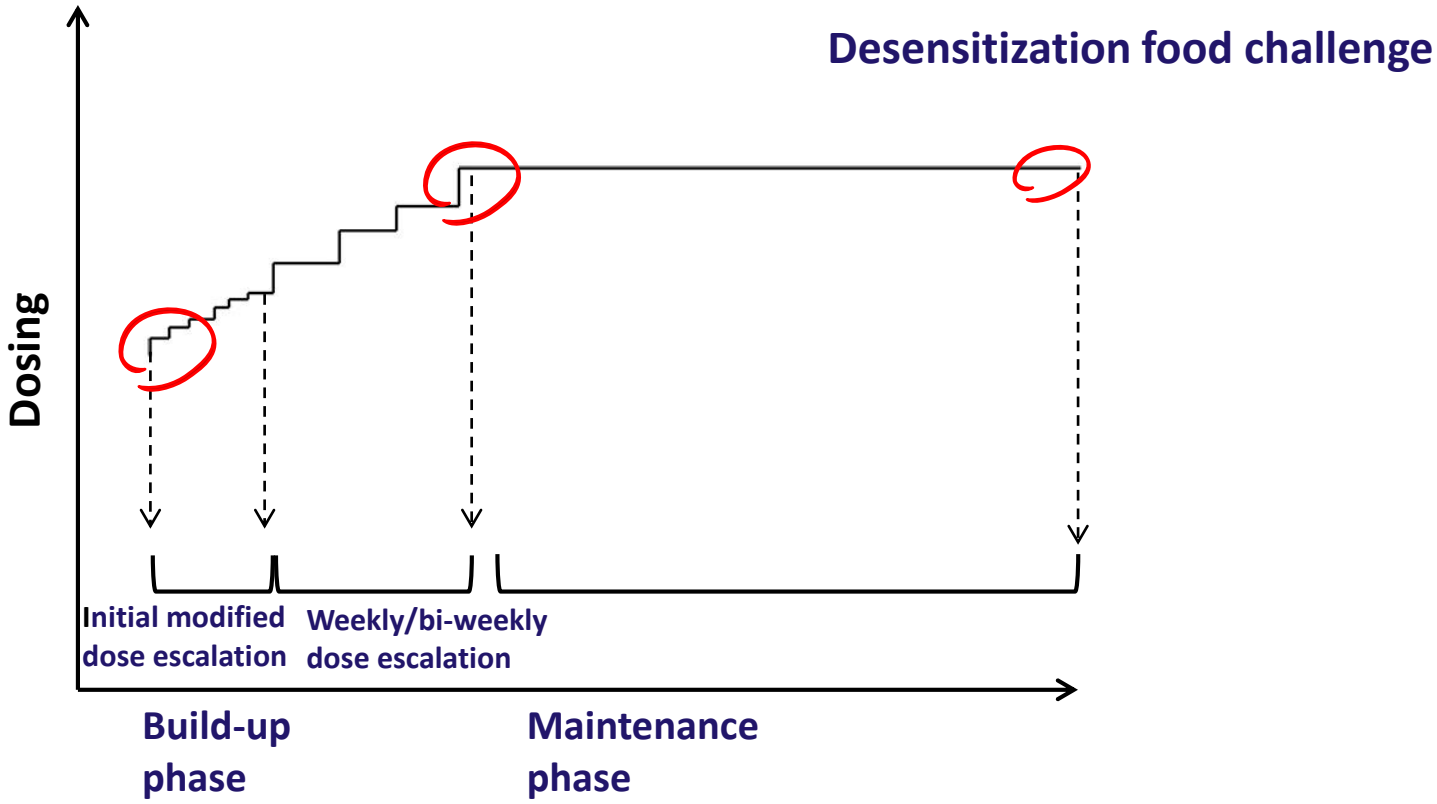
Paradigm of food immunotherapy – OIT/SLIT

Allergy → **Tolerance**



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Nowak-Wegrzyn JACI March 2011

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- **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

Egg OIT

Desensitization

	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)

