Biologic Drugs: Innovative Treatments to Target Food Allergy

Presented by
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Today's Presenter

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Biologics for Food Allergy

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Objectives

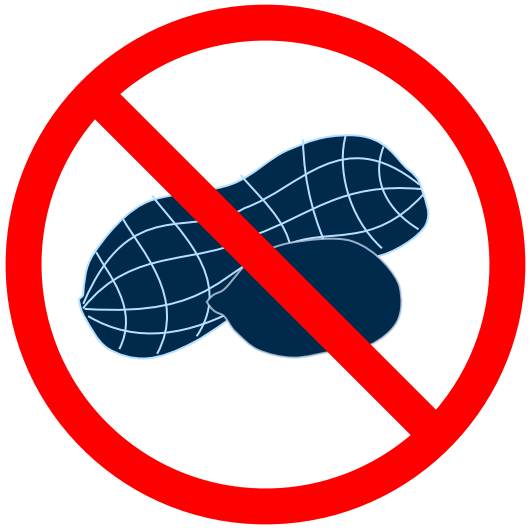
- To provide an overview of the biology of allergic reactions and illustrate how biologics work

- To discuss the therapeutic potential of biologics for ***Food Allergy***

Unmet Treatment Need in Food Allergy

Current Standard of Care

Strict Avoidance



Management of Reactions

(e.g., epinephrine, antihistamines)

Primary Prevention

- Early introduction to prevent development of food allergy

Investigational Treatments

- Several immunotherapy treatments under clinical investigation
- Other approaches, such as biologics and vaccines, in early investigation

The Risk of Accidental Exposure Is Constant and Widespread

Avoidance is difficult to achieve and requires the participation of a variety of stakeholders[1]

Birthday and other parties: Particularly when children are younger and will eat what is given to them

Friends and family: Some report "well-meaning" family insisting a little bite of peanut won't hurt

Social activities: Young children especially can share snacks without adults knowing

Packaged foods: Labels can be hard to comprehend; risk can be mistakenly assigned based on precautionary allergen labeling

School: Substitute teachers, lunch rooms and other parents are all sources of stress

ICER
Food Allergy report

Patients with food allergy and their caregivers experience tremendous anxiety and stress, and report poor quality of life[2]

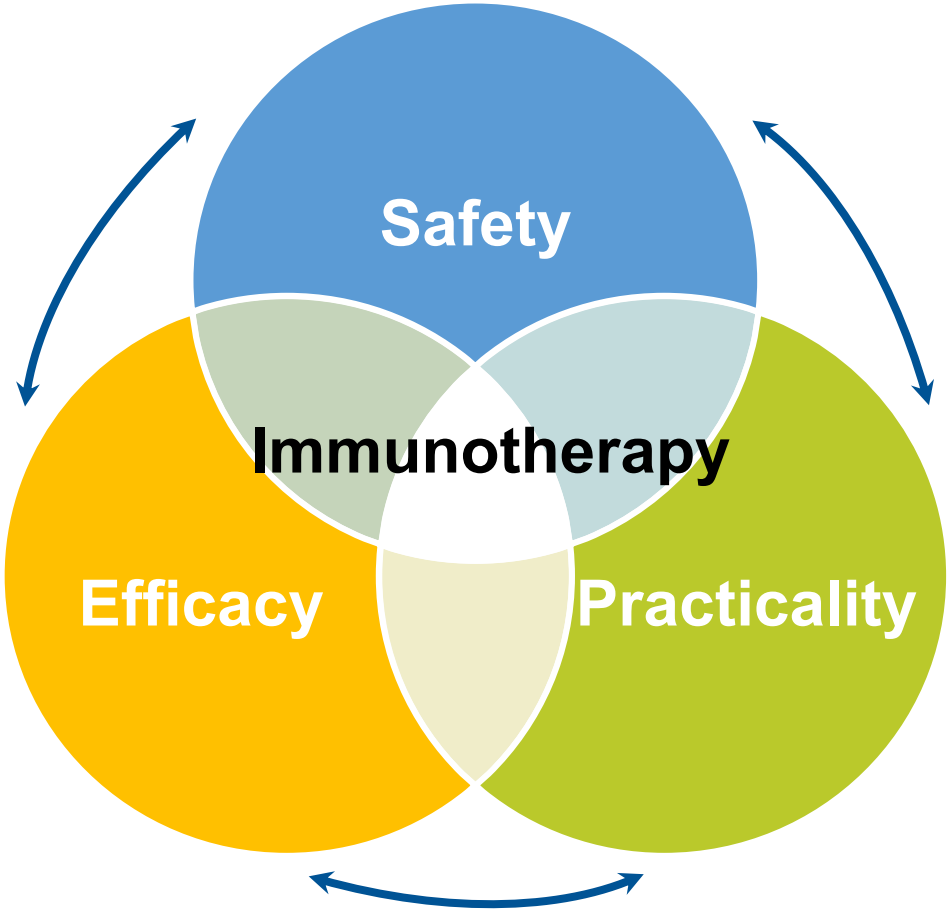
Patients may feel restricted in where they go and/or where they live due to fear of accidental exposure

