



UPDATE ON FOOD ALLERGY

EPINEPHRINE AUTOINJECTORS TO NEW TREATMENT

Food Allergy Update

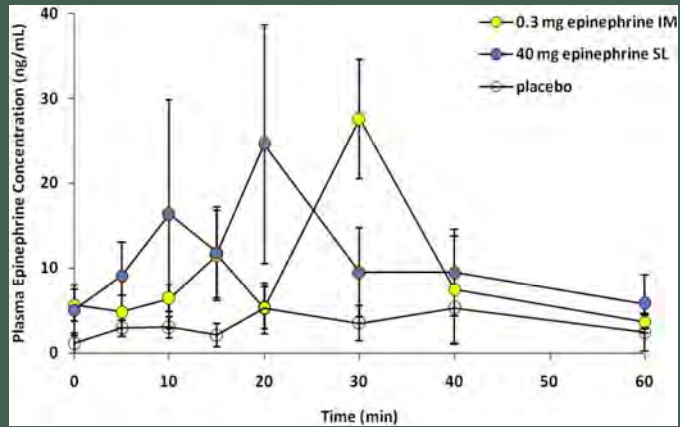
- Epinephrine devices
- Food allergy **avoidance**
- Food allergy **testing**
- Food allergy **prevention**
- Food allergy **treatment**

Current Epinephrine Devices

- Drawbacks
 - Temperature instability
 - Size
 - Injection
 - Cost
 - Compliance



Sublingual Epinephrine



Simons JACI January 2013



[Terms and Conditions](#)

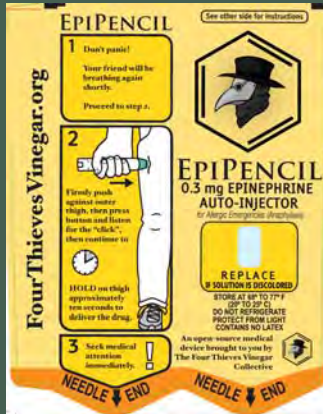
Sublingual Epinephrine

Rapidly Disintegrating Sublingual Epinephrine Tablets

- Sublingual tablet 30 mg taste masked with citric acid to disguise bitter taste for children
 - equivalent serum levels of EpiPen Jr 0.15 in validated rabbit model
- New design incorporated epinephrine as nano-crystals to increase absorption
 - Compared original 40 mg to nano-crystal 20 mg to EpiPen 0.3
 - Serum levels did not differ significantly
 - Therefore nano-crystal formulation able to cut dose in half

Simons E JACI 2013,2014

DIY EpiPencil (\$30)



DO NOT TRY THIS AT HOME



Dr. Michael Laufer



EpiPen Smart Case

- Locator
- Separation Alerts
- Expiration Alert
- Temperature Monitor
- Support Circle



Preorder 2017

Avoidance

FALCPA: Food Allergen Labeling and Consumer Protection Act 2004

<p>Nutrition Facts</p> <p>Ingredients: Enriched flour (wheat flour, malted barley, niacin, reduced iron, thiamin mononitrate, riboflavin, folic acid), sugar, partially hydrogenated cottonseed oil, high fructose corn syrup, whey (milk), eggs, vanilla, natural and artificial flavoring, salt, leavening (sodium acid pyrophosphate, monocalcium phosphate), lecithin (soy), mono- and diglycerides.</p> <p>Any Cookie Company College Park, MD 20740</p>	<p>(1) Include the name of the food source in parentheses following the common or usual name of the major food allergen in the list of ingredients in instances when the name of the food source of the major food allergen does not appear elsewhere in the ingredient statement for another allergenic ingredient.</p> <p>OR</p> <p>(2) Place the word "Contains:" followed by the name of the food source from which the major food allergen is derived, immediately after or adjacent to the list of ingredients, in a type size that is no smaller than that used for the ingredient list.</p>	<p>Nutrition Facts</p> <p>Ingredients: Enriched flour (flour, malted barley, niacin, reduced iron, thiamin mononitrate, riboflavin, folic acid), sugar, partially hydrogenated cottonseed oil, high fructose corn syrup, whey, eggs, vanilla, natural and artificial flavoring, salt, leavening (sodium acid pyrophosphate, monocalcium phosphate), lecithin, mono- and diglycerides.</p> <p>Contains: Wheat, Milk, Egg, and Soy.</p> <p>Any Cookie Company College Park, MD 20740</p>
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FDA.GOV