Jones AAAAI 2012, Burks/Jones NEJM 2012;367:233

Supported by NIH-NIAID U19AI066738 and U0AI066560

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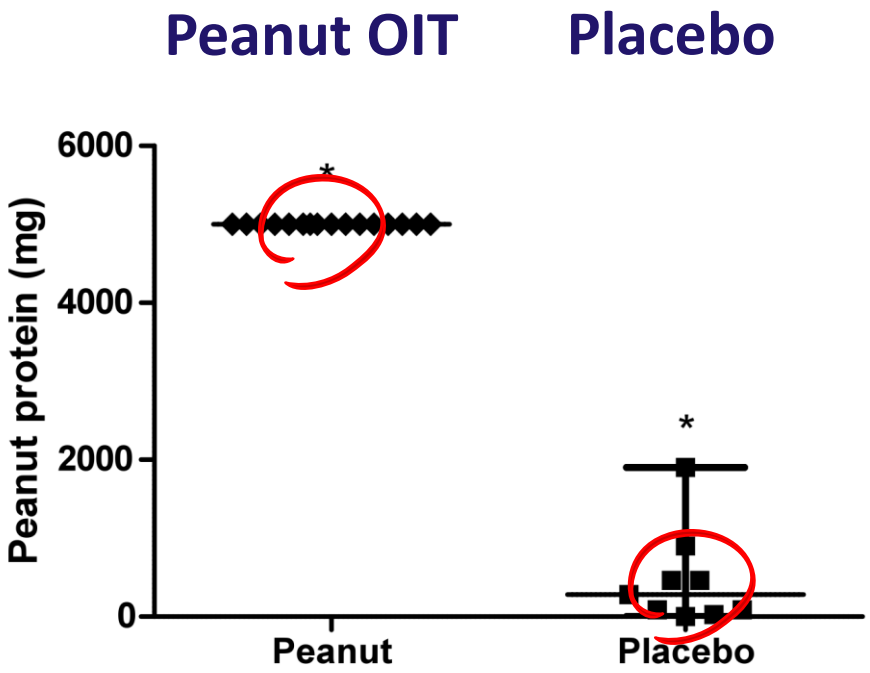
    – 25 subjects – 16 - active treatment; 9 – placebo (3 withdrew)

  – 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



*P<.001

Varshney et al. JACI March 2011

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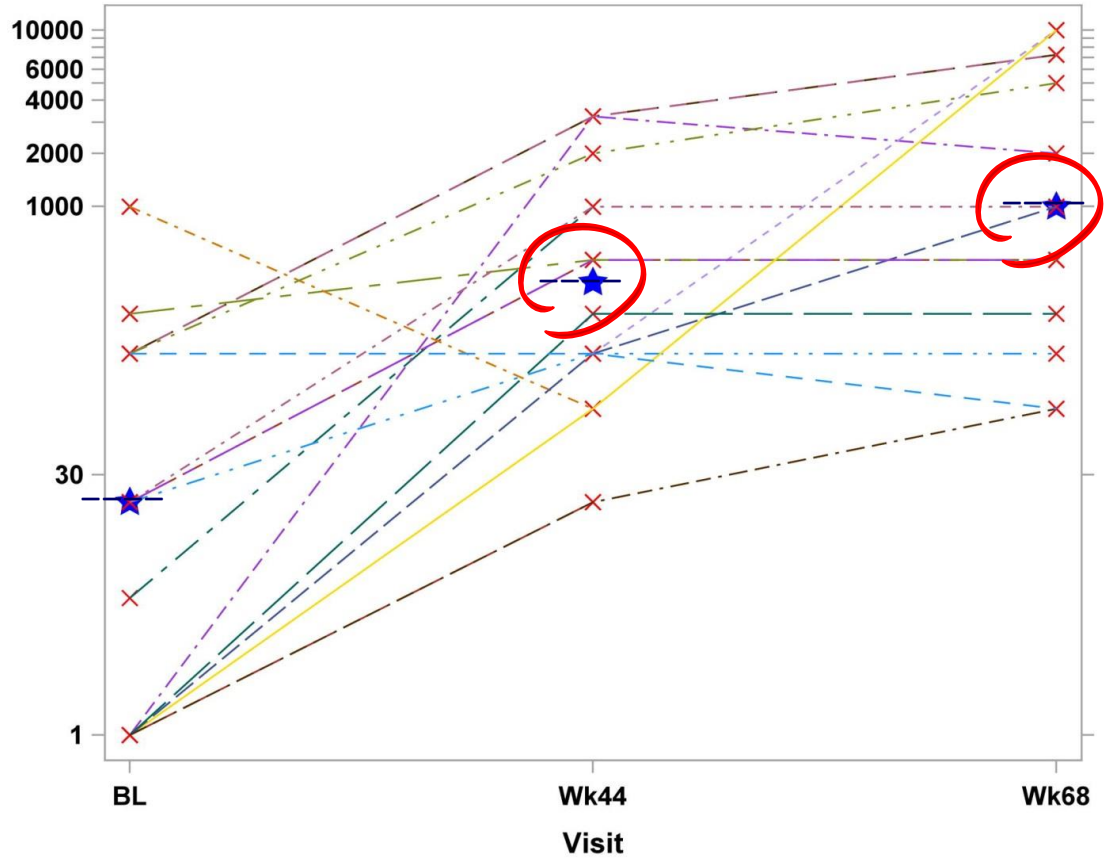
    - 40 subjects – adolescents and young adults, peanut SLIT or placebo

