You race. Kids win. 5K, 10K & kids' fun run. Sunday, June 24.

Join our 2018 Center Summer Scamper Team — support allergy & asthma research and enjoy a fun-filled morning with the Center Community

Register at

https://my.supportlpch.org/allergyasthma

for the Sean N. Parker Center for Allergy & Asthma Research Scamper Team

8TH ANNUAL summer scamper

Benefiting Lucile Packard Children's Hospital Stanford

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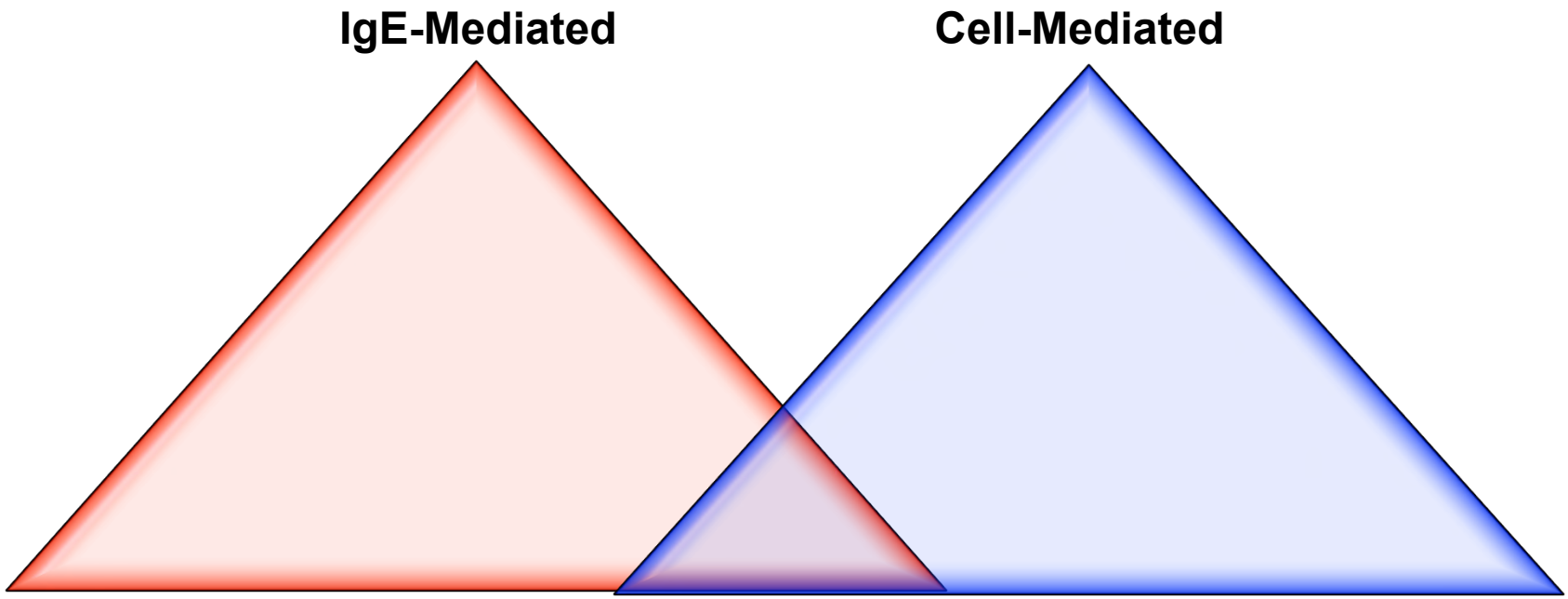
State of the Center: Moving Forward Together

April 26, 2018

Kari Nadeau, M.D. Ph.D.

Stanford MEDICINE | Sean N. Parker Center for Allergy & Asthma Research

Allergy is a spectrum of type 2 immune-related pathologies



Molecular reactions of the immune system leading to various kinds of allergic response—whether through the skin, lungs, or stomach—are very similar

- Studies of molecular changes in eczema can lead us to important discoveries about what happens in food allergy.
- Drugs approved for one type of allergy show promise in helping stop or slow other allergic reactions.

Impact of Food Allergy

A MAJOR, GROWING ISSUE

- 6 million children under 18
- 2 kids per classroom
- 50% increase from 1997-2011
- Costs $25B/year in U.S.

GENETIC & ENVIRONMENTAL

- Genetic predisposition alone can't explain rise
- In 65% of those diagnosed neither parent had a FA

PREVENTION OPPORTUNITY IS REAL

- Prospective controlled studies validate hypotheses generated by retrospective birth cohorts
- Education and compliance required
- Families & care teams must actively partner

MORE THAN JUST PEANUTS

- 8 foods cause 90% of food allergies
- 30% of patients are allergic to more than one food
- 15% of those diagnosed acquire FA as adults

THERAPIES NOW IN DEVELOPMENT

- Driven by deep mechanistic insights
- Promising…
  but not complete or curative

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Impact of Asthma

- Increasingly common, **1 in 12 people**; 25 million in the US, increasing rates
- High morbidity: 2 million ER visits/yr
  High mortality: 10 die every day
- $56 billion dollars per year is spent on asthma patient care in the U.S.
- Disparity in racial and socioecomonic rates and outcomes

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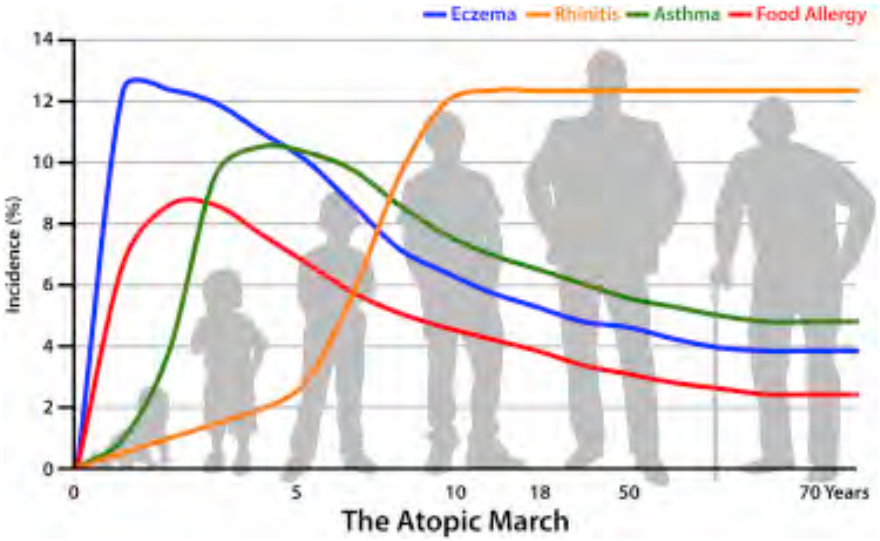
Asthma and food allergy are common in the pediatric population

- 14% of children around the world experience symptoms (GINA 2014)
- 4-8% of children have food allergy (Muraro 2014)
- **Children with food allergy are at 2 times greater risk of developing asthma compared to non-allergic children**
- Food allergy is reported to be a significant causative factor for severe or life-threatening asthma attacks in children
- Asthmatic children with multiple allergies are at greater risk of developing asthma with increased severity.
  (Wang 2005; Schroeder 2009)

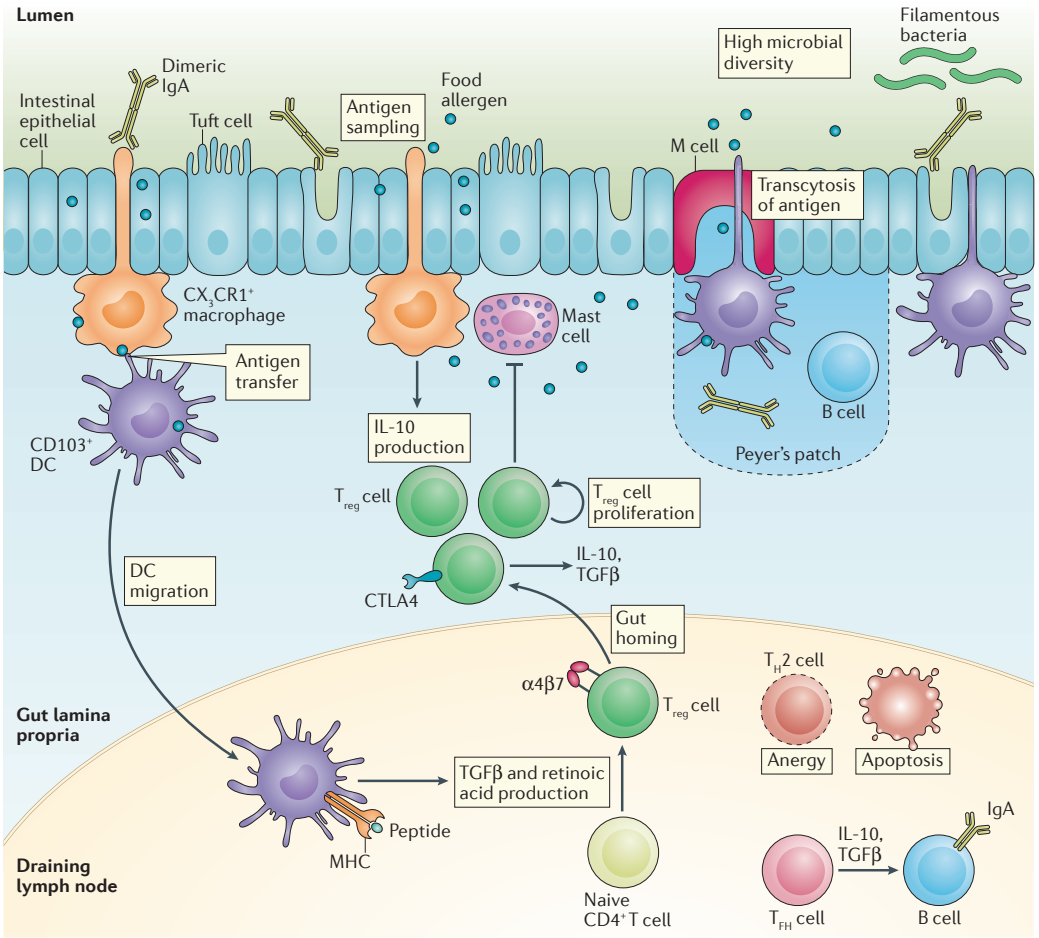
Atopic Dermatitis is associated with food allergy and there is an increased risk of developing asthma and allergic rhinitis

- AD may be the initial manifestation of atopy with progression to food allergy, asthma and allergic rhinitis
- Not yet definitively proven whether the atopic march is causal
- Research into identifying effective interventions is currently underway



Eosinophilic Esophagitis (EoE)

- Estimated prevalence of 0.4% in Western countries
- Occurs in both children and adults
- Most adults are males in 20-30s
- Dysphagia (difficulty swallowing) with solid food impaction
- **Often coexisting allergic disorders (IgE-mediated food allergy, asthma, allergic rhinitis, atopic dermatitis, etc.)**
- **Important to understand relationship with food allergy immunotherapy**



Immune tolerance to oral antigens in the gut

Yu, et al, *Nature Rev Immun* 2016

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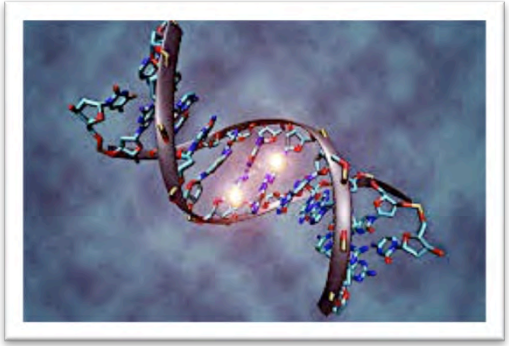
Discoveries: Immunology, genetics, and environment are the keys to prediction and prevention

- There is a **critical time period during fetal and infant and adult development** in which the immune system can be programmed to become allergic.
- Using precision medicine, we have begun to develop ways to prevent this **unnecessary turn to allergy** and create long-lasting beneficial effects in overall wellness.
- Cures for near fatal allergies and asthma are possible but **safety needs to improve.**
- Current **diagnostics for allergies and asthma have limitations.**
- Still no commercially available test to **determine when allergy or asthma resolves permanently.**



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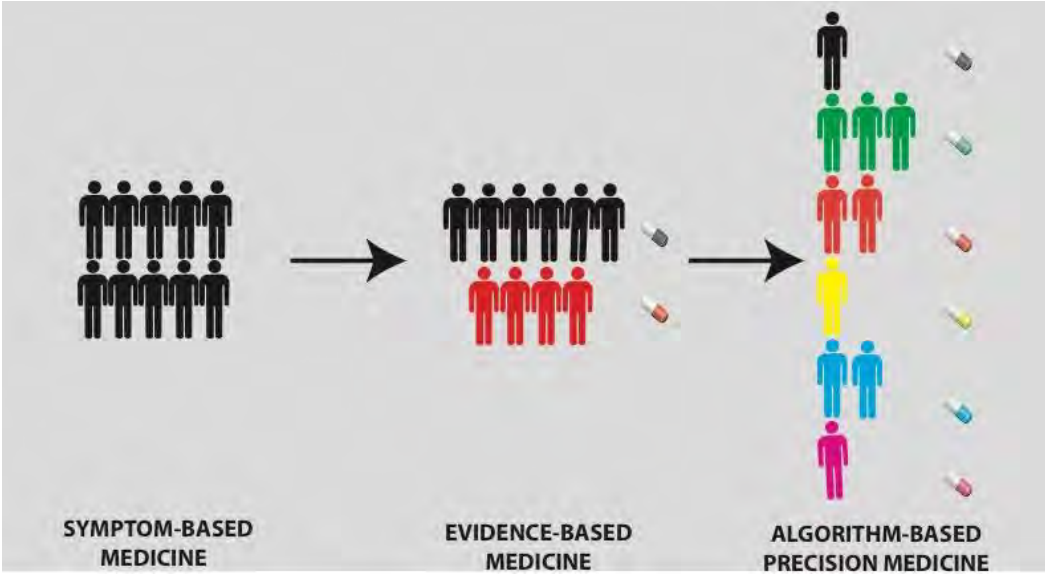
Questions from patients about therapy for Food Allergies

- What dose will protect me from ever having an allergic reaction again?
  - Possibly 300 mg daily
- How long do I have to be on therapy to be successful (in the patient's mind, "cured")?
  - As long as stay on daily therapy, you will be successful
- Will I ever be cured? If so, how long will it last?
  - We don't use that word but, we are tracking people long term (recently published Andorf, et al)
- Will I be able to eat ad lib or do I need to take the food every day?
  - Every day until 4-5 yrs out
- Can I take therapy for one food and get protection for my other food allergies?
  - no
- Will I have allergic reactions during the therapy?
  - yes
- How does it work?
  - Studying this now
- Is there anything I can do to make it work better?
  - Yes…

Excellent Questions….

