Novel Treatments for Food Allergy

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Today's Presenter

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Background: Food Allergy

- **Prevalence:**
  - 5.9 million school age children
  - 18% increase since 1997

Branum 2009 Pediatrics

- **Why more food allergy?**

Rook – CEI – 2010

- **Peanut allergy**
  - Prevalence ~1%
  - Most common cause of anaphylaxis in children that are taken to the emergency department
  - 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?**

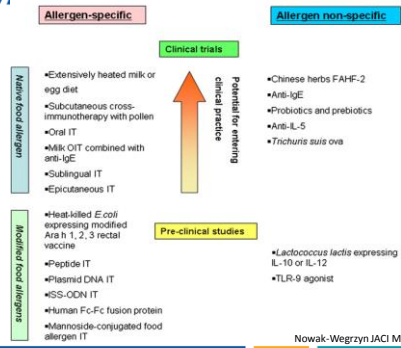
Food Allergy Immunotherapy Goals

- **Goals of treatment are two-fold**
  - Clinical desensitization
    - tolerate more food on treatment than before starting
  - Eventual clinical tolerance
    - off treatment can tolerate food – how long off treatment?
    - no good definition of tolerance – issue in all of allergic diseases
    - **"sustained unresponsiveness"** – N Eng J Med 2012

Clinical Research Basics

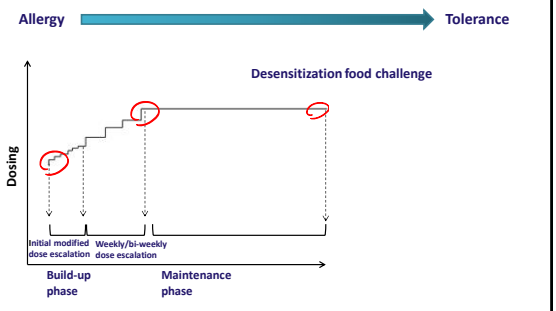
- Phases
  - Phase 0
  - Phase 1
  - Phase 2
  - Phase 3
  - Phase 4
- Design
  - Randomized
  - Blind
  - Placebo-controlled

Approaches to Food Allergy Immunotherapy



Nowak-Wegrzyn JACI March 2011

Paradigm of food immunotherapy



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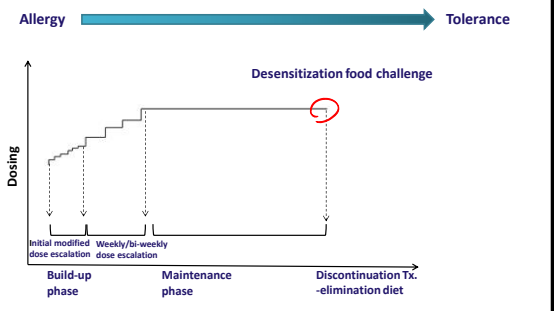
Paradigm of food immunotherapy



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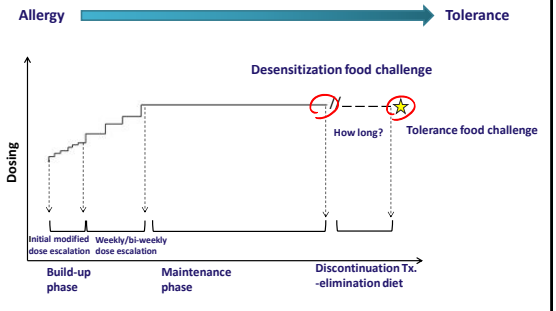

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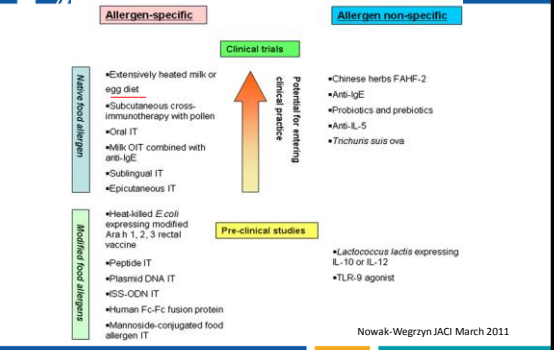
Approaches to food allergy immunotherapy



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Potential Effect of Heated Milk & Egg

- 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%] Heated Cow's Milk (HCM) tolerant – baked-milk products only
  - 23 [23%] Allergic – could not tolerate milk in any form

Nowak-Wegrzyn, Sampson et al. *JACI* 2008

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Potential Effect of Heated Milk & Egg