Can we produce long-term tolerance in allergic diseases? CoFAR – Peanut SLIT

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

OFC Successfully Consumed Dose



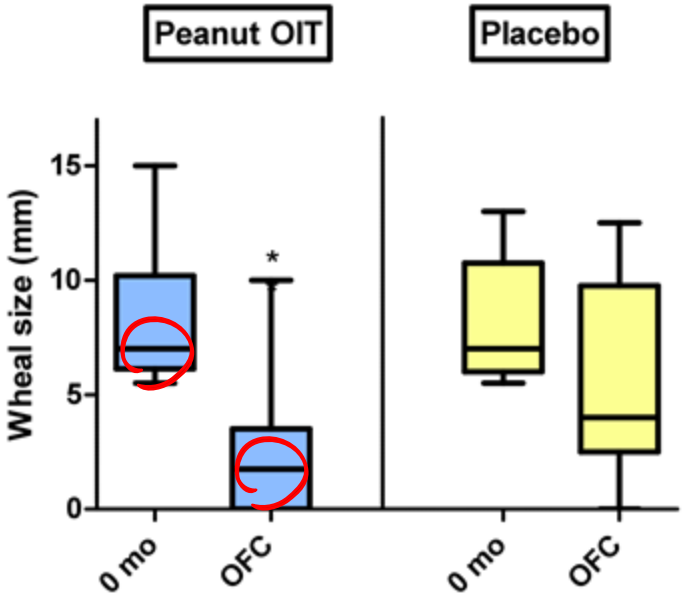
Week 68 - compared to Week 44 (P = .05)
Week 68 – compared to Baseline (P = .009)

Fleischer et al. JACI January 2013

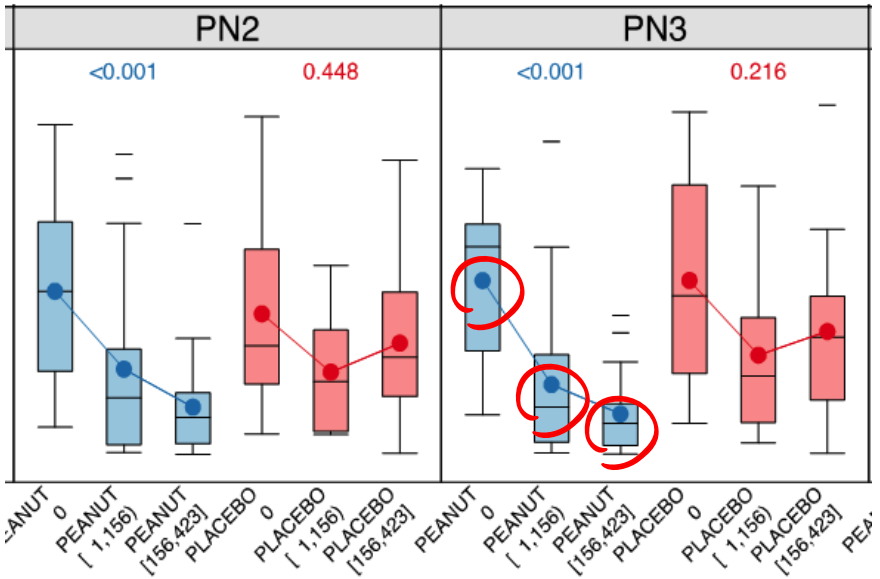
Can we produce long-term tolerance in allergic diseases?