We are getting there and we still have a series of studies to perform first

A paradigm shift towards precision medicine: From symptom-based medicine to evidence-based medicine to algorithm-based medicine



Muraro, et al, *Allergy* 2017

Unmet need for comprehensive prognostics for allergy resolution

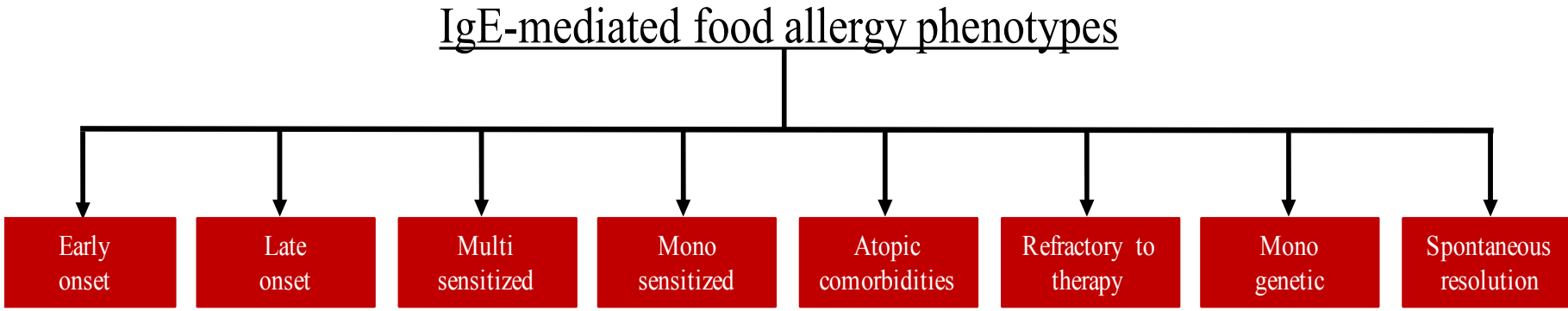
What is allergy resolution?

- Need to distinguish between desensitization versus immune tolerance
  - Refractory responses or persistence of disease despite therapy: ‘daily allergic symptoms to less than 300mg of allergen for at least 3 months’
  - Desensitization or Non Tolerance: allergic response upon re-challenge after a period of withdrawal post immunotherapy
  - Immunological ‘tolerance’: no allergic reaction upon re-challenge after a period of withdrawal post immunotherapy

Currently there is no commercially available test to determine allergy resolution in therapy trials

Mechanistic studies inform diagnostic and prognostic tests

Possible Phenotypes of Food Allergy



Muraro, et al, *Allergy* 2017

The Center at Stanford Combines 6 Integrated and Interdependent Disciplines

Research Science:

- Find the cure and the cause

-To treat and to prevent

Inpatient Research:

- Clinical trials to try new therapies

As 'First to…'

Ambulatory Wellness Research:

- Overall Wellness Focus
- Multi specialty Clinic

'One stop shopping'

Training & Education:

-Teaching the community

-Training the new scientists and clinicians in the field

Community Outreach and Community Building:

- To have community-based participation

Computation Research:

Data Sharing to build bridges and break down barriers

Recent Center Accomplishments

- 35 Papers published since April 2017
- 20 clinical trials to date, recruiting for 5, 10+ more on the horizon
- Hired two new NPs, clinical research center manager, and expanded administrative and research staff
- 8 Seed Grants awarded since 2015 — Gupta (NU), Akdis (SIAF), Nayak, Parsonnet, Luby, Sonnenberg, Oettgen (Harvard), Darmstadt
- National recognition on U.S. Senate floor by Senator Whitehouse regarding impact of climate change on health
- Internationally recognized as WAO Center of Excellence, CoFAR Center, FARE Center of Excellence, Chaired inaugural GRC in Food Allergy
- Collaborations inside and outside of Stanford, sharing data, technology, tissue samples, and expertise as far as Switzerland, London, France, Australia, and South Africa.
- Partners in the community with FARE, EAT, FASI, Safe + Fair, LPFCH and others

Moving Forward Together

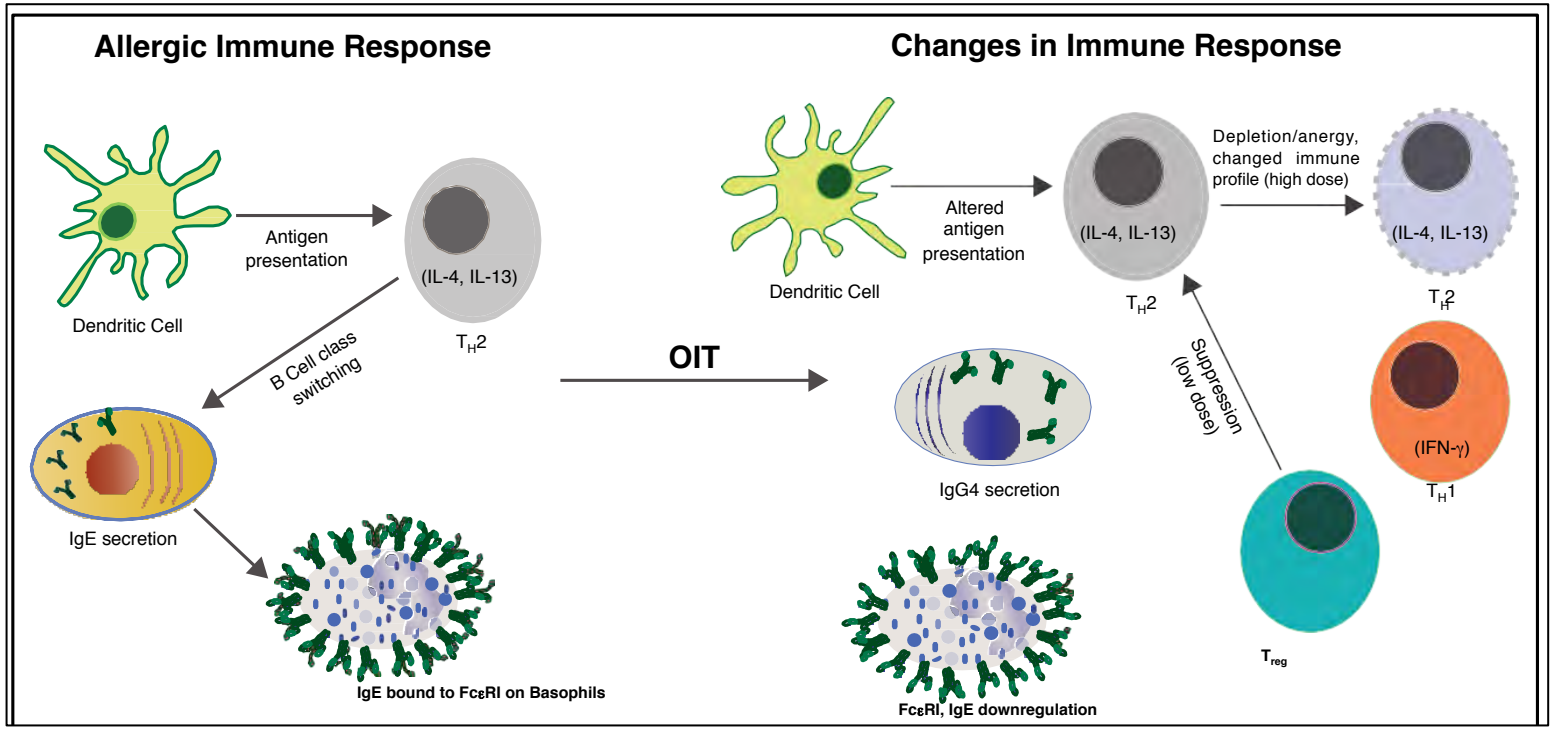
- Sensitive and specific biomarkers for determination of Food Allergy endotypes, risk of developing allergies, reaction severity, and prognosis with treatment are essential components in the path towards precision medicine.
- While progress has been made in discovery of these biomarkers, further validation and quantification is needed to allow their translation into practice in the clinical management of allergic disease.
- Findings from collaborative groups and human immunological translational studies will contribute to the drive towards precision medicine in Food Allergy and will have implications for all atopic diseases.

Recent Results of Food Allergy Research

Tina Sindher, M.D.

Stanford MEDICINE | Sean N. Parker Center for Allergy & Asthma Research

FA OIT induces changes in T cells, B cell responses (IgE and IgG4), and basophil activation



Hussey Freeland, et al, *Curr Opin in Immun* 2016

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Influential Factors in Food Allergen Immune Therapy

- Genetics? Age?
- Duration of therapy?
- Disease specific?
- Allergen specific? (allergen? Peptide? Epitope?)
- Will the mechanism of immune therapy allow for “bystander” effects?
- Will conformation of the protein play a role?
- Dose specific?
- Can we use adjuvant therapy to increase the dose to examine the role of anergy? What is the best maintenance dose? Can it be decreased after a period?
- Organ specific? What is the gastrointestinal response to IT?
- Route of dosing? (EPIT, SLIT, OIT, other)

Phase III EPIT — Viaskin Patch System (DBV Technologies)

- Breakthrough Therapy and Fast Track designations by the FDA for peanut allergy
- **PEPITES** (Peanut EPIT Efficacy and Safety) Phase III trial
  - Daily 250 µg peanut patch safety and efficacy in children 4 -11 years of age
    - Responder at 12 months
      - Baseline ED ≤10mg, 12-month ED ≥300mg
      - Baseline ED >10mg, 12-month ED ≥1,000mg
    - Significant increase in tolerability at 12 months
      - 35.3% of patients responding to Viaskin Peanut 250 µg vs 13.6% placebo (p=0.00001)
    - Mean CRD of 900mg (median 444mg) vs 360mg (median 144mg) at 12 months
    - No imbalance in SAEs observed
      - None were qualified as severe anaphylaxis
    - Most commonly reported AEs were application site reactions

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https://media.dbv-technologies.com/d286/ressources/_pdf/5/4257-PR-PEPITES-topline-results-FINAL.pdf

Phase III OIT with AR101 (Aimmune Therapeutics)

- CODIT™
  - Pull apart peanut protein capsules/sachets up to 300mg daily
  - Standardizing OIT dosing
    - Plans for other allergens
  - Protection against accidental exposure only

After one year

- 76.6% (96.3% finishing) tolerate 443mg vs 8.1% placebo
- 67.2% (84.5% finishing) tolerate 1043mg vs 4% placebo
- 50.3% (63.2% finishing) tolerate 2043mg vs 2.4% placebo

12.4% dropout due to adverse events; over half GI

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http://ir.aimmune.com/news-releases/news-release-details/aimmune-therapeutics-presents-results-positive-pivotal-phase-3

Can the effects of Food Allergen OIT last?

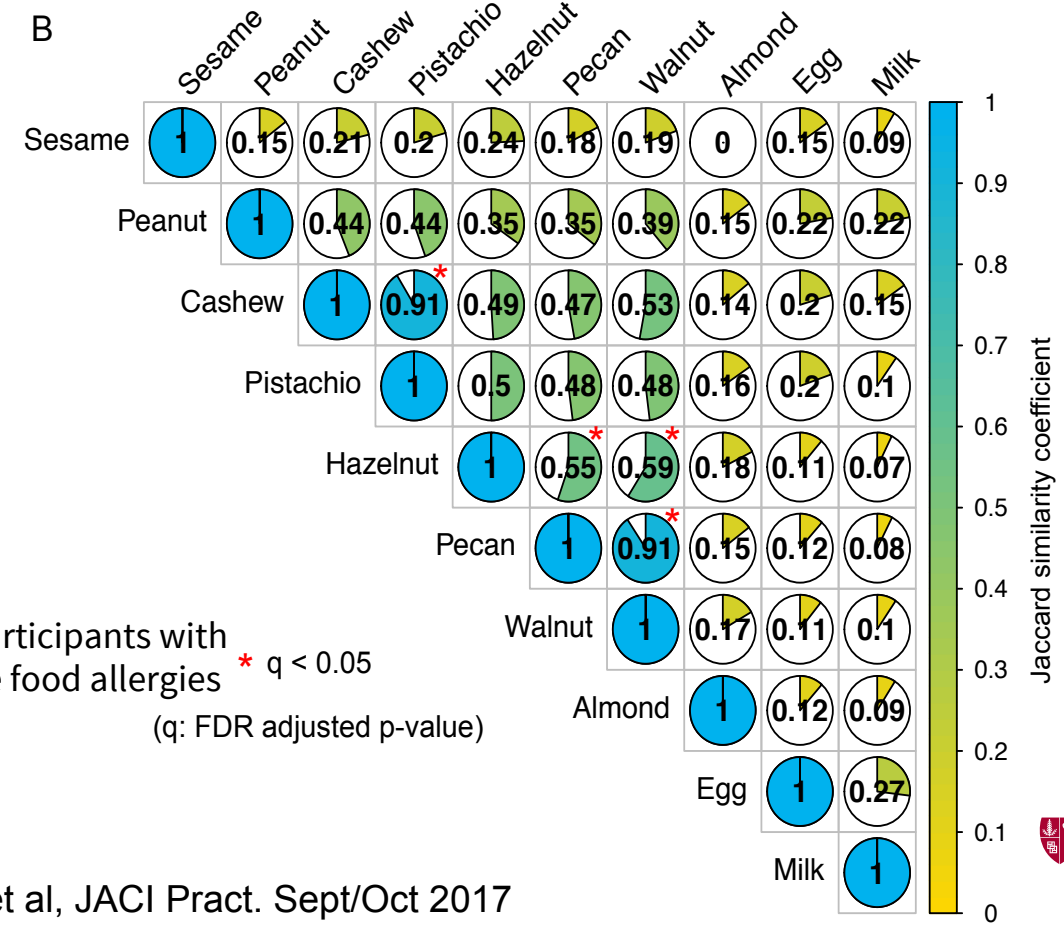
Can desensitization last?