Avoidance Cross-Contact

- Precautionary labeling (“ may contain”)
 - Voluntary and unregulated
 - Wording cannot be used to asses level of risk
 - Excessive use leads to risk taking*
 - Negates purpose of labeling

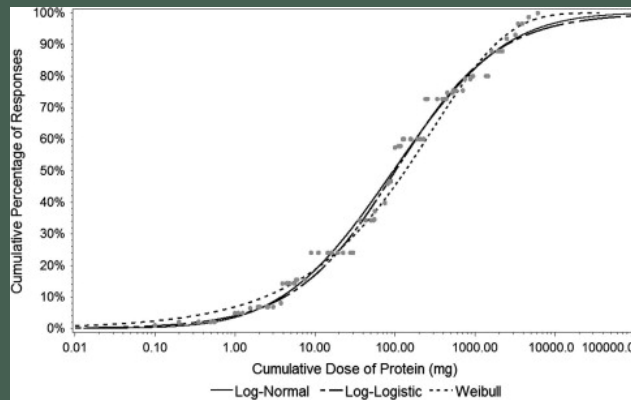
*Barnett Allergy 2011

Avoidance VITAL

- Voluntary Incidental Trace Allergen Labeling
 - Developed by the Allergen Bureau of Australia and New Zealand
 - Single simple standardized precautionary statement to assist food producers in presenting allergen advice consistently for allergic consumers
 - Green
 - Yellow
 - Red
- VITAL® Scientific Expert Panel (VSEP)
 - Collaboration between the Allergen Bureau, Food Allergy Research & Resource Program (FARRP) of the University of Nebraska & the Netherlands Organisation for Applied Scientific Research (TNO)
- VITAL calculator
 - Available to food industry using recipe and allergen status of raw materials to complete label declaration

Allergenbureau.net

Probability distribution models for individual peanut thresholds



Taylor et al Food and Chemical Toxicology 2014

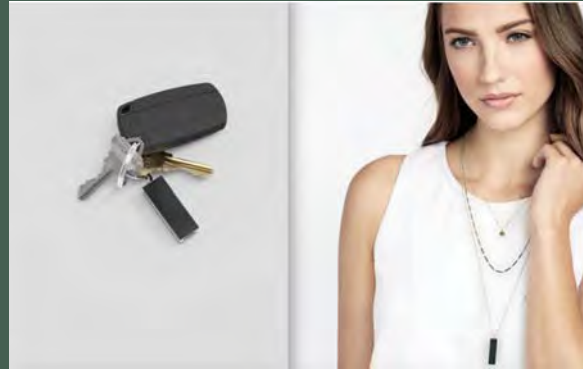
Avoidance VITAL Thresholds

Allergen	mg Protein	Risk
Peanut	0.2	ED01
Milk	0.1	ED01
Egg	0.03	ED01
Hazelnut	0.1	ED01
Soy	1.0	ED05
Wheat**	1.0	ED05
Cashew	2.0	ED05
Sesame	0.2	ED05
Mustard	.05	ED05
Shrimp	10	ED05

**Note: wheat-allergic consumers would be largely protected by foods containing <20 ppm gluten

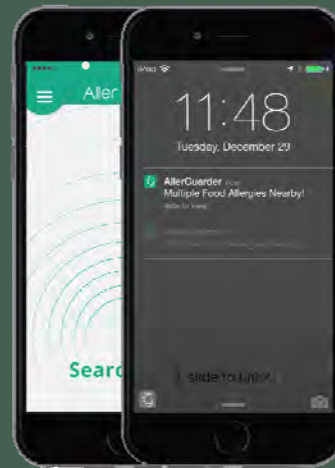
Taylor et al Food and Chemical Toxicology 2014