Effector cell suppression

Skin prick test-mast cell

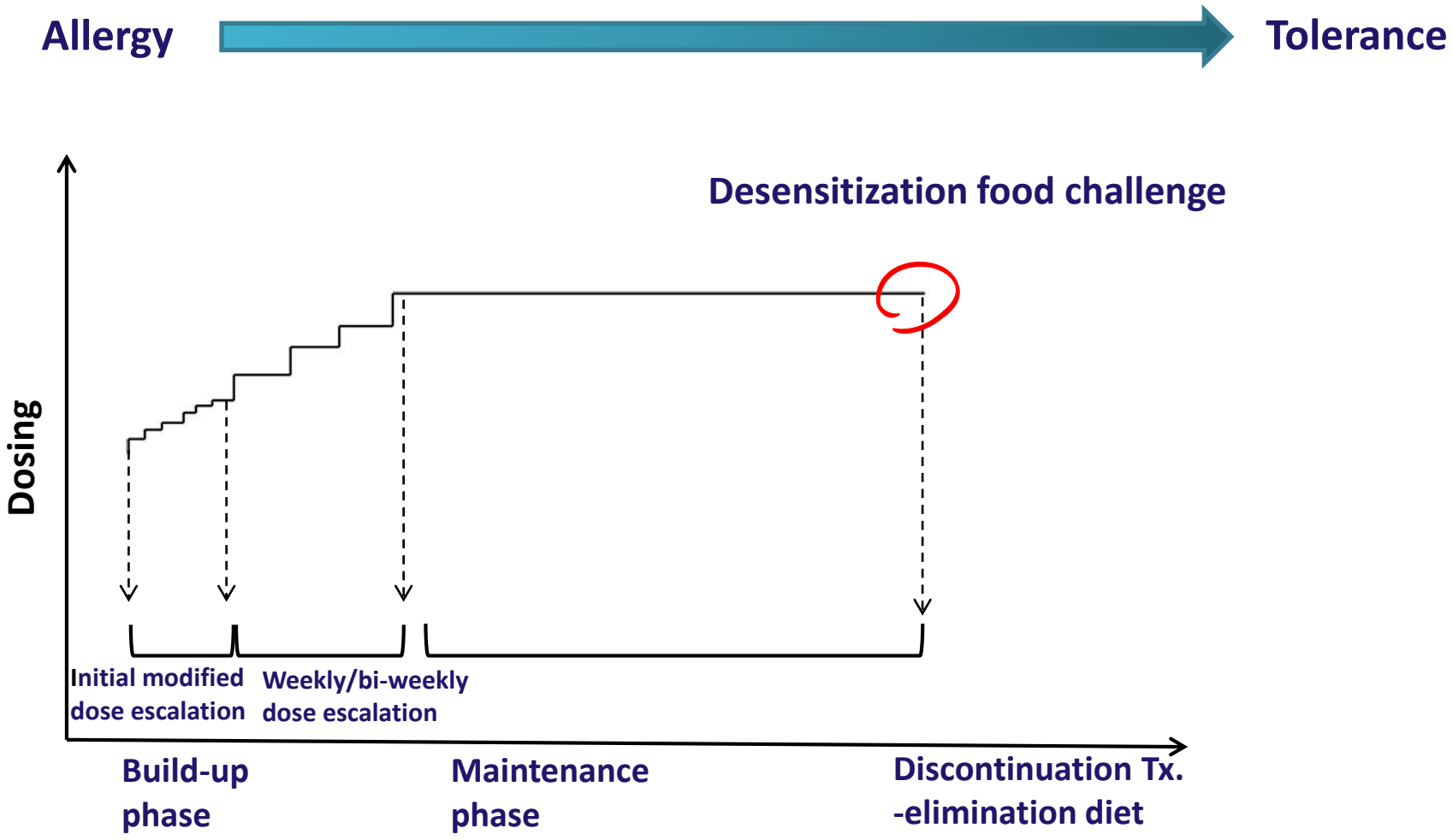


Basophil activation assay
CD 63+



Varshney, JACI 2011

Paradigm of food immunotherapy – OIT/SLIT



Nowak-Wegrzyn JACI March 2011

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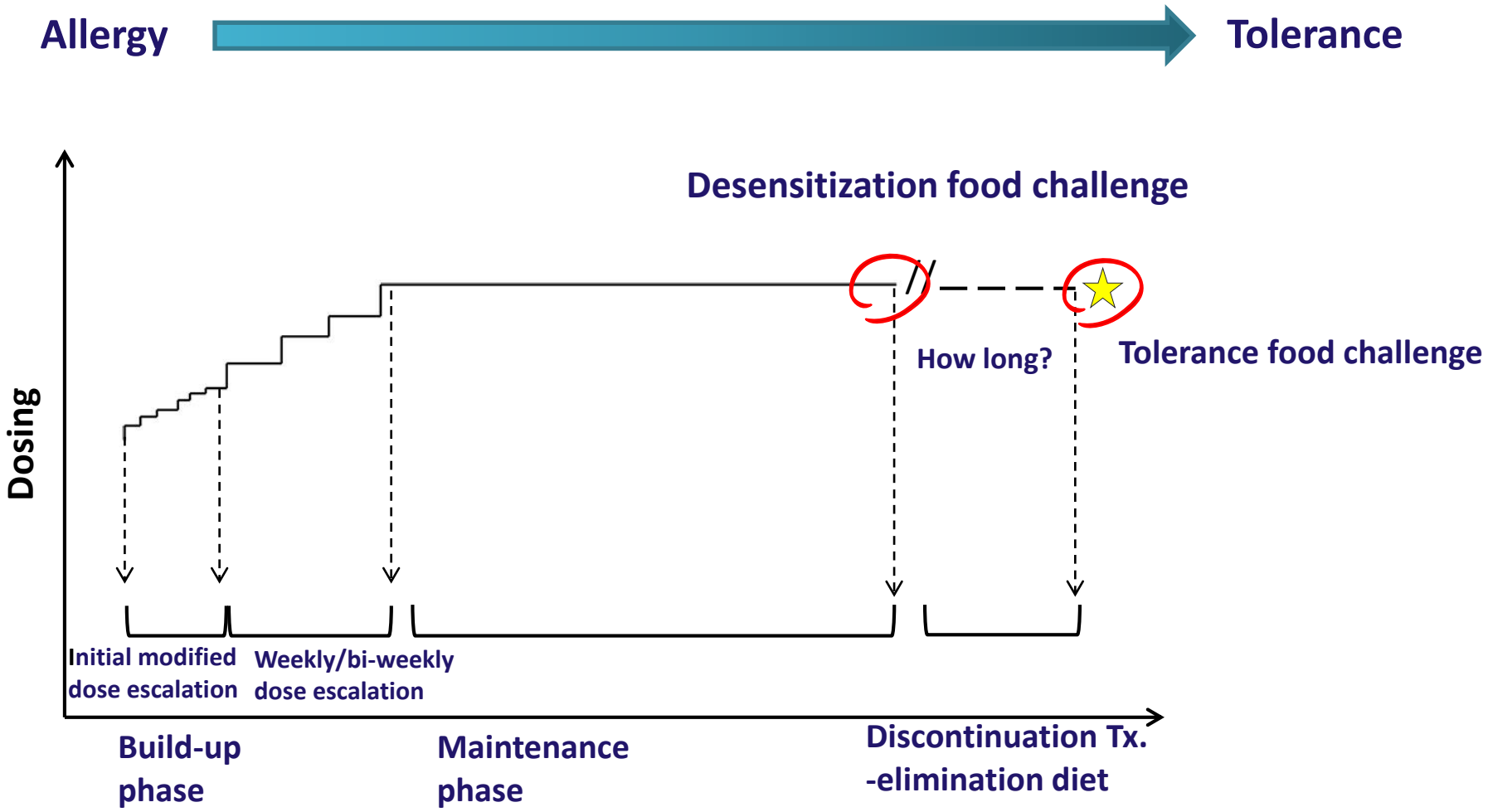

Nowak-Wegrzyn JACI March 2011

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10 gm tolerance OFC + open egg (24 mo.)	0***	29	0/15 (0%)** (n=0)	11/40 (27.5%)** (n=29)

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10 gm tolerance OFC + open egg (~36 mo.)	N/A	13	N/A	18/40 (45%)# (n=13)

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10 gm tolerance OFC + open egg (~36 mo.)	N/A	13	N/A	18/40 (45%)# (n=13)
10 gm tolerance OFC + open egg (~48 mo.)	N/A	8	N/A	22/40 (55%)#