If we test how well the food allergen is tolerated in long term follow up periods of daily OIT, does the patient maintain the same level of desensitizaton?

If we test for withdrawal to the food allergen after a period of OIT, how long can sustained unresponsiveness last?

- Burks, Jones, Wood et al. NEJM 2012--- 6-8 weeks withdrawal egg 28% sustained UR
- Vickery, et al. JACI 2014--- 4 weeks withdrawal peanut 50% sustained UR
- Syed, et al. JACI 2014--- 3 months withdrawal peanut 35% sustained UR
- Jones, et al. 2016 Long lasting Egg OIT: N=40, 4-6 weeks off OIT, then add lib unbaked egg, 55% sustained UR at 4 yrs
- Nowak-Wegrzyn, et al. Long term baked Milk: N=85, 72% tolerant to unheated milk after about 7 yrs

Baseline DBPCFCs: Cashew/pistachio and walnut/pecan/hazelnut food allergies often occurred concomitantly in individuals



n= 60 participants with multiple food allergies

* q < 0.05

(q: FDR adjusted p-value)

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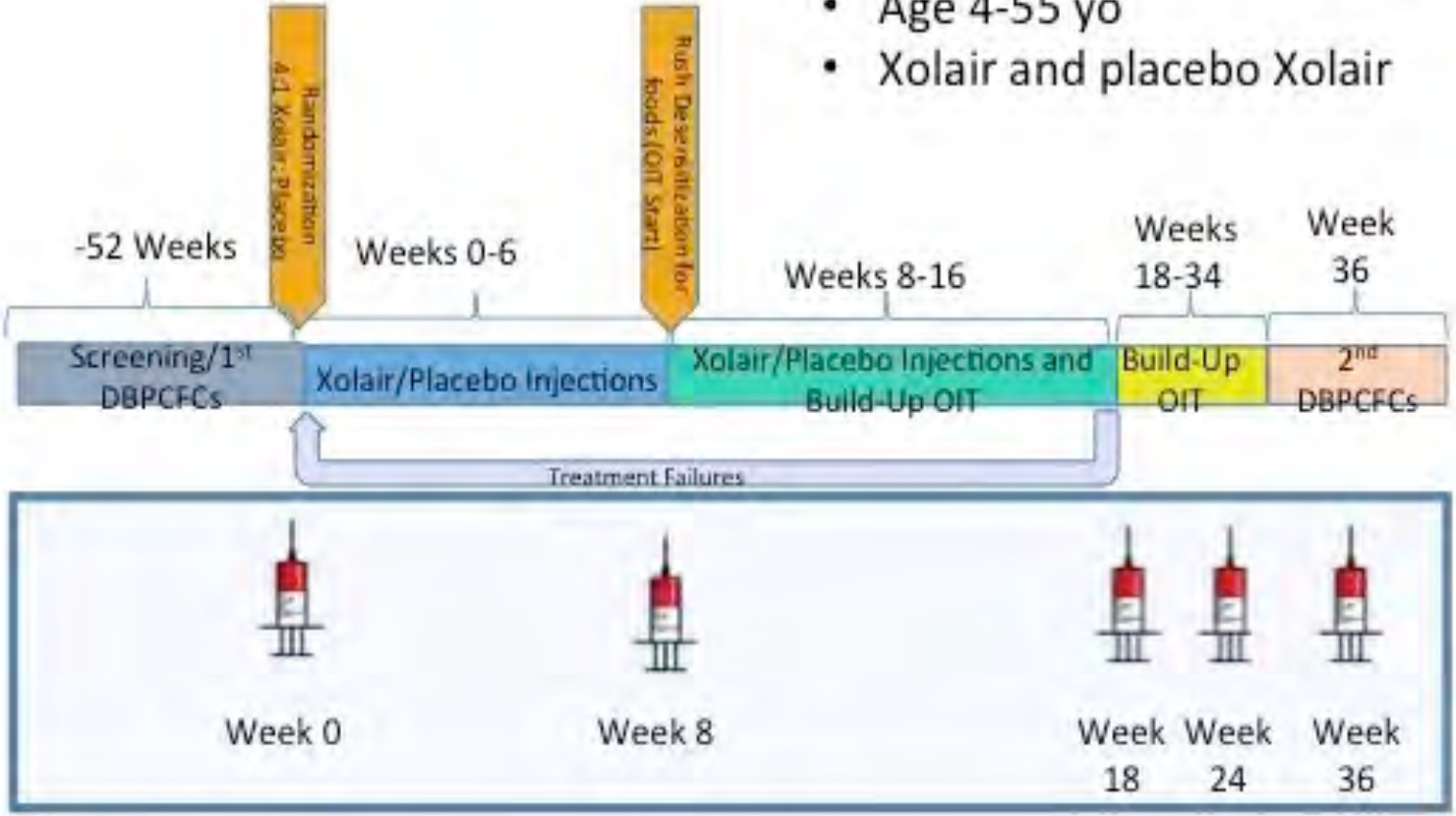
Andorf et al, JACI Pract. Sept/Oct 2017

Anti-IgE Antibody (MAPX)

- Multi-allergen study (up to 5 allergens)
- Age 4-55 yo
- Xolair and placebo Xolair



Primary endpoint reached:

Andorf, et al, Lancet Gastro & Hep, Dec 2017

Anti-IgE Antibody (MTAX)

Multi-center study, treatment through Week 30 identical to MAPX

- Randomized to 0mg, 300mg, or 1g maintenance therapy after desensitization
- Insight into sufficient daily dosing to maintain tolerance after desensitization
- Evaluating proportion able to tolerate ≥2g of at least 2 of their allergens after 6 weeks of lower maintenance dosing

Publication of results soon

- **Preliminary results currently on clinicaltrials.gov**
- **Findings highlight**
  - **Ability to reduce dose after achieving desensitization**
  - **Importance of continuing some level of exposure after desensitization**

Results of long term follow up at Stanford

- 46 participants who previously passed 2 g challenge were placed on a low dose (300 mg) or high dose (2 g) maintenance dosing
- Safety results did not differ between the low and high group
  - Reactions recorded in 2.29% of maintenance doses
  - 88.9% of allergic reactions were mild
  - 10.69% moderate
  - 0.41% severe
    No anaphylaxis or epinephrine used
- Frequency of allergic adverse events decreased over time
- Regardless of group (low vs. high) a significant trend of increasing allergen-specific IgG4/IgE ratios continued throughout the study

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Andorf, Monahar, et al., Allergy, Asthma & Clin Immuno, Dec 2017

Meta-analysis: Allergen immunotherapy for IgE-mediated food allergy

- AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. This **evidence comes mainly from studies in children, and it is therefore still unclear if AIT is effective for adults.**
- Pooling of safety data demonstrated an increased risk of local and systemic reactions with AIT. No fatalities were reported during AIT. Only one study assessed QoL (23), which reported no comparative results between OIT and the control group.
- No data investigating cost-effectiveness of AIT for food allergy.

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Nurmatov, et al, Allergy, 2017

Future Therapies

- Many Phase 2 and 3 studies underway currently (ITN, CoFAR, DBV Technologies, Aimmune, etc.)
- Community Based Participation
- Working together, including many centers globally----private and academic
- Improve therapies from OIT---- focus on improving SAFETY and efficacy
- Possible use of combination therapy in specified patient populations
- Focus on mechanisms to discover new targets for rationally-designed drugs
- Establish consistent endpoints
- Establish similar entry criteria
- Establish “threshold” level for majority for maintenance
- Establish “minimum time” period for maintenance
- Customize and personalize medicine—Mechanistic studies needed

Primary literature: Tanabe S (2007) , Chuang YH, et al. (2009) , Chua, et al. (2006), Li XM, et al. (2003), DeLong JH, et al. (2011), Li X, (1999),
Reviews: McWilliams, et al. (2012) , Yang, et a. (2013), Jones, et al. (2014).

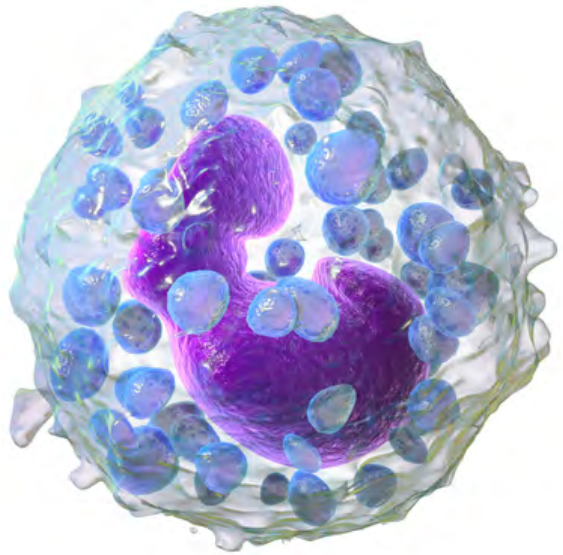

Photo by Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". *WikiJournal of Medicine* 1 (2). DOI:10.15347/wjm 2014.010. ISSN 2002-4436.

Analyzing basophils* in allergic diseases

Stephen J. Galli, MD

** Basophils usually are only 1-2% of all white cells in the blood.*

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What is an “allergic reaction”?

- “Allergic” means that one is **already reactive**, due to known (or unknown) prior exposure to the allergen (food).
- ***Left:*** Allergic people have **IgE antibodies** that bind to **FcεRI** (high affinity receptors) on surface of (1) **mast cells** (located in **tissues**) and (2) **basophils** (circulating in **blood**).
- ***Right:*** On **re-exposure** to allergen, mast cells and basophils **rapidly (in seconds to minutes)** release histamine and other mediators.

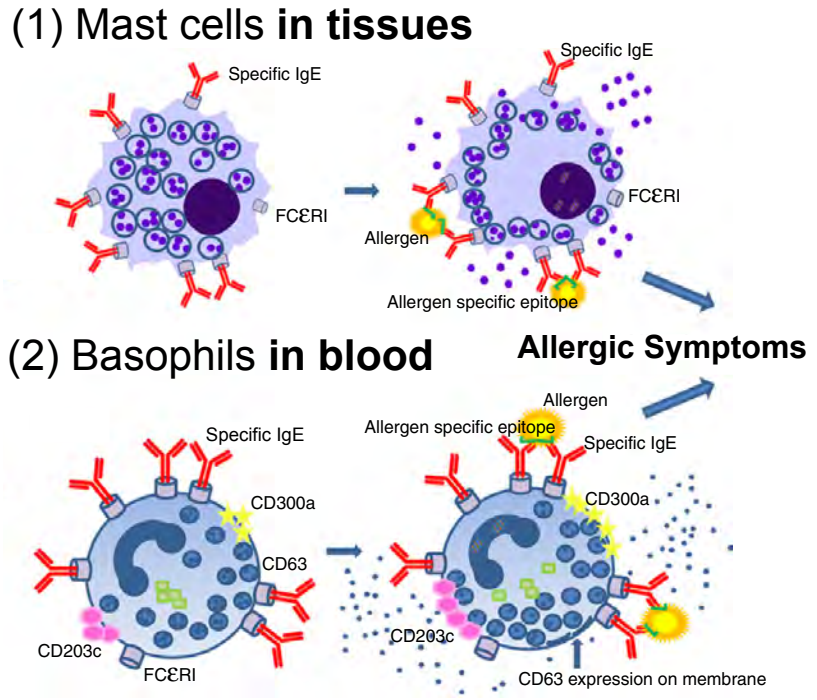


Illustration is from Figure 1 in Broekman HCH, Eiwegger T, Upton J, Bøgh KL: IgE – the main player of food allergy. *Drug Discovery Today: Disease Models* 2015; **17-18**:37-44.

What to test to document susceptibility to an "allergic reaction"?

- Food allergies are (mostly) caused by **IgE** antibodies **vs. food components** that bind to **FcεRI** (high affinity receptors) on surface of (1) **mast cells** (located in tissues) and (2) **basophils** (circulating in blood).
- In people who are sensitized (i.e., they **already have IgE to food allergens**), it is simpler to test **blood basophils** than **tissue** mast cells.