Avoidance Allergen detection kit



Detect peanut at 1-2 ppm

Avoidance Smart Wristband



Testing Advance methods

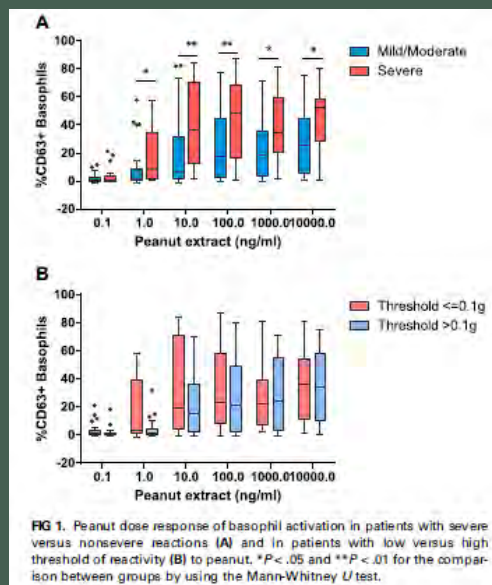
- Positive skin prick test or food specific IgE have unacceptable rate of false positives
- Future testing methods appear to better predict clinical reactivity to food
 - Component resolved diagnostics
 - Food specific IgG4 blocking antibodies*
 - DNA methylation biomarkers**
 - Basophil activation test (BAT)
 - Predicts severity and threshold
 - Needs fresh blood sample, labor intensive, 10-15% non-reactive (false negative)

*Santos JACI 2015:135

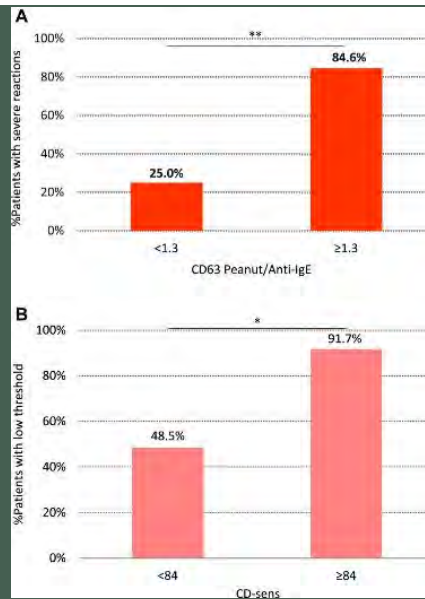
**Martino JACI 2015:135

Testing BAT

- Stimulation of basophils to allergen induces expression of cell-surface proteins
- Antibodies to proteins detected with flow cytometry
- CD63 most common marker



Testing BAT



Santos et al JACI 2015; 135:179-86

CD-sens = $1/EC_{50} \times 100$ (half maximal effective concentration)

	Pollen Cross-reactive	LTP	Storage seed proteins, albumins, globulins
Peanut	Ara h 8	Ara h 9	Ara h 1, 2, 3, 4, 6, 7
	Ara h 5		
Hazelnut	Cor a 1	Cor a 8	Cor a 9, Cor a 14
	Cor a 2		
Cashew			Ana o 1, 2, 3
Walnut	Jug r 5	Jug r 3	Jug r 1, 2, 4
Soy	Gly m 4	Gly m 1	Gly m 5, 6
	Gly m 3		
Wheat	Tri a 12	Tri a 14 (baker's asthma)	Tri a 19 (w-5 gliadin) Tri a 21, 26, 28