***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***
- ***Other tolerant subjects continue on ad libitum egg diet***

Jones AAAAI 2012, Burks/Jones NEJM 2012;367:233

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Results - Efficacy

Oral Food Challenge Overall Success Rates Egg OIT Subjects*

	Desensitization (D) 10 g OFC	**Sustained Unresponsiveness (SU)** 10 g OFC + open feeding of egg
24 months**	30/40 (75%)	11/40 (27.5%)
36 months	32/40 (80%)	19/40 (47.5%)***
48 months	32/40 (80%)	22/40 (55%)***

* Placebo subjects discontinued from study at 24 months; none passed a 10 g OFC.
** Burks AW, et al, NEJM 2012:267:233-43.
*** 1 subject added egg to diet without OFC; classified as sustained unresponsiveness.

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UNC HEALTH CARE
Children's

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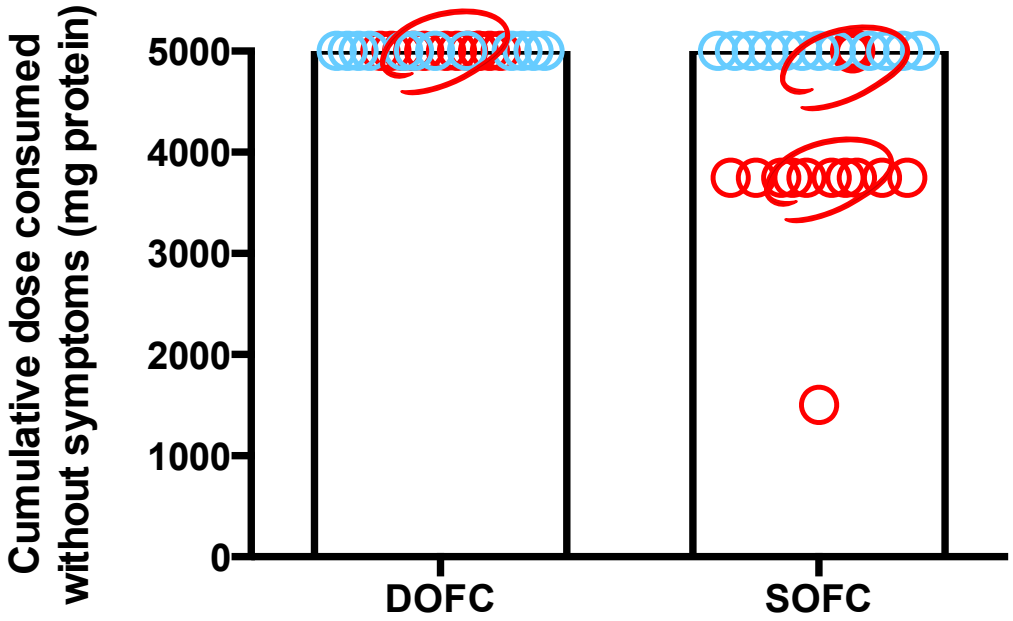
Can we produce long-term tolerance in allergic diseases?

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%)

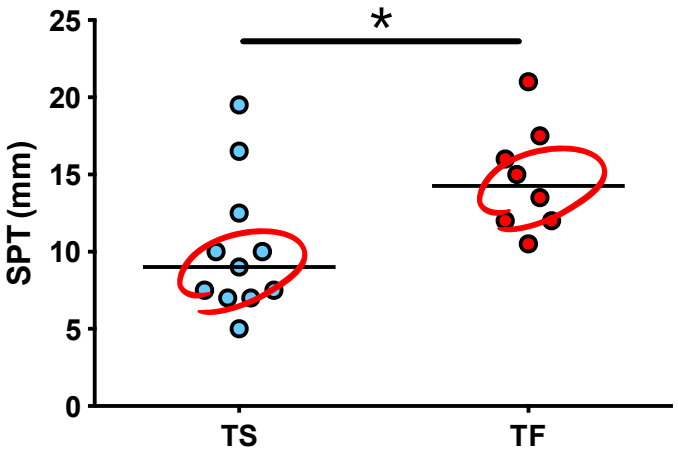
Cumulative dose for OFC – post peanut OIT



Treatment Successes (TS)
Treatment Failures (TF)