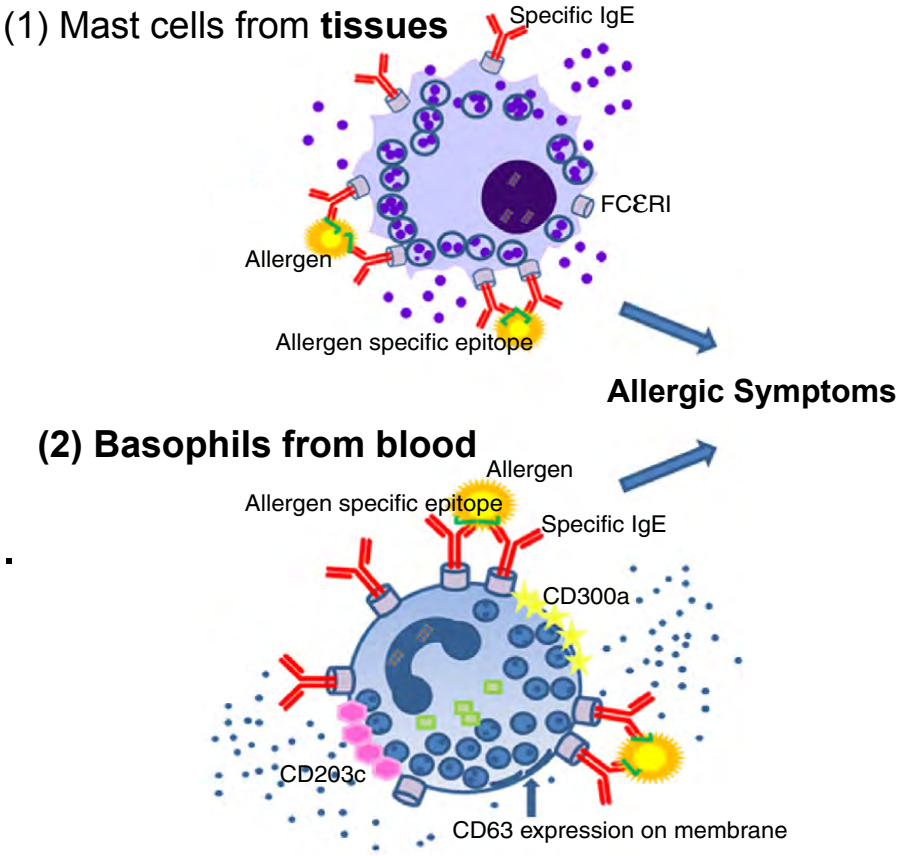
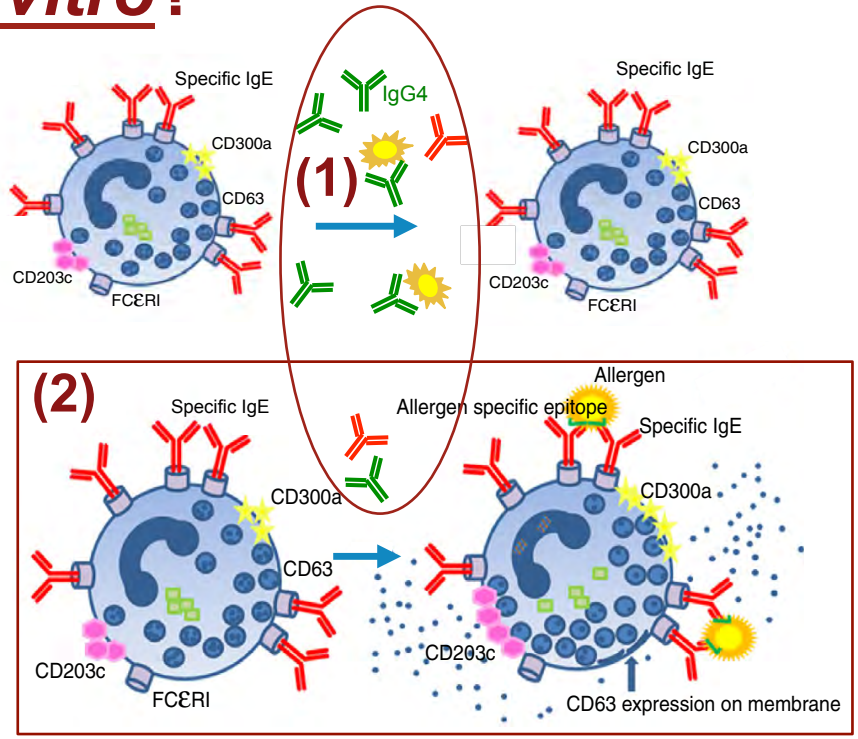


Illustration is from Figure 1
in Broekman HCH, Eiwegger T, Upton J, Bøgh KL: IgE – the main player of food allergy. *Drug Discovery Today: Disease Models* 2015; **17-18**:37-44.

How can allergic reactivity be assessed by testing blood basophils *in vitro*?

- ***In vivo*, active** food allergic reactions are caused by IgE antibodies vs. food components (on mast cells [**top**] and basophils [**bottom**]) and **need immediate treatment – no time for testing!**
- **However, the risk to develop an active reaction** can be assessed ***in vitro*** by testing: (1) blood for IgE (and certain IgG [IgG4]) antibodies, and, more accurately, **(2) basophil reactivity to the food allergen (in blood).**



Modified from Figure 1 in Broekman HCH, Eiwegger T, Upton J, Bøgh KL: IgE – the main player of food allergy. *Drug Discovery Today: Disease Models* 2015; **17-18**:37-44.

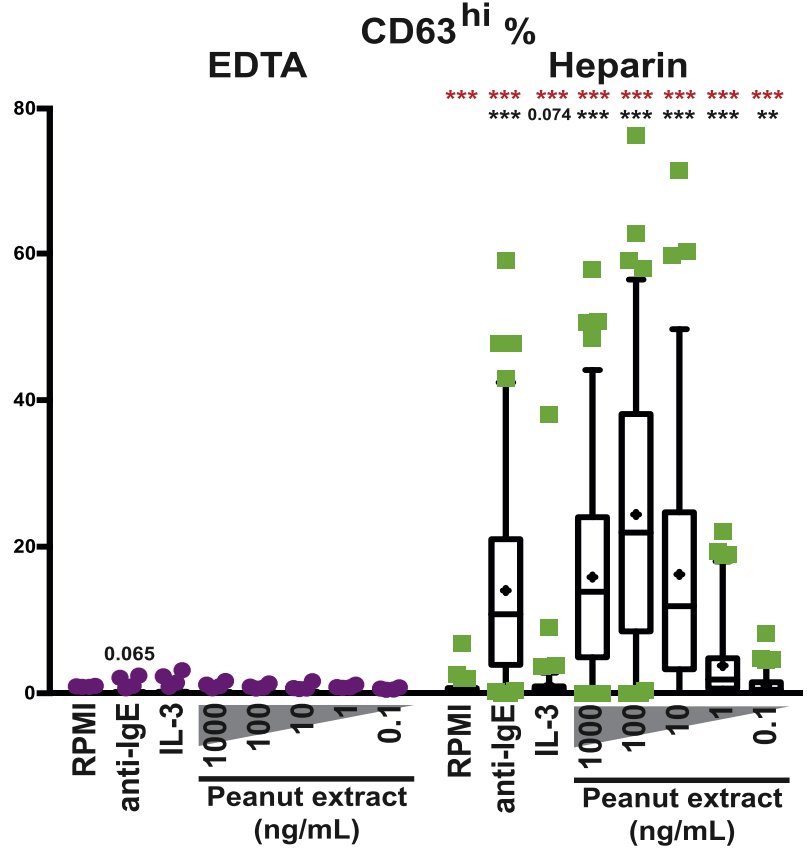
Unfortunately, there is no “standard” test for basophil activation by food allergens.

- Tests vary in **how** the basophils are prepared for testing, and **what tests of basophil activation** are done.

- We developed an approach for testing **blood basophil** reactivity to the food allergen that can be performed in heparinized blood maintained at 4^{o}C for 24 hours

  (Mukai K, Gaudenzio N, Gupta S, Vivanco N, Bendall SC, Maecker HT, Chinthrajah RS, Tsai M, Nadeau KC, Galli SJ. Assessing basophil activation by flow cytometry and mass cytometry in blood stored 24 hours before analysis. *J Allergy Clin Immunol* 2017; **139**:889-99.e11)

Our test for basophil activation by food allergens (peanuts) – *using standard flow cytometry**.



* Testing for % of surface $CD63^{hi}$ basophils in blood anti-coagulated with heparin (not with EDTA) and stored at 4°C for 24 hours

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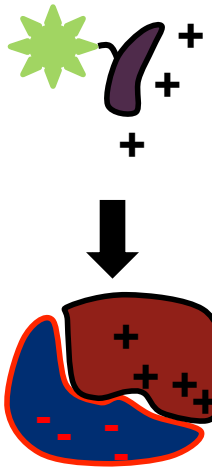
A new test of basophil activation by food allergens – *based on detecting degranulation*.



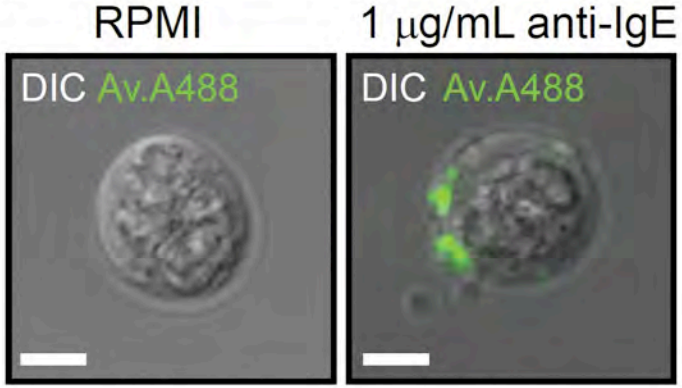
Fluorochrome-coupled avidin (cationic)

Proteases (cationic)

Proteoglycans (very anionic)

Human basophils

Confocal microscopy analysis

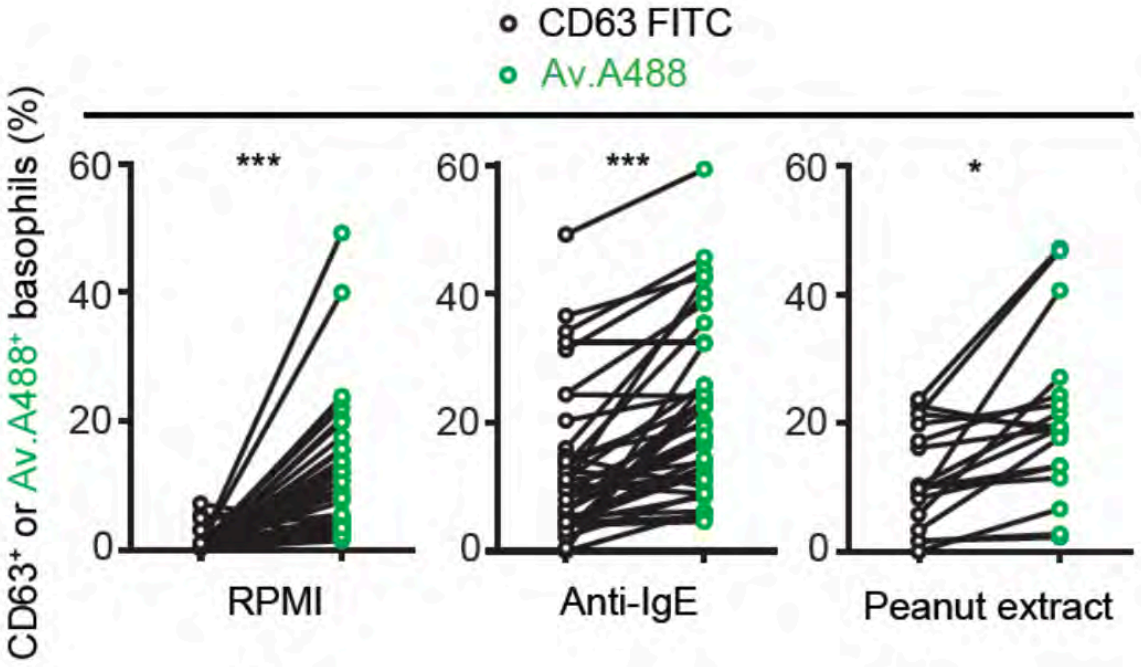


Avidin binds to **released** basophil granule proteoglycan, **directly detecting basophil degranulation** without need for "indirect" assessment of degranulation with conjugated antibodies.

(Mukai K, Chinthrajah RS, Nadeau KC, Tsai M, Gaudenzio N*, Galli SJ* (* co-corresponding authors). A new fluorescent-avidin-based method for quantifying basophil activation in whole blood. *J Allergy Clin Immunol* 2017; **140**:1202-6.e3)

With our new test, people with food allergy have basophils with *evidence of past/ongoing activation*.

In contrast to standard basophil activation testing with conjugated antibodies (**CD63 FITC**), our new test (**Av.A488**) detects basophils at "baseline" (in medium alone [**RPMI**]) with evidence of **past activation** in food allergic donors.