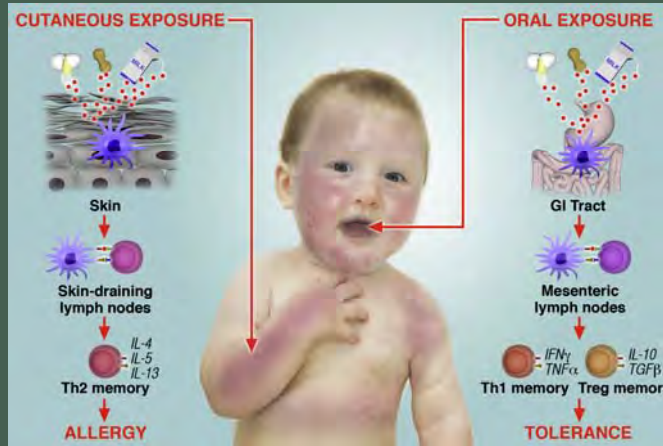
PRP-10

Profilin

Adapted from Nowak slide 2016

Prevention

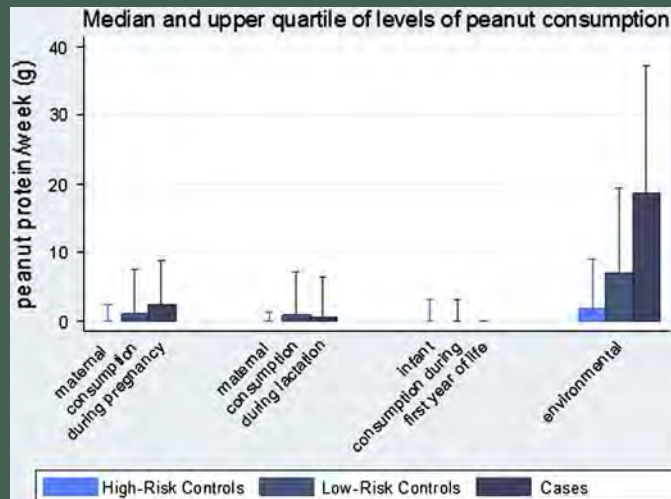
Dual-Allergen-Exposure Hypothesis (“Lack Hypothesis”)



Lack, JACI June 2008

[Terms and Conditions](#)

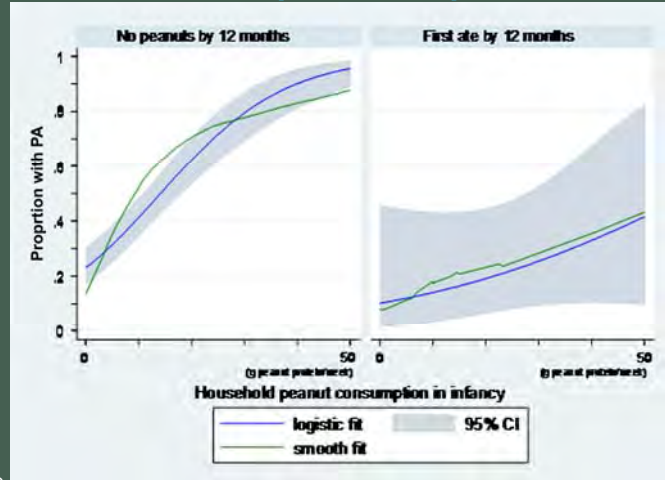
Household peanut consumption as a risk factor for the development of peanut allergy



Lack JACI February 2009

[Terms and Conditions](#)

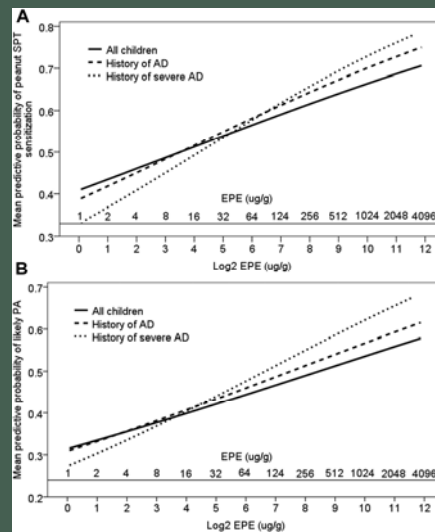
Infant/household peanut consumption as a risk factor for the development of peanut allergy



Lack JACI February 2009

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Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy



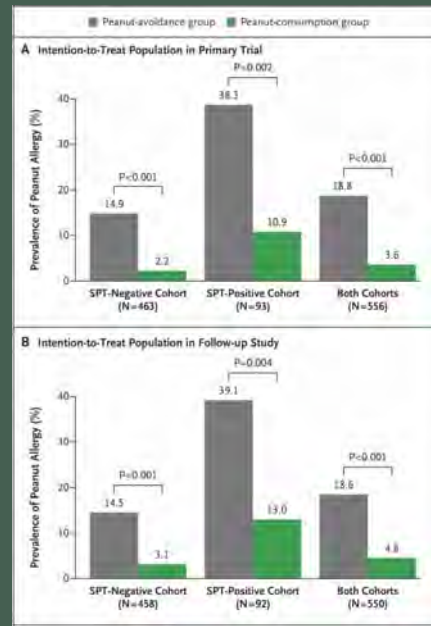
Lack JACI January 2015

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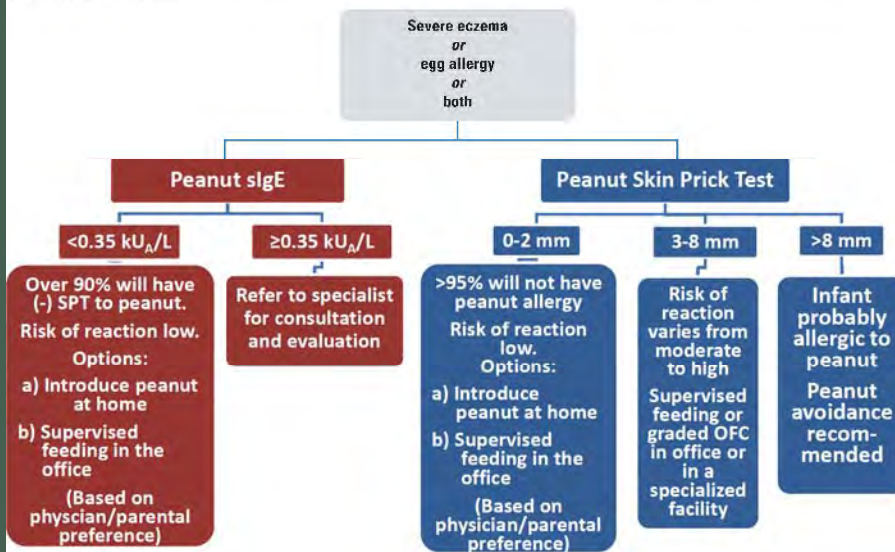
Prevention LEAP-on

- 556 children in LEAP study instructed to **avoid peanut for 12 months**
 - To assess if they were desensitized or truly tolerant (sustained unresponsiveness)
- Results:
 - Rate of adherence high (90% in avoidance group and 69% in consumption group)
 - At 72 months (60 months LEAP, 12 months off)
 - Peanut allergy **significantly more prevalent among peanut avoidance group**
 - 18.6% vs 4.8%
 - Three new cases developed in each group
 - Ara h 2 IgE less in the consumption group
 - Peanut IgG 4 higher in consumption group

DuToit NEJM 2016



Recommended Approaches for Evaluation of Children With Severe Eczema and/or Egg Allergy Before Peanut Introduction



2016 NIAID

LEAP QUESTIONS

- Is 2 grams of peanut protein three times per week necessary?
 - Israeli infants ingest about 2 grams per week
- Is dosing necessary until age 5?
- Do the results apply to other foods?



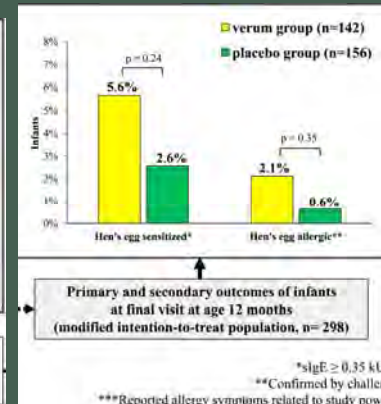
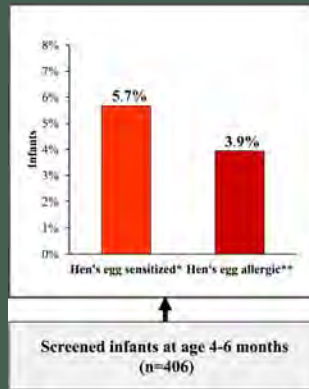
Prevention Enquiring About Tolerance(EAT)