•~75% of allergic children tolerate extensively heated product in a food challenge

- Associated with reductions in:
  - Specific IgE
  - Prick Skin Test
  - Basophil activity
  - Lymphocyte - Treg cell activity
- Accelerated tolerance development
- Questions –
  - effective dose
  - degree of heating
  - role of the food matrix

Lemon-Mule H. JACI 2008:122:977; Nowak-Wegrzyn A. JACI 2008:122:342; Schrieffer WG. JACI 2009:123:43

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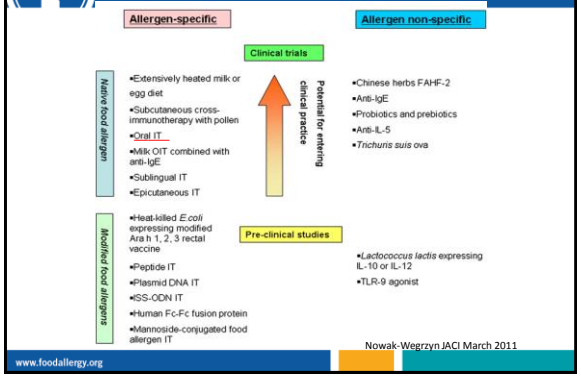
Approaches to food allergy immunotherapy



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Methods of Immunotherapy

- **Oral IT (OIT)**
  - swallowed with food
- **Sublingual IT (SLIT)**
  - sublingually then swallowed
- **Differences**
  - Dose: mg vs. mcg, route, digestion

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Jones - J Allergy Clin Immunol 2013

Oral Immunotherapy (OIT) – Eggs & Peanut

- Multiple clinical studies on OIT conducted worldwide
  - Evidence from 2 clinical OIT studies
    - **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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OIT – CoFAR3 Egg Study

- **Clinical findings in OIT study of food allergy**
  - **CoFAR egg OIT** - Jones, Burks, Sampson et al NEJM July 2012
    - 55 subjects (> 5 yrs) – 40-egg OIT, 15-placebo
    - Multiple centers involved in the study
    - Investigators and families did not know if they received study drug or placebo
    - Treatment through 48 weeks

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OIT – CoFAR3 Egg Study

Clinical desensitization

	Placebo	Egg OIT
5 gm desensitization callenge (10 Month)*	0/15 (0%)	22/40 (55%)
Continue OIT 12 months		
10 gm desensitization challenge (22 Month)*	0/15 (0%)(n=1)	30/40 (75%)(n=34)

* P <.001

Jones, Burks, Sampson et al. NEJM July 2012

www.foodallergy.org

OIT – CoFAR3 Egg Study

CoFAR3 egg OIT – sustained unresponsiveness (permanent tolerance?)

	Placebo	Egg OIT
5 gm desensitization challenge (10 Month)*	0/15 (0%)	22/40 (55%)
10 gm desensitization challenge (22 Month)*	0/15 (0%)(n=1)	30/40 (75%)(n=34)
Off OIT 4 weeks		
10 gm tolerance challenge (23 Month)** (27.5%)(n=29)	0/15 (0%)(n=0)	11/40
Continue OIT 12 months		
10 gm tolerance challenge (~36 Month) (45%)(n=13)	N/A	18/40

* p<.001
** p=.025

Jones, Burks, Sampson et al. NEJM July 2012

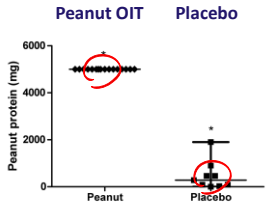
www.foodallergy.org

OIT – Peanut OIT Study

- **Clinical findings in OIT study of peanut allergy**
  - **Peanut OIT** – Varshney, Jones, Burks et al. JACI March 2011
    - 25 subjects – 16 - active treatment; 9 – placebo (3 withdrew)

OIT – Peanut OIT Study

Peanut OFC – 12 months of treatment



*P<.001

Varshney et al. JACI March 2011

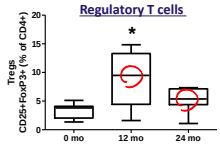
OIT – Peanut OIT Study

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

Vickery, Jones, Burks et al

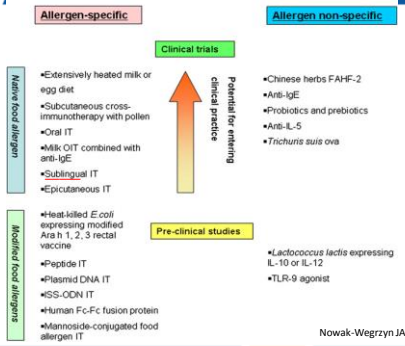
How Peanut OIT Changes the Body's Response