(Mukai K, et al. *J Allergy Clin Immunol* 2017; **140**:1202-6.e3)

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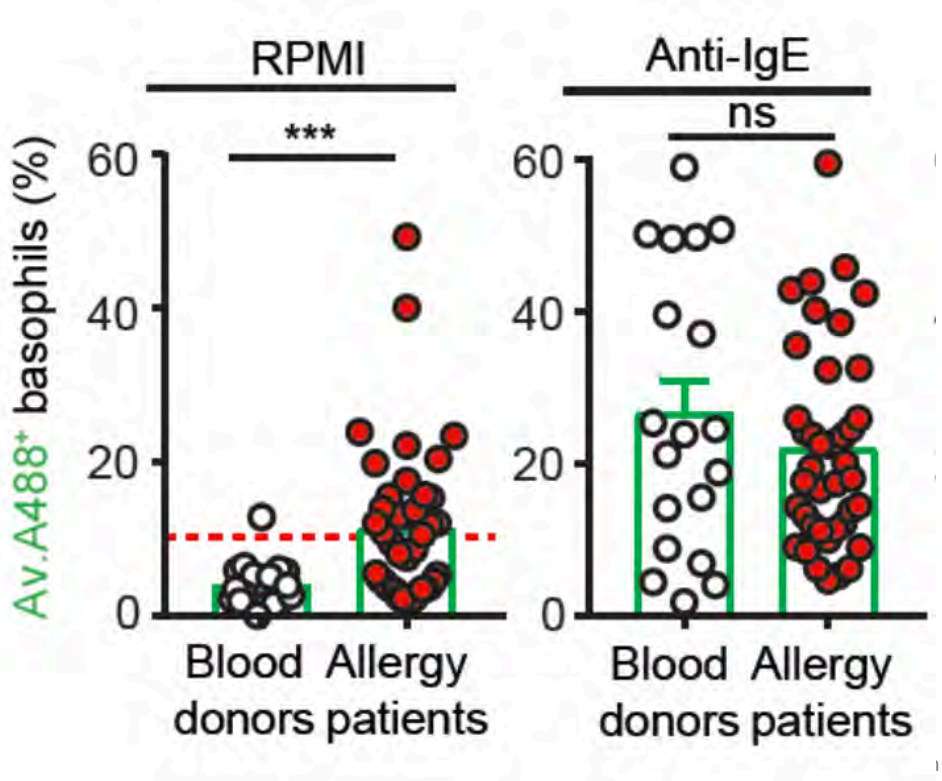
With our new test, food allergic people (in red) have basophils with *evidence of past/ongoing activation*.

- Our new test (with **Av.A488**) detects basophils with evidence of **past activation** in medium (**RPMI**)-treated basophils of food allergic donors (**red** symbols) compared to non-allergic donors (**white** symbols).

(Mukai K, et al. *J Allergy Clin Immunol* 2017; **140**:1202-6.e3)



Summary: New forms of basophil testing are providing new insights into food allergy.

- We have developed a **standard basophil activation test** (with antibodies vs. CD63) that can be performed on **blood stored 24 hours at 4ºC – *promising more uniformity of such testing***.
- This test documents that OIT results in **the loss in sensitivity of basophils** of food allergic subjects to induction of IgE-dependent allergic reactions by small amounts of food allergen – **this *in vitro* assay may largely replace the need for *in vivo* food challenges**.
- We have developed a **rapid, inexpensive new test, based on detection of the basophil's granule contents**, that also can detect basophils with apparent evidence of **past activation** in food allergic donors.

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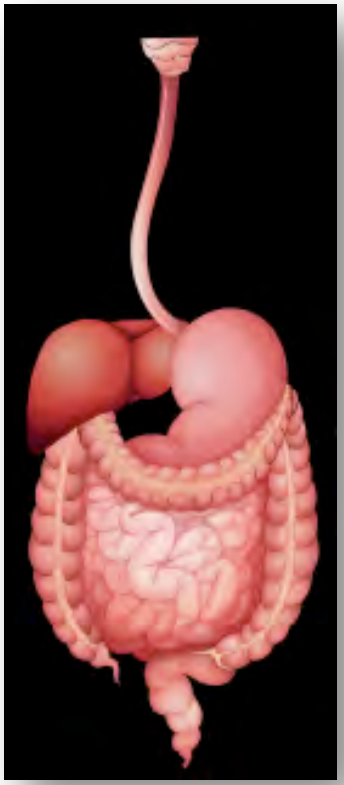
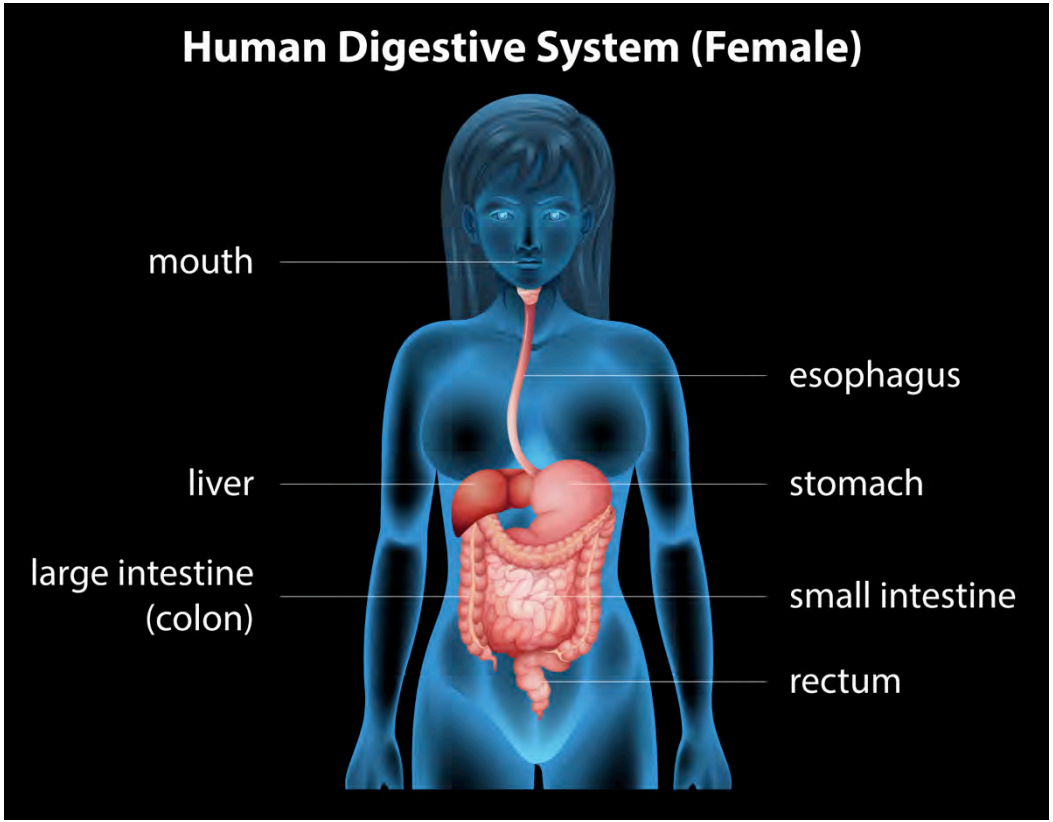


Eosinophilic Gastrointestinal Disease

Nielsen Q. Fernandez-Becker, MD, PhD

Stanford MEDICINE | Sean N. Parker Center for Allergy & Asthma Research

The Gastrointestinal (GI) Tract



- **Digestion**
- **Absorption**
- **Motility**
- **Immune function**

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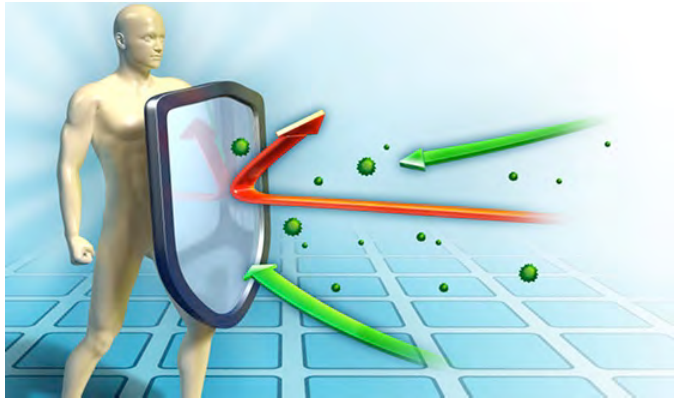
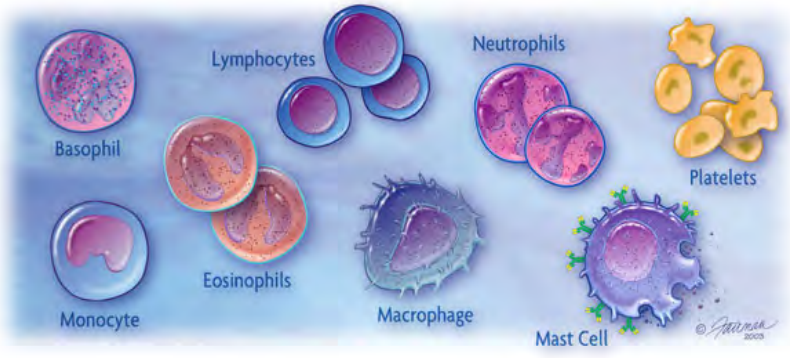
GI tract is our biggest immune organ and helps keeps us healthy…





Immune cells

Immune dysfunction = disease

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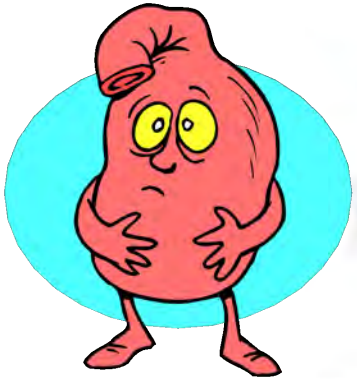
https://www.liverdoctor.com/strengthen-immune-system-selenium/

When things go wrong in GI tract...