- 1303 exclusively breast-fed 3-month infants
 - **General population** (vs LEAP)
 - Randomly assigned to introduce peanut, **cooked** egg, milk, sesame, whitefish, wheat (skin tested and challenged if + first)
 - Controls exclusive breast-feeding until 6 months
 - Looked at food allergies at 1 year and 3 years of age
- Results:
 - ITT: 5.6% food allergy early vs 7.1% standard (N.S.)
 - Per-protocol: Prevalence of any food allergy lower in early group (2.4% vs. 7.3%)
 - **Significant for peanut (0 vs 2.5%) and egg (1.4% vs 5.5%)**
 - Trend for milk and sesame, 0% wheat allergy both groups
 - Early introduction of all 6 foods **not easily achieved** but was safe

Perkin et al NEJM 2016

Hen's Egg Allergy Prevention HEAP

- 406 4-6 month infants **general population**
- Placebo vs **raw** egg powder 3 times per week
- 17 of 23 sensitized (egg-IgE) underwent challenge
 - 16 positive
 - 11 anaphylactic episodes
- Outcome sensitization and allergy at a year
 - **No evidence of egg allergy prevention**



Bellach et al JACI 2017

Starting Time for Egg Protein STEP

- 820 4-6 month infants of **atopic mothers, no eczema**
- Daily raw whole egg powder vs rice powder
 - **Cooked** egg introduced to both groups at 10 months
- Raw egg challenge at 12 months
- Results:
 - No anaphylactic reaction with study powder
 - No difference in egg sensitization or positive challenge between group
 - Of the 6% that had a reaction, 90% were tolerating cooked egg
 - Vs 31% (1 anaphylaxis) in **STAR** (Solids Timing for Allergy Research) **moderate to severe eczema**
- Conclusion:
 - **No evidence that regular intake of egg at 4-6 months in high risk infants without eczema** alters risk of egg allergy

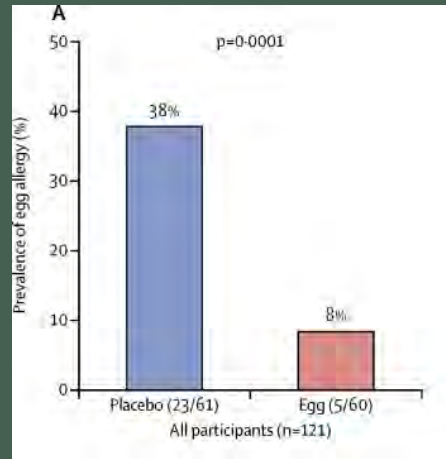


STEP Palmer JACI 139 2017 STAR Palmer JACI 132 2013

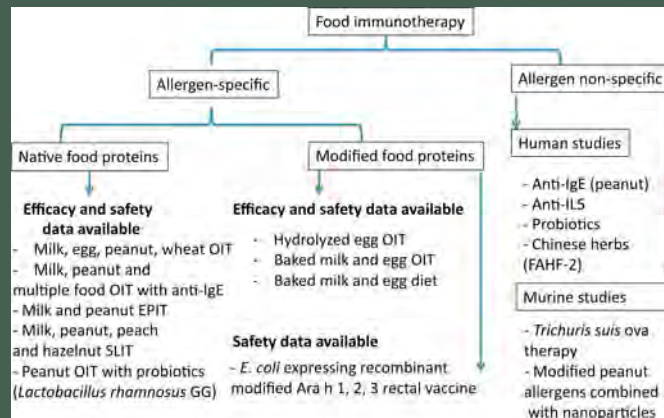
Prevention of Egg allergy with Tiny amount InTake study PETIT

- Based on author's experience with egg immunotherapy (small amount can be introduced even if sensitized)
- 147 4-5 month Japanese infants with **eczema**
 - **Heated** egg powder daily (50 mg 6-9 months, 250 mg 10-12 months) vs placebo (squash)
 - 50 mg = 25 mg egg protein = 0.2 g boiled egg
 - First dose supervised
 - Eczema treated aggressively
- **Study ended early due to interim analysis of benefit**