Skin prick tests – peanut OIT

A



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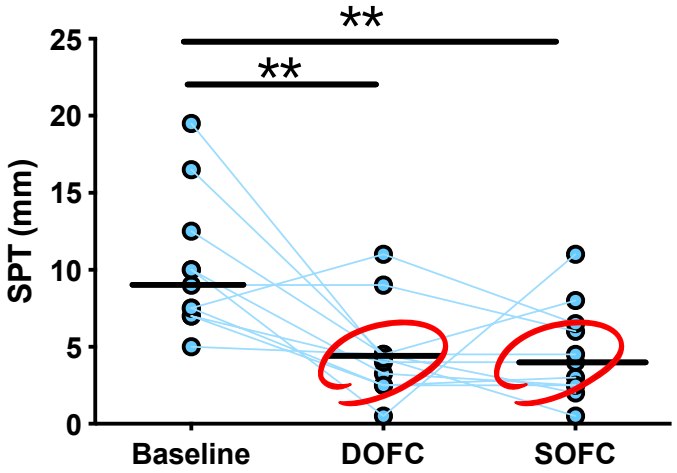
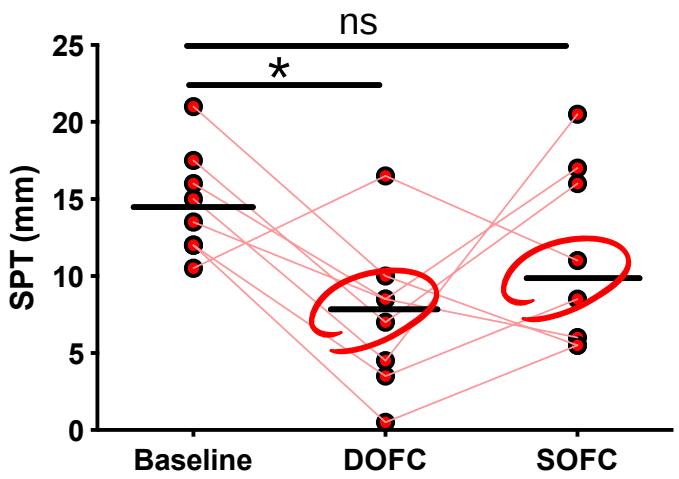
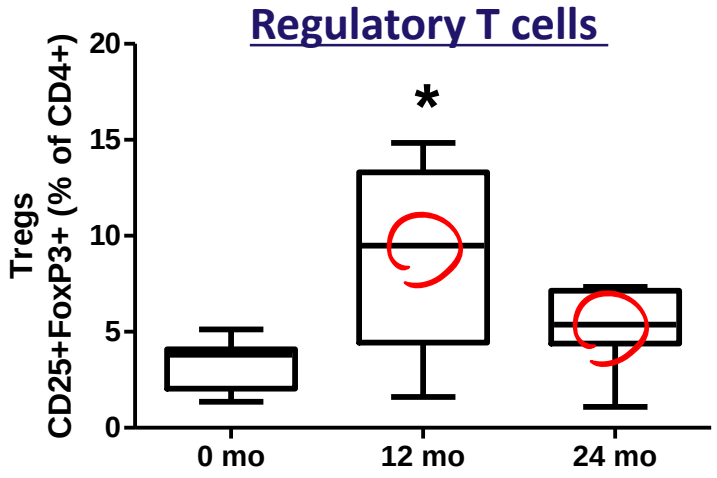




Peanut OIT changes antigen-specific T regs and suppresses the T_H2 response to peanut