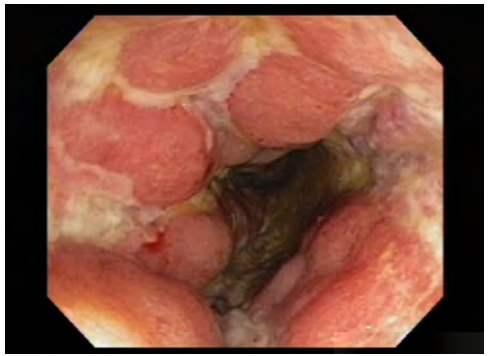
Immune mediated GI disease

- **Inflammatory Bowel disease (IBD)**
  -Crohn's disease
  -Ulcerative colitis

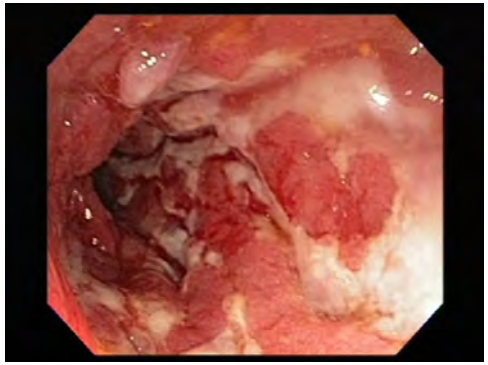
- **Celiac Disease**

- **Eosinophilic GI disorders (EGID)**

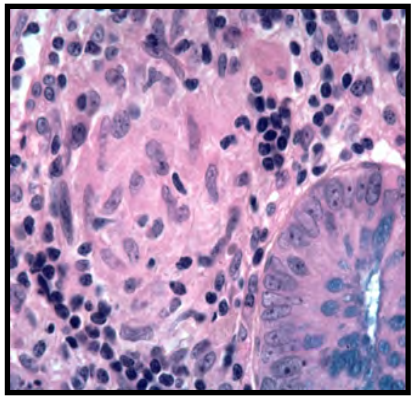
Inflammatory Bowel Disease



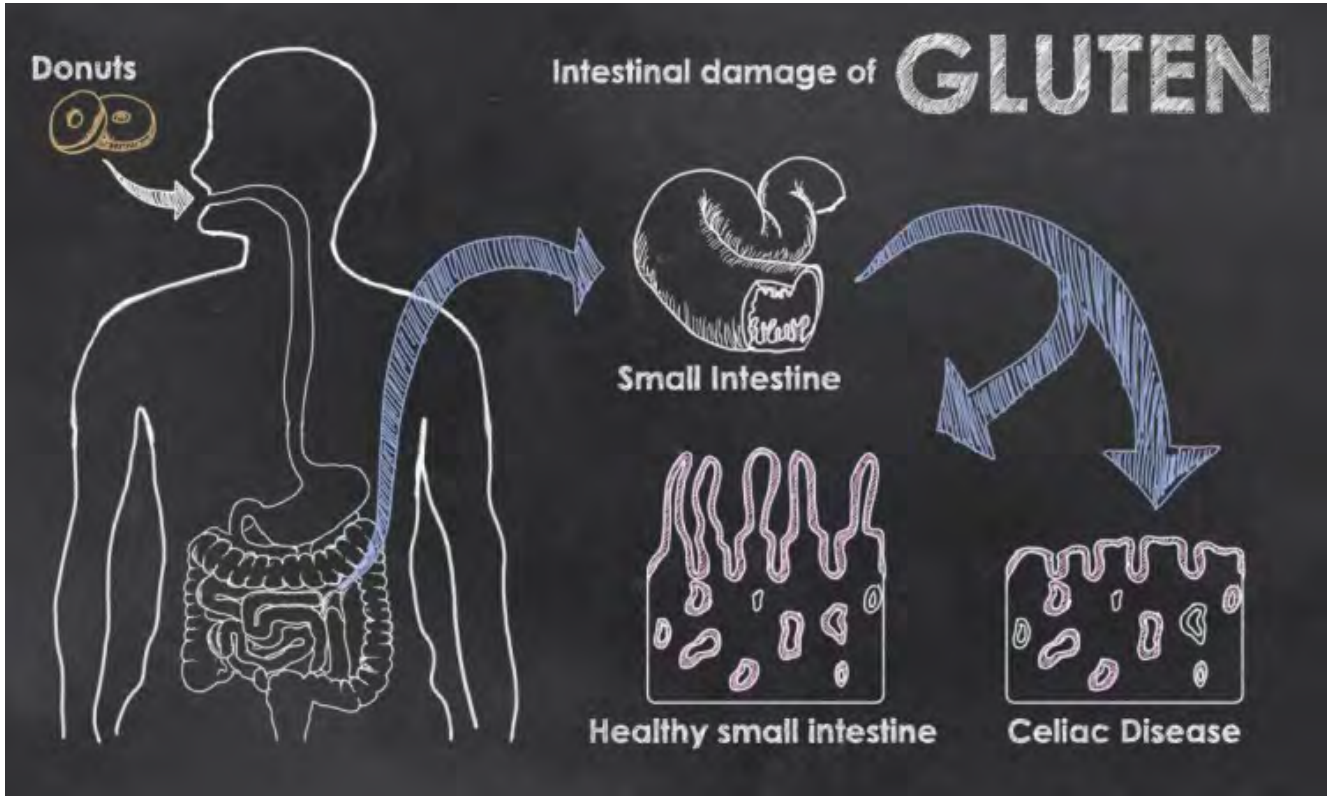
Sigmoid colon



Terminal ileum

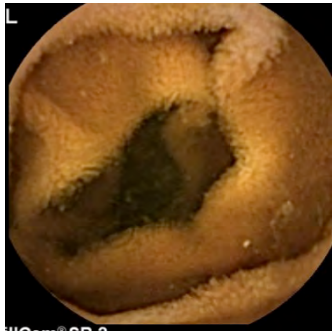


Celiac Disease

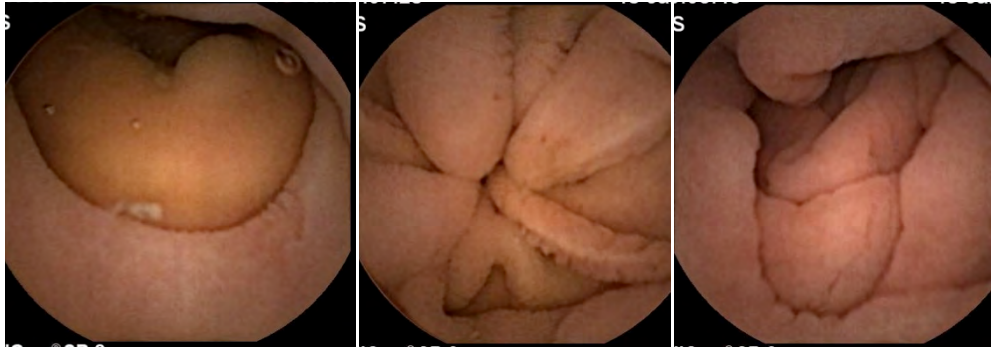


https://www.goodforyouglutenfree.com/information-celiac-disease/

Celiac Disease

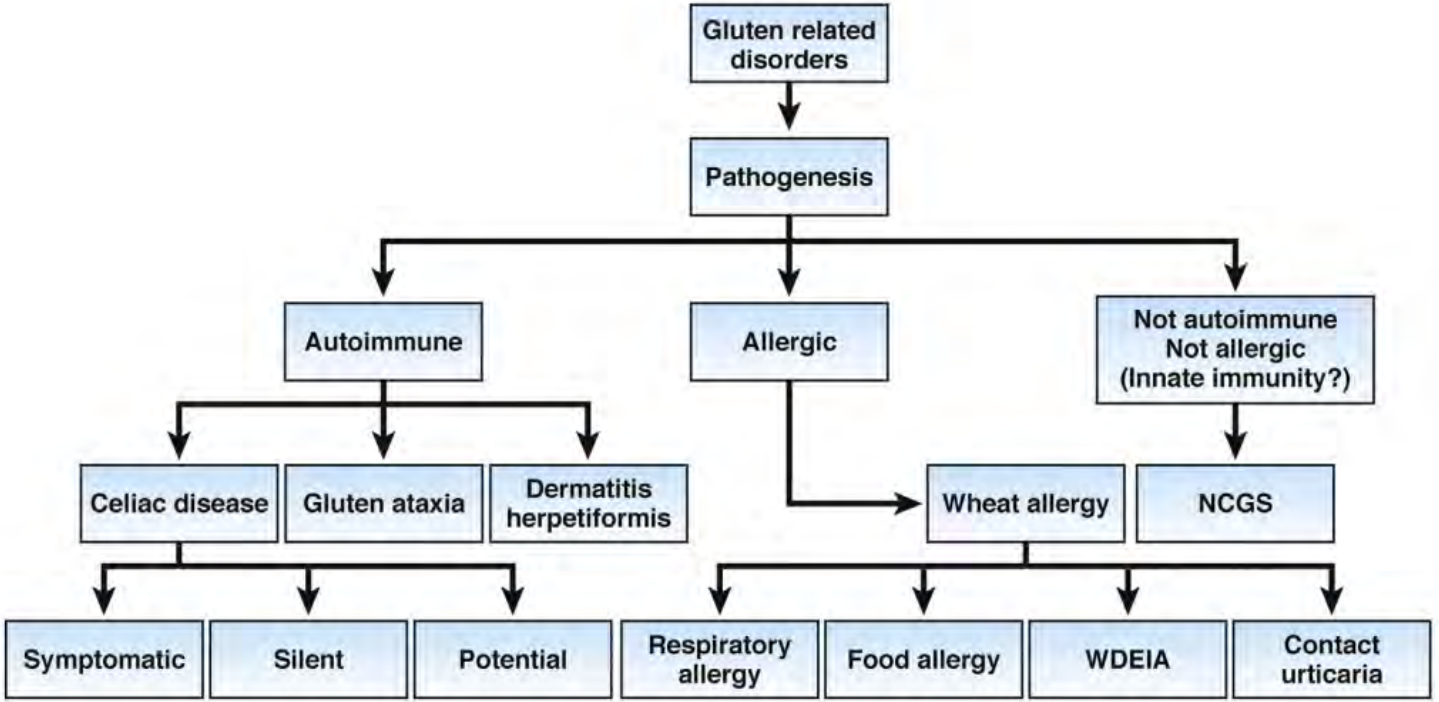


Normal



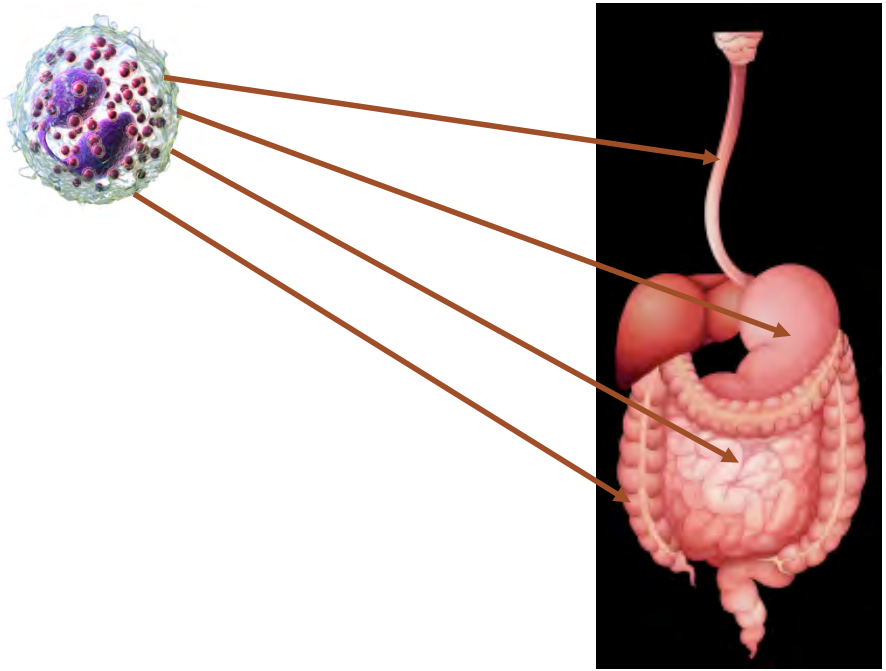
Celiac disease

Non-celiac gluten sensitivity (NCGS), Wheat Allergy and Celiac disease

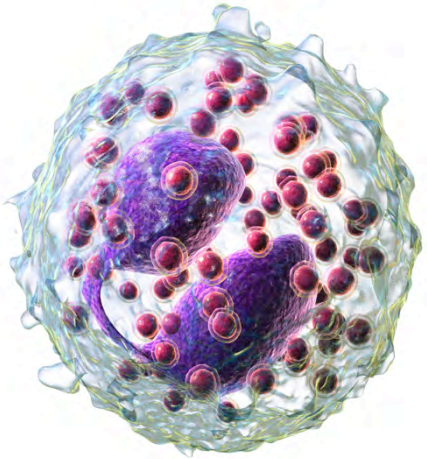


Fasano et al. Nonceliac gluten and wheat sensitivity. Gastroenterology. 148: 1195-1204

What is eosinophilic GI disease?



What are Eosinophils?



Eosinophils are a type of white blood cell
That was first discovered in 1846

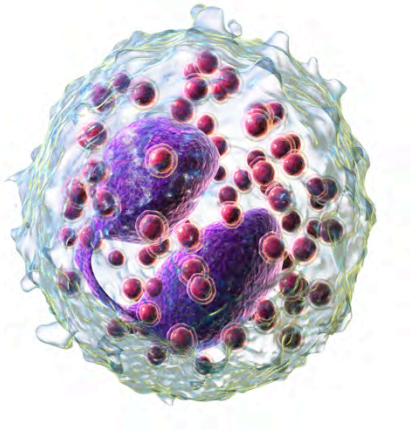
Eosin = red dye
Philic = loving
ie. look red under microscope

What do Eosinophils do?

Eosinophils:

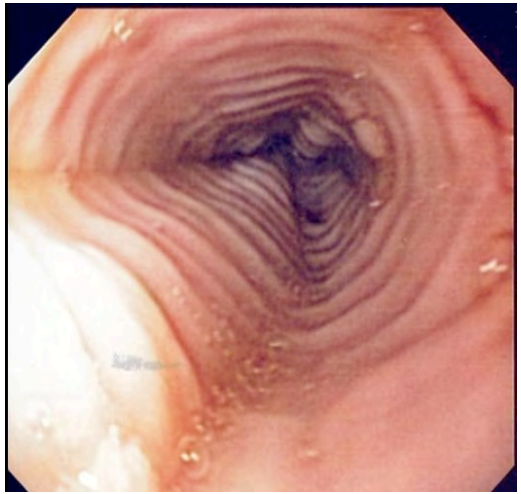
Protect us from parasites, viruses
Are involved in development
Play a role in allergic diseases

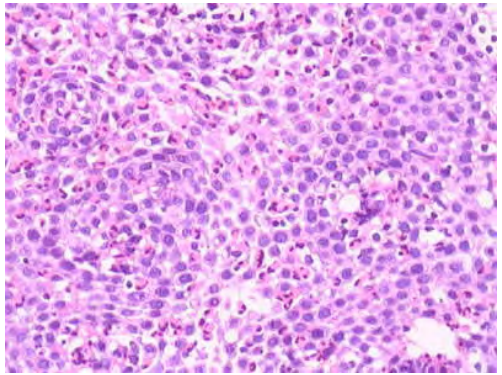
- **-bronchial asthma**
- **-allergic rhinitis**
- **-atopic dermatitis**
- **-eosinophilic GI disease**



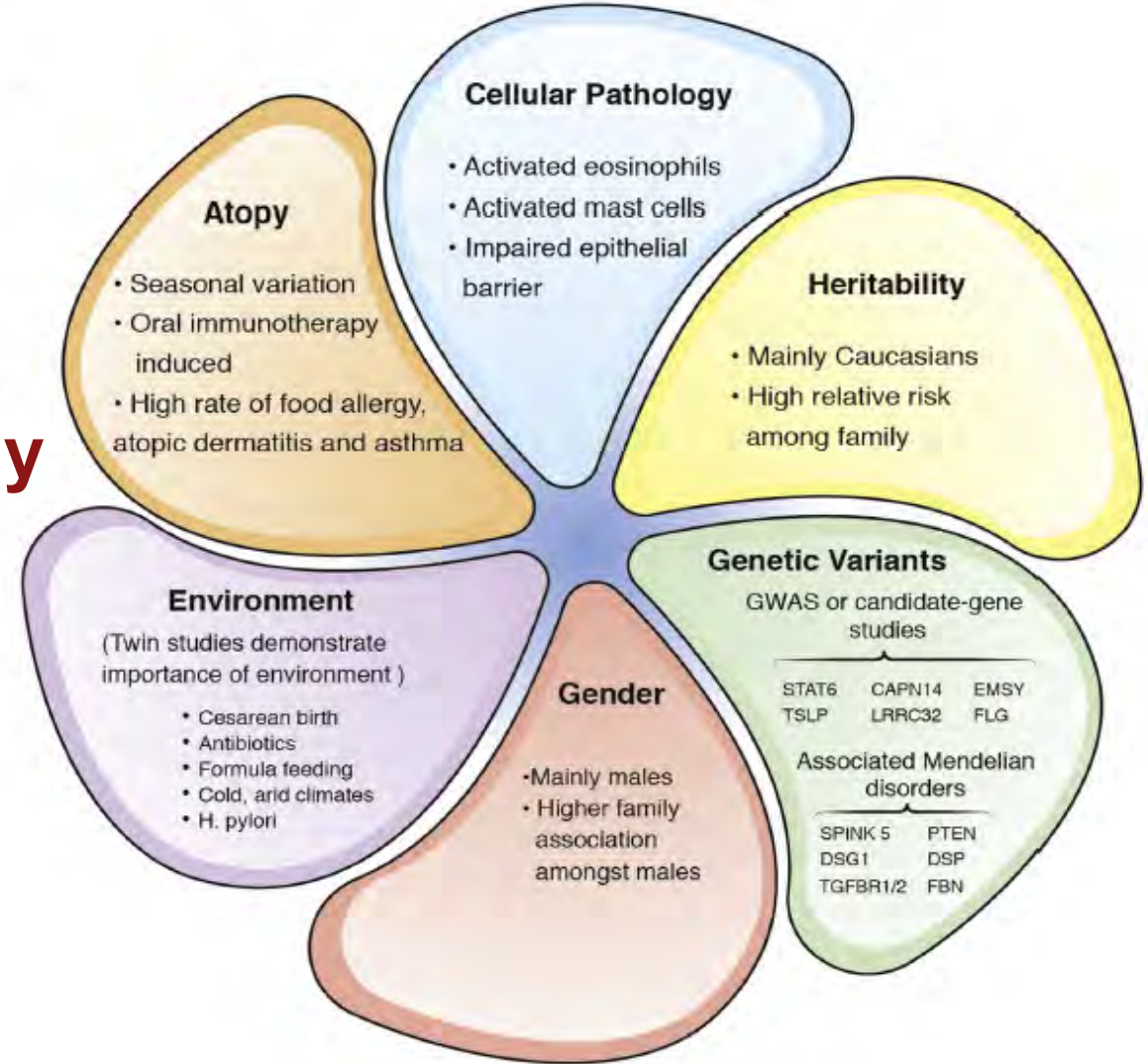
Eosinophilic Esophagitis

Clinicopathologic disease characterized by symptoms of esophageal dysfunction and esophageal eosinophilia