Natsume et al Lancet 389 2017

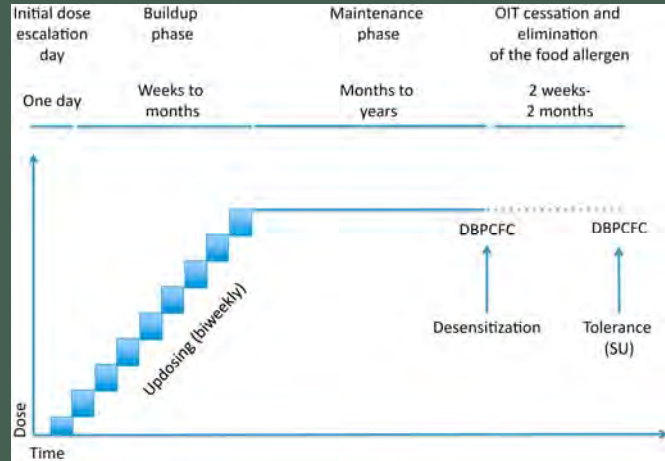


Treatment IMMUNOTHERAPY



Gernez, Nowak-Węgrzyn JACI in practice March 2017

FOOD IMMUNOTHERAPY PROCEDURE



Gernez, Nowak-Węgrzyn JACI in practice March 2017

[Terms and Conditions](#)

AR101 Peanut immunotherapy

- Phase II study 100% tolerated 443 mg and 78% 1043 mg in 4-21 year olds
- Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults
 - Study expedited through FDA and anticipate completion November 2017
 - 4-55 year olds
 - Peanut immunotherapy using pull-apart capsules or sashets and CODIT (characterized oral desensitization immunotherapy) dose escalation starting at 0.5 – 300 mg

Aimmune therapeutics



ORAL IMMUNOTHERAPY

Most of the patients treated with OIT achieve desensitization; however, **only a minority achieves sustained unresponsiveness**.

The safety and efficacy outcomes of peanut OIT appear to be **superior in infants and young children** compared with older patients suggesting a distinct advantage to initiating immunomodulatory treatment early in life.

The long-term adherence to OIT is negatively affected by the **chronic gastrointestinal symptoms**, and there is a small risk of treatment-emergent **eosinophilic esophagitis**.

OIT affords better efficacy but is associated with **higher frequency of systemic side effects** compared with SLIT and EPIT.

Gernez, Nowak-Węgrzyn JACI in practice March 2017

IMMUNOTHERAPY FOR FOOD ALLERGY

Combination of **OIT and omalizumab enhances safety of OIT but appears to have no significant effect on efficacy**. Additional strategies including combining OIT with probiotics or Chinese herbal medicine are currently being investigated.

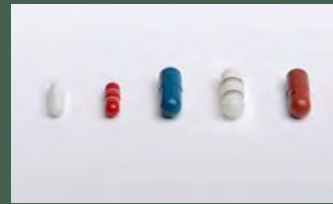
Efficacy of **SLIT is limited by the low dose of allergen** delivered sublingually; SLIT is generally **well tolerated** with majority of adverse reactions being mild oral pharyngeal pruritus.

EPIT appears to be safe and well tolerated with majority of adverse reactions being local skin rashes and pruritus

Gernez, Nowak-Węgrzyn JACI in practice March 2017

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Epicutaneous Immunotherapy



Milk and Peanut being studied, Egg being developed

VIPES – Viaskin Peanut Efficacy and Safety

Summary of key data in VIPES with Viaskin 250 µg

	Viaskin 250 µg	Placebo
All patients		
Number of patients	56	56
Response rate (%)	50.0	25.0
LS mean CRD (mg)	548.5	162.5
Mean CRD increase from baseline (mg)	979.2	269.5
Median CRD increase from baseline (mg)	385.0	0.0
Fold-increase in IgG4* (x)	12.0	1.3
Children		
Number of patients	28	31
Response rate (%)	53.6	19.4
LS mean CRD (mg)	476.6	86.2
Mean CRD increase from baseline (mg)	1,121.0	60.8
Median CRD increase from baseline (mg)	400.0	0.0
Fold-increase in IgG4* (x)	19.1	1.1
Adolescents		
Number of patients	18	18
Response rate (%)	38.9	22.2
LS mean CRD (mg)	456.9	180.9
Mean CRD increase from baseline (mg)	825.4	298.1
Median CRD increase from baseline (mg)	300.0	0.0
Fold-increase in IgG4* (x)	3.3	1.7