Mechanistic results - UNC and Arkansas peanut OIT studies

Kulis, Jones, Burks et al. AAAAI 2012

Approaches to food allergy immunotherapy



Nowak-Wegrzyn JACI March 2011

Sublingual Immunotherapy (SLIT) – Peanut Studies

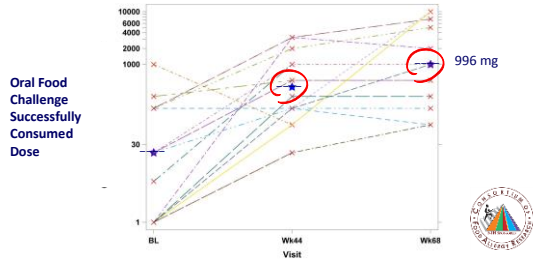
- Few clinical studies on SLIT worldwide
  - CoFAR peanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
  - Peanut SLIT – Kim, Burks et al. JACI 2011

SLIT – Peanut Studies

- **Clinical findings in SLIT study of peanut allergy**
  - **CoFAR peanut SLIT** – Fleischer, Burks, Sampson et al. JACI Jan 2013
    - 40 subjects – adolescents and young adults
      - peanut SLIT or placebo

SLIT – Peanut Studies

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



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

Fleischer et al. JACI January 2013

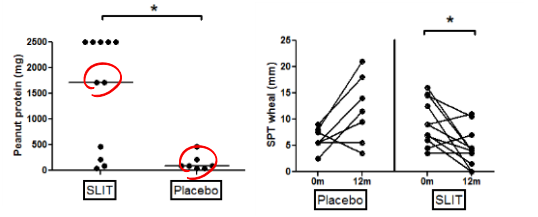
SLIT – Peanut Studies

- **Clinical findings in SLIT studies of peanut allergy**
  - Peanut SLIT – Kim, Burks et al. JACI 2011

Peanut SLIT – Young Children

Results: Food challenges and Skin Prick Tests

- Age 1 to 11 years
  - peanut IgE ≥ 7 kU/L and clinical history of reaction within 60 min of peanut ingestion
- Subjects randomized to SLIT or placebo on entry
- Underwent 5 g (2500 mg protein) food challenge after 12 months



Kim, J Allergy Clin Immunol, 2011;127:640

Critical Knowledge Gaps in OIT/SLIT Research

Summary - consistent results

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

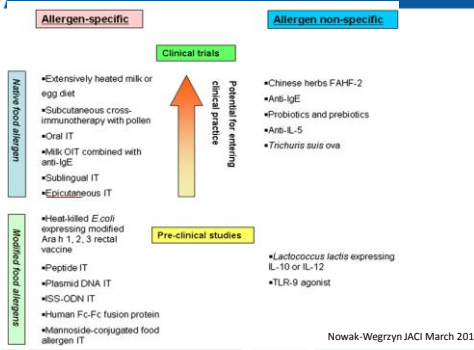
2. **Allergic side effects** - primarily gastrointestinal at the beginning
   - viral infections, exercise
   - **OFF** therapy – recent Hopkins report of worsening symptoms

3. **Mechanistic studies** - mast cell, basophil, B-cell and T-cell changes

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

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

Approaches to food allergy immunotherapy



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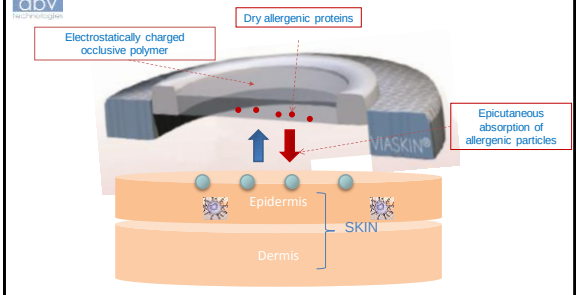
VIASKIN ®: How it Works