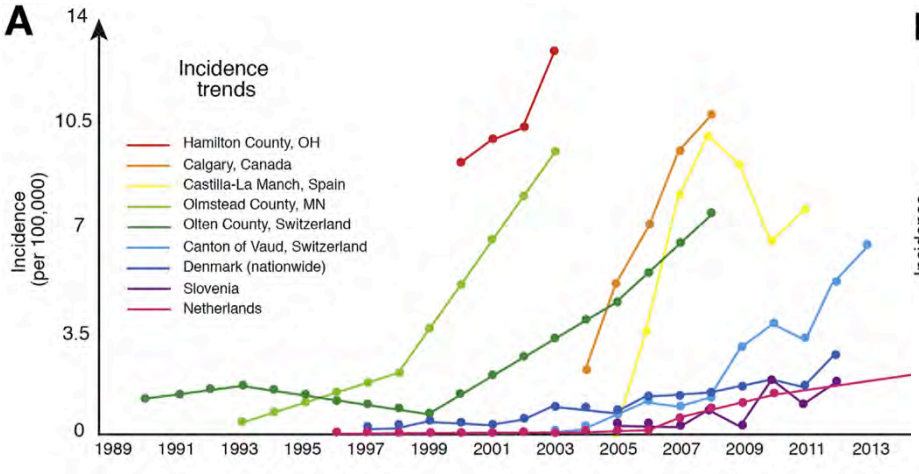


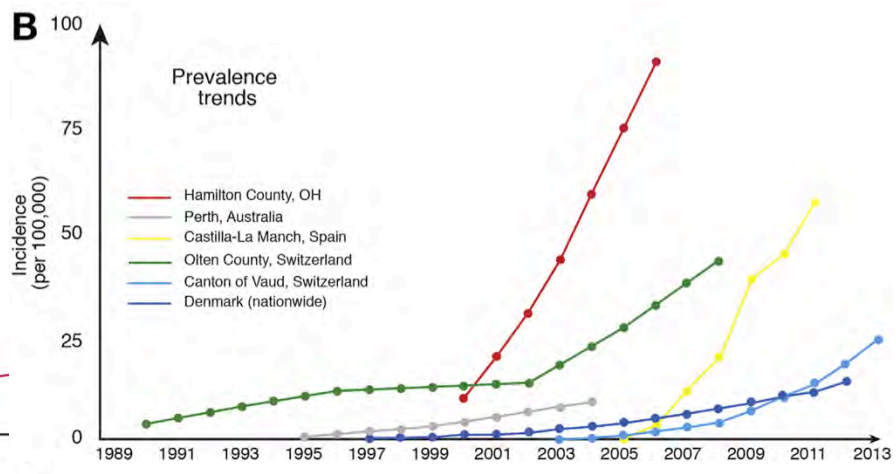
Eosinophilic esophagitis pathophysiology



Gastroenterology 2018;154:333–345

Epidemiology



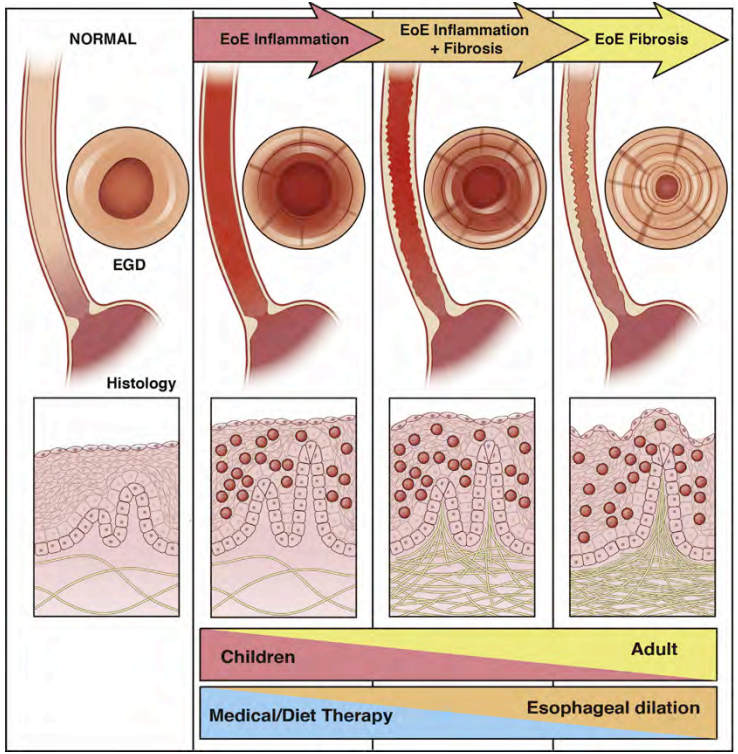


Gastroenterology 2018; 154:319

Eosinophilic esophagitis: Clinical Presentation

Table 1. Symptoms of EoE in Children vs Adults

Children	Adults
Failure to thrive	Dysphagia
Feeding difficulties	Eating slowly
Nausea and vomiting	Solid food avoidance
Abdominal pain	Avoidance of social eating
Heartburn	Chest pain
Picky eating	Heartburn



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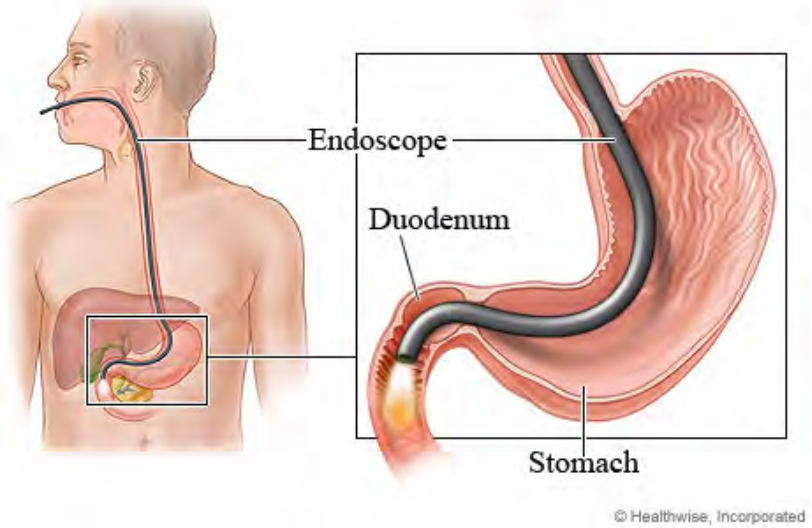
Gastroenterology 2018; 154:319
Gastroenterology 2018; 154:346

Eosinophilic Esophagitis: Diagnosis

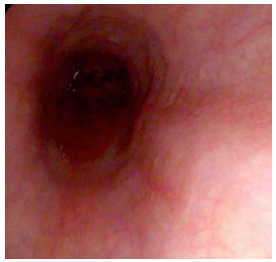
- 2-4 biopsies should be obtained from at least two locations in the esophagus (distal and proximal)
- Higher the number of biopsies the higher the diagnostic yield.
- with 6-9 biopsies sensitivity close to 100%



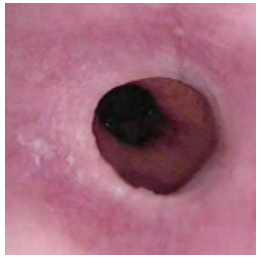
Gut 2016; 65:524
Dellon et al, Am J Gastroenterol 2013

Eosinophilic Esophagitis

Normal



Eosinophilic esophagitis



EoE: therapy: 3 Ds

Drugs:

- Proton Pump Inhibitors (PPI)
- Topical Steroids

Diet:

- Elemental Diet
- Elimination diet (Six Food elimination diet)

Dilation

Gastroenterology 2014;147:1238-1254

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Goals of treatment

1. Improve symptoms
2. Histologic remission: <15 Eos/HPF
3. Improve esophageal function
4. Maintain esophageal lumen >15 mm

Emerging therapies

Table 2. Emerging Therapies in EoE

Emerging Therapies	Type	Mechanism
RPC4046	Anti–IL-13 antibody	IL-13 regulates multiple genes within the EoE transcriptome, including eotaxin-3, desmoglein 1, periostin, and filaggrin
OC000459	CRTH2 inhibitor	CRTH2 is important for chemotaxis of eosinophils
Reslizumab/mepolizumab	Anti–IL-5 antibody	IL-5 specifically stimulates expansion of eosinophils
Dupilumab	Anti–IL-4Rα antibody	IL-4rα is a high-affinity receptor for IL-4, which induces Th2 cell differentiation, and receptor for IL-13
Benralizumab	Anti–IL-5Rα antibody	IL-5Rα is the high-affinity receptor for IL-5, which stimulates expansion of eosinophils. The drug depletes eosinophils

CRTH2, chemoattractant receptor-homologous molecule; EoE, eosinophilic esophagitis.

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Gastroenterology 2018;154:333–345

Eosinophilic Gastroenteritis

Involved organ	Mean eosinophil density in normal conditions	Minimum eosinophil count required for diagnosis	Histopathologic features	Clinical manifestations
Esophagus	<5/hpf	15/hpf in the epithelial layer	Elongated papillae and basal zone hyperplasia of the epithelial layer with eosinophilic infiltration of the lamina propria and muscularis mucosae Eosinophilic microabscesses	Esophageal dysfunction, including dyspagia, food impaction and GERD-related symptoms
Stomach	2/hpf in lamina propria† No intraepithelial eosinophils†	>20–30/hpf	Sheets of eosinophils, edema, eosinophilic degranulation and cryptitis	Dyspepsia, nausea/ vomiting, epigastric pain, gastric outlet obstruction and ascitis
Duodenum	10/hpf in lamina propria Minimal intraepithelial eosinophils	>20–30/hpf	Sheets of eosinophils, edema, eosinophilic degranulation, cryptitis Eosinophilic infiltration of lamina propria, muscle fibers and serosal layer Hypertrophic muscle layer	Gastric outlet obstruction, abdominal pain, diarrhea, weigh loss, malabsortion findings, perforation and ascitis
Ileum	13/hpf in lamina propria† Minimal intraepithelial eosinophils†	>20–30/hpf	Sheets of eosinophils, edema, eosinophilic degranulation, cryptitis Eosinophilic infiltration of lamina propria, muscle fibers and serosal layer Hypertrophic muscle layer	Abdominal pain, small bowel perforation, small bowel obstruction and ascitis
Large bowel	8–30/hpf†	>20–50/hpf (depending on location)	Eosinophil and lymphocyte infiltration of the lamina propria and the presence of intraepithelial eosinophils in the crypts	Diarrhea, bloody diarrhea, abdominal pain and constipation
Bile ducts/ pancreas	Unknown	Unknown	No data available	Jaundice, cholestasis, epiastralgia, altered liver function tests and dilated bile ducts

Expert Rev. Gastroenterol. Hepatol. 6(5), 591-601

Why do we need to treat?