www.dbv-technologies.com

250 mg = 1 peanut

EPIT Studies

- VIPES **Viaskin Peanut's Efficacy and Safety** (Phase IIb)
- **OLFUS-VIPES Open Label Follow Up Study**
 - 6-11 year old children from VIPES
 - Previously received either placebo or one of the three doses
 - 250 mcg patch for an additional three years
 - 83.3% responded (compared to 53% at VIPES completion)
 - Cumulative Reactive dose
 - 61% reached 1000 mg or more (4 peanuts) (double VIPES)
 - 39% reached 5050 mg or more
- **PEPITES Peanut EPIT Efficacy and Safety Study** (Phase III)
 - 4-11 year olds 250 mcg dose. Estimated completion August 2017
- **RELISE Real Life Use and Safety of EPIT** (Phase III)
 - 40 11-year olds 250 mcg dose, no challenges

Shreffler JACI February 2017

Food Allergy Herbal Formula 2 (FAHF-2)

- 9 Herb formula based on Chinese herbal formula *Wu Mei Wan*
- Mice studies:
 - Beneficial immunoregulatory effects
 - Completely prevented peanut anaphylaxis
 - Results sustained after treatment stopped
- Human Study
 - 12-45 year-old peanut, tree nut, sesame, fish or shellfish allergy
 - 10 tablets three times per day for six months
 - Food challenge before and after treatment
 - Primary end point: percentage of subjects who could consume, without dose-limiting symptoms, 2 g of protein or a greater than 4-fold increase in pre-study dose

Li, X JACI 2015

FAHF-2 in media



- Book discusses the evolution of FAHF-2 including case reports of private patients in Dr. Li's practice and single case report of a patient in the FAHF-2 phase II study (Food Allergy Bitch)
- Son reacted at 3 peanuts before the study, 9 peanuts after the study, but slightly less 3 months after stopping the study, then was able to add baked milk, butter and soy into diet
- Subsequently passed additional food challenges

FAHF-2 Results

- Significantly more placebo treated subjects had improvements in allergen dose
- Adherence
 - Non-adherence increased over the course of the study
 - 44% had poor adherence for at least 1/3 of study period
- No difference in adverse events
- No difference in immunologic changes between groups

Li, X JACI 2015

FAHF-2 Possible reasons for study failure

- Possible reasons for failure to meet end point criteria:
 - More withdrew from active group (21% vs 5%)
 - Poor adherence
 - Extrapolated dose from mice 80%
 - Short treatment duration (2-3 years = 7 mouse weeks)
 - Mice were exposed to peanut monthly
 - OIT/SLIT/EPIT more effective in younger age
- Future directions
 - Optimize dose
 - Refined formulation will require fewer tablets
 - Increase duration
 - Combine with OIT

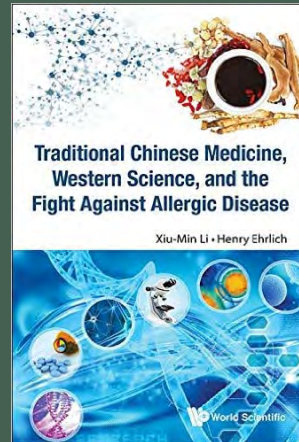
Li, X JACI 2015

Traditional Chinese Medicine

- FAB later blog:

"Was this kid truly allergic to all these foods and the FAHF-2 really helped? Or were his parents and doctors just really overprotective [by not doing]...food challenges that should have been done years ago?"

I don't know."



Oral Mucosal Immunotherapy OMIT



Target Langerhan cells

Intromune Therapeutics