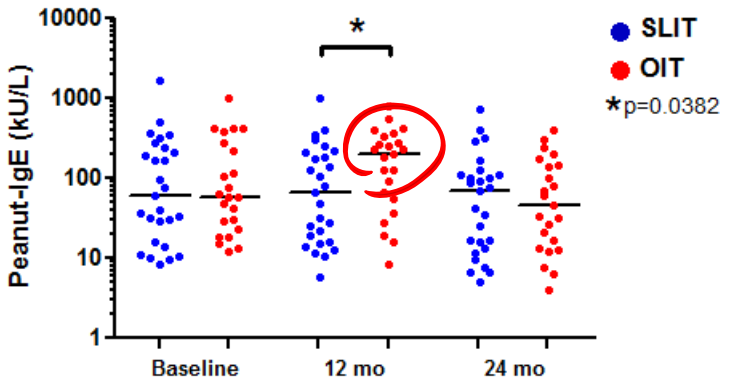


Mechanistic results - UNC and Arkansas peanut OIT studies

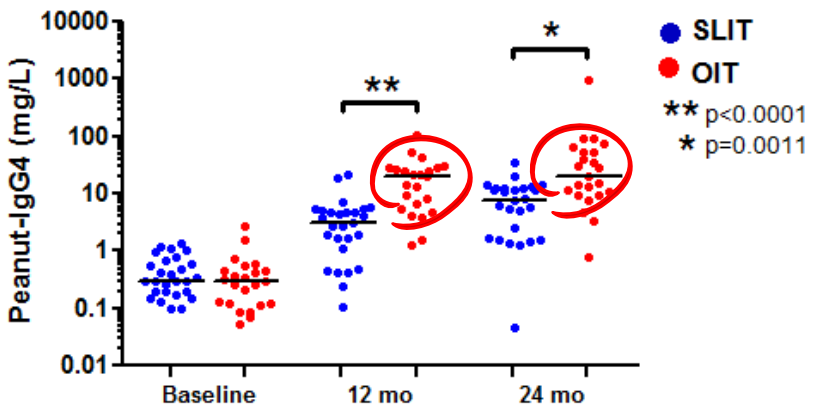
Kulis, Jones, Burks et al. AAAAI 2012

Direct comparison of OIT and SLIT
Peanut IgE and IgG4 – Pass and Fail Tolerance Challenges

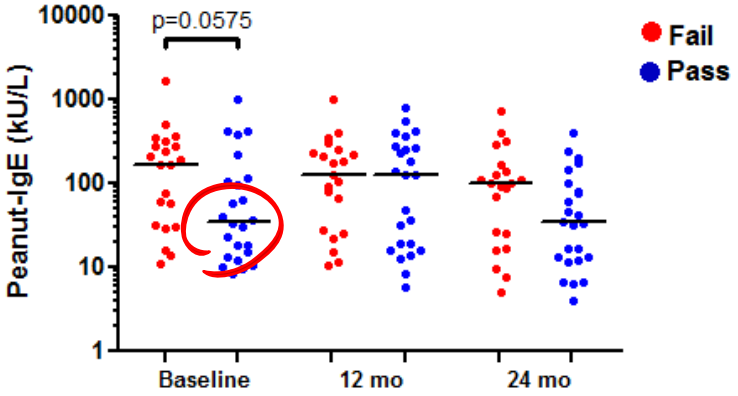
Peanut IgE



Peanut IgG4



Peanut IgE



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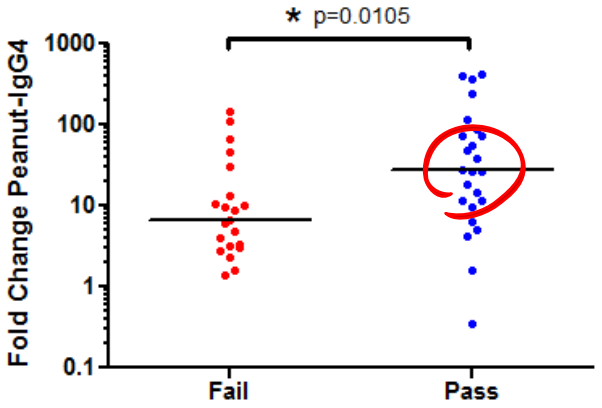

Critical knowledge gaps in food OIT/SLIT research

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** - mast cell, basophil, B-cell and T-cell changes

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

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Patriarca et al. Aliment Pharmacol Ther 2003;17:459-65
Meglio P, et al.. Allergy 2004;59:980-7
Buchanan AD et al. J Allergy Clin Immunol 2007;119:199-205
Staden U, et al. Allergy 2007;62:1261-9
Longo G, et al. J Allergy Clin Immunol 2008;121:343-7
Jones SM, et al. J Allergy Clin Immunol 2009
Skripak JM et al. J Allergy Clin Immunol 2008;122:1154-6
Blumchen K et al. J Allergy Clin Immunol 2010;126:83-91
Varshney P et al. J Allergy Clin Immunol March 2011
Jones SJ, Burks AW, Sampson HA et al – CoFAR 2011

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

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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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