Supportive Services: When Social, Emotional, and Behavioral Concerns Arise

Marte J. Matthews, MA, LMFT

Stanford MEDICINE | Sean N. Parker Center for Allergy & Asthma Research

When Social, Emotional & Behavioral Concerns Arise

Social concerns

Examples: clinging to parents, refusing to participate socially, acting immature for their age

Emotional concerns

Examples: feeling scared, worried, or annoyed a lot of the time, shutting down, crying, grumpy, or unexplained headaches, stomach aches, or other aches & pains

Behavioral concerns

Examples: arguing with parents, refusing to cooperate with parent's requests, procrastinating & avoiding doing things

When Social, Emotional & Behavioral Concerns Arise

FEAR

- Fear, by itself, is not “bad.”
- Fear, can be very helpful in just the right amount
- Too much fear can do more harm than good

When Social, Emotional or Behavioral Concerns Arise

When we *accept* our fears,

instead of fighting them,

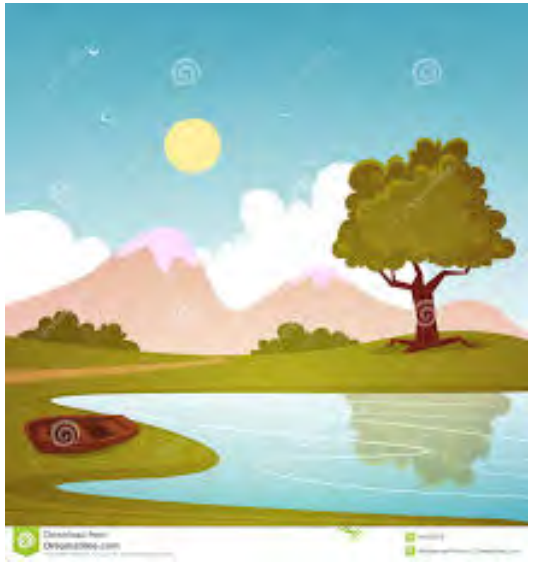
we can learn ways

to manage fears better.

When Social, Emotional & Behavioral Concerns Arise

Coping Style: RELAXATION

Coping Style: DISTRACTION



When Social, Emotional & Behavioral Concerns Arise

Relaxation Technique:

"Box"

Breathing

When Social, Emotional & Behavioral Concerns Arise

Distraction Technique:
Change the
Channel

When Social, Emotional & Behavioral Concerns Arise

HURTFUL THINKING

OMG, my friend is having a party, but I'm scared. What if they have all this food I can't eat? Forget it! I don't want to go anyway!

HELPFUL THINKING

I'm getting freaked out. What can I do? I need to figure out how to deal with this. OK, I need to take a break to calm down. We can call ahead and ask about the food. We can offer to bring a safe food to share that would taste good for everybody. I can eat enough before I go the party so I won't be too hungry. I know my friend Aisha will help me because she 'gets it.' Maybe I can go.

When Social, Emotional & Behavioral Concerns Arise

Fears *can* be put in their place

& kept at the right size.

You can learn ways to stay calmer,

and be happier,

one step at a time.

FAMILIES FACING FOOD ALLERGIES

A Free Monthly Support Group in San Jose for parents and guardians of kids of any age with food allergy.

12 NOON	**May 22**	**7:30 PM**	**June 26**
	July 24		**August 28**
	September 25		**October 23**

3880 S. Bascom Ave, near Highways 85 & 17

***RSVP* for details including suite # and security code:**
marte@childfamilygroup.com

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Food Allergy Immunotherapy:
Current & Future Directions

Andrew Long, PharmD

Stanford MEDICINE | Sean N. Parker Center for Allergy & Asthma Research

Food Allergy Background

Incoming food broken down by antigen-presenting cells

- Fragments presented to naïve T cells
- In certain proinflammatory micro-environments
  - Causes activation & differentiation into T helper 2 cells
    - Th2 cells promote B cell IgE antibody production
      - Allergen-specific IgE rest on mast cells and basophils

Allergen re-exposure

- IgE on mast cells and basophils bind the allergen
- Mast cell/basophil activation and release mediators of allergic response

Treatment

Historical standard

- Avoidance of offending allergens, epinephrine in cases of exposure

Currently no FDA-approved treatment

- Several therapies in phase III

Basic strategies

- Repeated exposure of naïve T cells to the antigen
  - Retrains immune response to allergen
  - Promotes differentiation to Th1 & ai-Treg cells, down-regulation of Th2
    - B cell production of IgG4
      - IgG4 can sequester allergen and bind inhibitory FcγRIIb
- Inhibiting immune pathways involved in inflammation & reaction
  - Increase tolerated allergen dose (non-specific)

Oral Immunotherapy (OIT)

Gradually increasing amount of food protein consumed daily

- High success rate in increasing tolerated dose

Limitations

- Slow process
- Potential AEs throughout treatment, highest during initial build-up
  - Mild-severe; primarily gastrointestinal
- Optimal dosing protocol unknown
- Optimal maintenance dose, frequency, and duration unknown
  - Mixed results for sustained unresponsiveness
- Restricted in patients with most severe food-induced anaphylaxis

Sublingual Immunotherapy (SLIT)

Allergen extracts kept under the tongue

- ~1000-fold less concentrated than OIT

Limitations

- Slow process
- Local reactions during initial dosing, lower than OIT
- Lack of evidence for long-term sustained unresponsiveness
- Restricted in patients with most severe food-induced anaphylaxis
- Data suggests less effective than OIT
  - Upcoming Glucopyranosyl Lipid A (Sanofi) adjuvant with peanut
    - Toll-like receptor 4 agonist
      - Increase immune response to extract

Epicutaneous Immunotherapy (EPIT)

Repeated application of tiny (µg) amounts of the allergen on the skin

- Epidermis is not vascularized
  - Minimizes systemic reactions caused by circulation of allergens
    - Suited for very young patients and those with severe allergies
    - Fewer, mostly local cutaneous reactions

Limitations

- Slow process
- Currently limited to one allergen at a time
- Lack of evidence for long-term sustained unresponsiveness

Emerging Therapies & Future Direction

Adjunct biological therapies

- Improving the **safety** and efficacy of desensitization
- Inhibiting specific immune system pathways driving the allergic response
  - Minimize or prevent reactions during immunotherapy
    - Facilitate safer exposure of naïve T cells to allergen
    - Higher initial allergen dosing, faster dose escalation
- Potential increase in durability of desensitization

Limitations

- No desensitization when used as monotherapy
- Lack of data (safety, tachyphylaxis, dosing, duration of protection)
- Potential Cost

Anti-IgE Antibody

Xolair (omalizumab; Genentech)

- Recombinant humanized IgG1 monoclonal antibody
  - Approved for asthma and CIU
- Selectively binds *free* IgE and inhibits binding to its receptor
  - Gradual reduction in surface-bound IgE
    - Increases tolerated allergen dose; decreases AEs

Addition to existing immunotherapies

- Significantly improves safety and speed of desensitization
  - Median per-participant percent of OIT doses with AE (27% vs 68%)
- Limited effects on the outcomes of efficacy given enough time
  - Majority of patients eventually reach maintenance dose

Xolair Limitations

Xolair

- Optimal dosing strategy unknown
  - Dose approved for asthma may not be ideal in food allergy
    - Weight & IgE based
      - Nomogram parameters are limited
      - Variation in basophil & mast cell turnover
      - Variation in IgE during therapy (cannot monitor IgE)
    - Partial/Non-responders at approved dosing
      - Role of IgE:Xolair complexes & basophil sensitization
      - Lack of baseline biomarkers to predict responders
    - Duration of therapy
- AEs (GI) reduced but still present

Anti-Interleukin 4Rα Antibody

Dupixent (dupilumab; Regeneron Pharmaceuticals)

- Human monoclonal IgG4 antibody
  - Approved for moderate-severe AD
  - Binds IL-4 receptor α and blocks IL-4 and IL-13-induced responses
    - Down-regulates Th2 cell number and function
    - Decrease release of proinflammatory cytokines, chemokines, IgE

Performed well in AD, asthma, nasal polyposis, and EoE trials

Hypothesized to be useful in the treatment of food allergy

  - Enhancing positive change in IgG4/IgE ratio
  - Decreasing adverse events, especially GI
    - Potential use in those with persistent GI despite Xolair

Anti-Interleukin 33 Antibody

IL-33 is a proinflammatory ‘alarmin’ that mediates atopic diseases

- Binding of IL-33 to its receptor on effector cells
  - Recruitment of additional proinflammatory cells
  - Release of disease-mediating cytokines (IL-4, IL-5, and IL-13)

ANB020 (AnaptysBio)

- Human monoclonal IgG1/kappa antibody
  - Selectively binds IL-33 and inhibits function/binding
    - Acts upstream, broadly across the key mediators of allergy
    - Potential advantage over agents blocking downstream pathways

Phase I trial in adults with peanut allergy

- Evaluating safety and decreased reactivity to FC 14 days post-therapy

DNA Peptide Vaccine

ASP0892 (ARA-LAMP-vax; Astellas Pharma)

- Vaccine consisting of a single DNA plasmid
  - Encodes major peanut allergens (Ara h1, h2, and h3)
    - Up to 95% of patients have IgE specific to these fragments
- Plasmid taken up by antigen presenting cells
  - Converted to peanut protein fragments within
  - Plasmid includes LAMP sequence
    - Increased presentation to T cells
    - Prevents allergen from leaving the antigen presenting cells
      - No circulating allergen, no IgE binding
      - Allows safe, continuous naïve T-cell allergen exposure

DNA Peptide Vaccine

Potential antigen exposure and desensitization without allergic reaction

Highly individualized

- Changing proteins encoded by the plasmid

Currently in Phase I study for adults with peanut allergy

- Short and long-term efficacy and safety
  - No OIT
  - Change in tolerated dose 3 months post-therapy
    - How long is the desensitization maintained post-therapy
      - Safely incorporate into diet vs initiate build-up vs booster

Probiotics & the Microbiome

Link between early dysbiosis and risk for food allergy

- Pre- & probiotics in initial prevention
  - *Lactobacillus rhamnosus* GG and *Bifidobacteria*
    - SCFA producers induce tolerogenic Treg and Th1 cytokine responses
- Combined daily probiotic with peanut OIT vs placebo (Tang et al.)
  - LGG at 20 billion CFU daily
  - *Potential* reduction in AEs during treatment, especially GI
  - *Potential* increase in sustained unresponsiveness (2 to 5 weeks)
    - Lack of peanut OIT arm

Probiotic supplementation may aid in the efficacy and tolerability of OIT

- Follow up study for peanut allergy, with goal to examine in cow's milk

Probiotics & OIT

Limitations

- Huge variety of individual bacterial strains
  - Optimal effects may be achieved by a combination
- Proper dosage, duration unknown
  - Therapeutic dosages of multiple strains lead to GI events
  - Ensuring accurate dosage maintained across lots and products
    - Sensitive to environmental and storage conditions
- Probiotics may contain milk or other allergens

Non-Food Allergy

- Add-on therapy for those with uncontrolled asthma
  - Fevipiprant
- EoE
- Environmental allergies
  - Dupilumab and grass scit

Summary

Peanut OIT & EPIT in Phase III

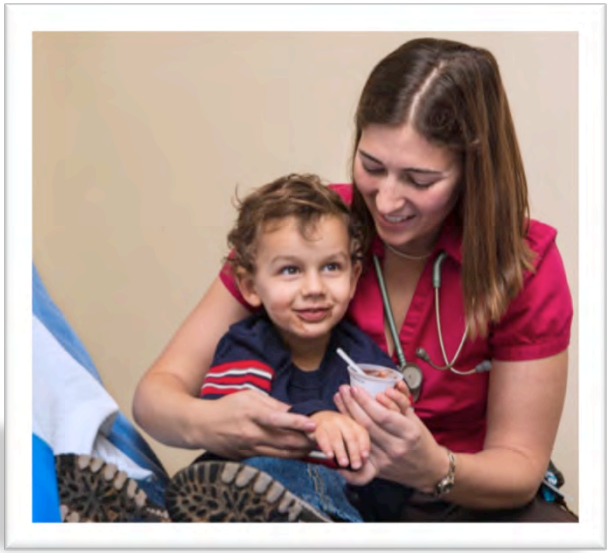
- Overall efficacious but slow, limited by risk of adverse events
  - First products may only cover accidental exposure
- Lack of sustained unresponsiveness

Biologic add-on therapies

- Window for safer introduction of food & immunotherapy
- Speed up rate of desensitization by increasing tolerated dose
- May increase the duration of sustained unresponsiveness

Current & future mechanistic studies

- Identify key mechanisms of desensitization and sustained unresponsiveness
- Novel biomarkers to monitor therapy efficacy/safety
- Novel therapeutic targets
  - Safe, permanent switch



Trials at the Center

- Ongoing
- Currently Recruiting
- Soon To Be Recruiting

Whitney M. Block, NP

Current Trials

Food Allergy-Peanut

- Aimmune
  - ARC004 (rollover of ARC003/ PALISADE)
  - ARC007/RAMSES
  - ARC008 (rollover of ARC004 and ARC007)
- Astellas*
- ITN/IMPACT
- POISED
- DBV
  - Epitope
  - PEOPLE (rollover of PEPITES)
  - REALISE

Food Allergy-Milk

- DBV
  - MILES

Food Allergy-Wheat

- Long term follow-up

Food Allergy-Multiple

- MIMiX

Asthma

- BI

Currently Recruiting Trials

Food Allergy-Peanut
- Astellas

Food Allergy-Milk
- IVORY

EoE
- FLUTE

Asthma
- ZEAL/SPIRIT

On the horizon trials

Food allergy-peanut
- Epitope Extension
- Sonofi (SLIT+adjuvant)
- Aimmune+Regeneron (dupi+peanut OIT)
- Astellas-Adolescents

Grass Allergy
- Regeneron (dupi+SCIT)

+at least 5 more late 2018/early 2019!

Learn more at ClinicalTrials.gov

To join our Allergy & Asthma Research Registry, visit: is.gd/snpregistry

With Appreciation to the Community, Patients and Families, Clinical and Laboratory Team and Collaborators

NIH National Institute of Environmental Health Sciences

NIH National Institute of Allergy and Infectious Diseases

NIH National Heart, Lung, and Blood Institute

FARE Food Allergy Research & Education

American Academy of Allergy Asthma & Immunology

Immune Tolerance Network

E·A·T End Allergies Together

EPA United States Environmental Protection Agency

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