VIASKIN®: THE NON-INVASIVE GATE TO ACCESS THE IMMUNE SYSTEM

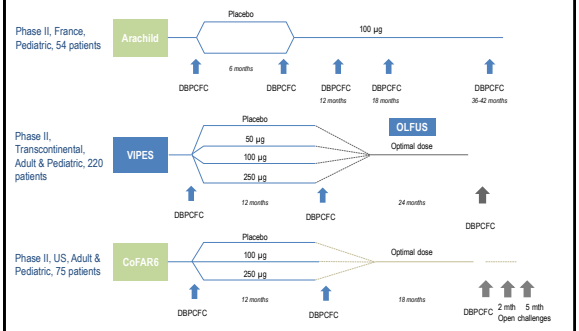


Epicutaneous Immunotherapy (EPIT): Cow's Milk Allergy

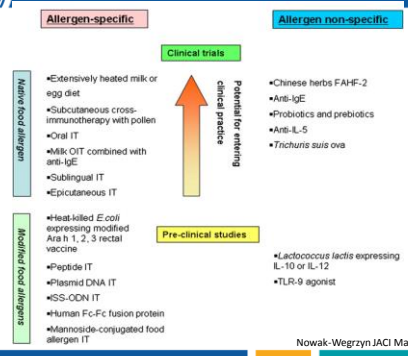
Phase II pilot randomized placebo-controlled Milk EPIT trial

- 16 children with severe IgE-mediated cow's milk allergy
  - 9 treated in Milk EPIT group & 7 children in Placebo group
- Baseline oral milk challenge performed (OFC1) :
  - all patients but one had a tolerance level <10 ml of milk. Many did not tolerate even 0.1 ml of milk
  - last patient could tolerate 17 ml
- 3 months of treatment
  - one Diallertest Milk was applied for 48 hours 3 times a week for 3 months
- Second milk challenge performed after the 3 months of treatment (OFC2)

Example of studies with EPIT in peanut allergy



Approaches to Food Allergy Immunotherapy



Nowak-Wegrzyn JACI March 2011

Anti-IgE

- Anti-IgE monoclonal antibody (Omalizumab) therapy –
  - has been used in 2 trials for peanut allergy
- Hu-901, a novel antibody, to increase the reaction threshold to peanut during a food challenge after treatment
  - approximately 25% of subjects were nonresponders

Leung - N Engl J Med 2003; 348:986-93

- A second major study - omalizumab in 26 subjects
  - stopped prematurely because of safety issues that included severe adverse reactions during food challenges
    - increase in tolerability to peanut in omalizumab-treated (44%) versus placebo-treated (20%) subjects

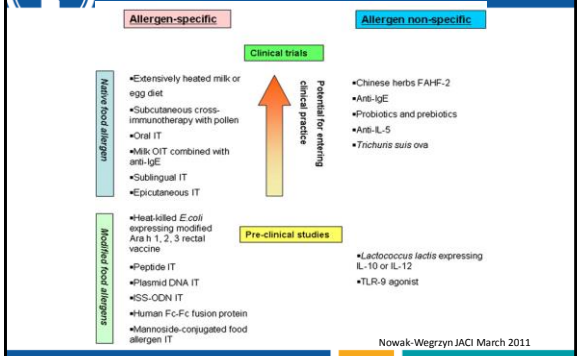
Sampson J Allergy Clin Immunol 2011;127:1309-10

Anti-IgE

- Being studied as both monotherapy and as an adjunct to oral immunotherapy (OIT)
- Pretreatment with omalizumab before and during OIT reduced side effects and the time to daily maintenance dosing in a pilot study of 11 patients with milk allergy

Nadeau J Allergy Clin Immunol 2011;127:1622-4

Approaches to Food Allergy Immunotherapy



Nowak-Wegrzyn JACI March 2011

Chinese Herbal Therapy

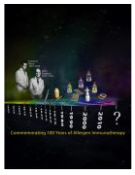
- Demonstrated benefits of Chinese herbal therapy in a mouse peanut allergy model – Li - J Immunol 2003
- Herbal formula FAHF-2 was developed as a formulation of 9 Chinese herbs to be used in clinical trials
- During an initial phase I study (early study in the FDA approval process)
  - subjects received FAHF-2 tablets or placebo 3 times per day for 1 week
  - treatment was well tolerated, with only minor gastrointestinal symptoms in a few subjects
- A phase II clinical trial (second phase of FDA approval process)
  - in progress in adolescents and adults with allergy to peanut, tree nuts, sesame, fish, or shellfish

Wang - Ann Allergy Asthma Immunol 2010;105:75-84

Food Allergy Immunotherapy: The Future?

Life-long?

Transient?



- **Not clear from the present studies in food allergy**
  - Clinical desensitization versus long lasting tolerance?
- **Food allergy**
  - Do not have ongoing exposure with food allergy

- **Major questions remaining**
  - Can we induce long-lasting tolerance at all in food allergy?
  - Can we induce long-lasting tolerance at all in any allergic disease?

January JACI 2011 cover image

Thank you!

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