Caregivers frequently miss work to help manage the safety of the places that their loved ones visit

Content courtesy of Dr. David Fleischer. University of Colorado Denver School of Medicine Aurora, CO.
ICER=Institute for Clinical and Economic Review1.
Dunn Galvin A et al. *Allergy*. 2015;70:1039-1051; 2. Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value: Full Evidence Report | ICER. July 10, 2019. https://icer-review.org/wp-content/uploads/2018/12/ICER_PeanutAllergy_Final_Report_071019.pdf. Accessed November 2019.

Immunotherapy Strategies Aim to Balance Efficacy, Safety and Practicality[1,2]

The goal of food immunotherapy is to safely protect against reactions due to accidental exposure with minimal disruption to daily life



1. FDA Advisory Committee Meeting. January 21, 2016 Transcript. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/UCM484938.pdf. Accessed February 8, 2018. 2. https://www.foodallergy.org/research-programs/overview. Accessed February 8, 2018.

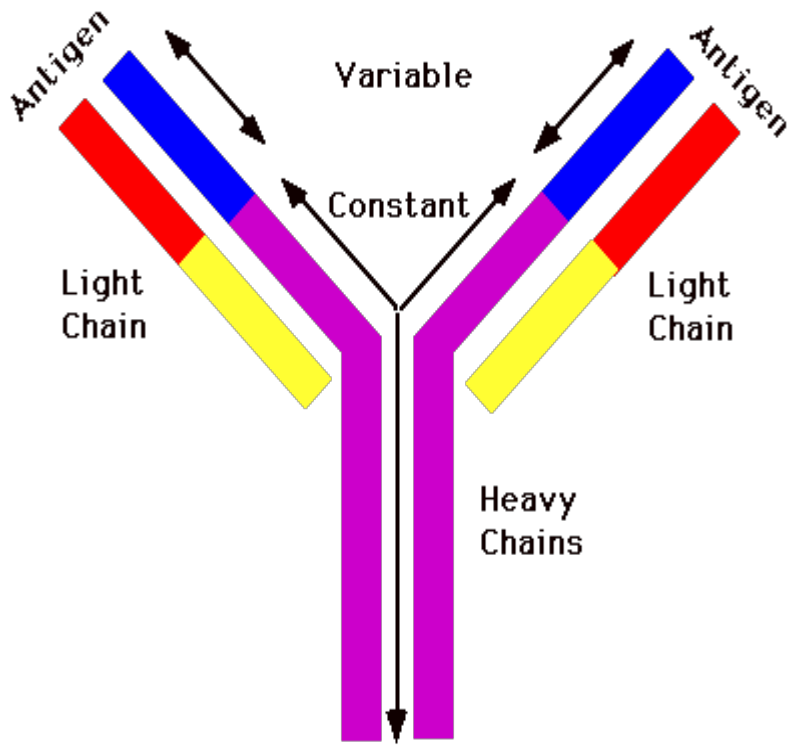
Biologics Defined

Biologic drugs (**biologics**) are products that are produced from living organisms or contain components of living organisms.

Biologic drugs include a wide variety of products derived from humans, animals, or microorganisms by using biotechnology.

Biologics are genetically engineered proteins that target specific parts of the immune system that fuel inflammation.

Food Allergy Biologics in Development: Monoclonal Antibodies

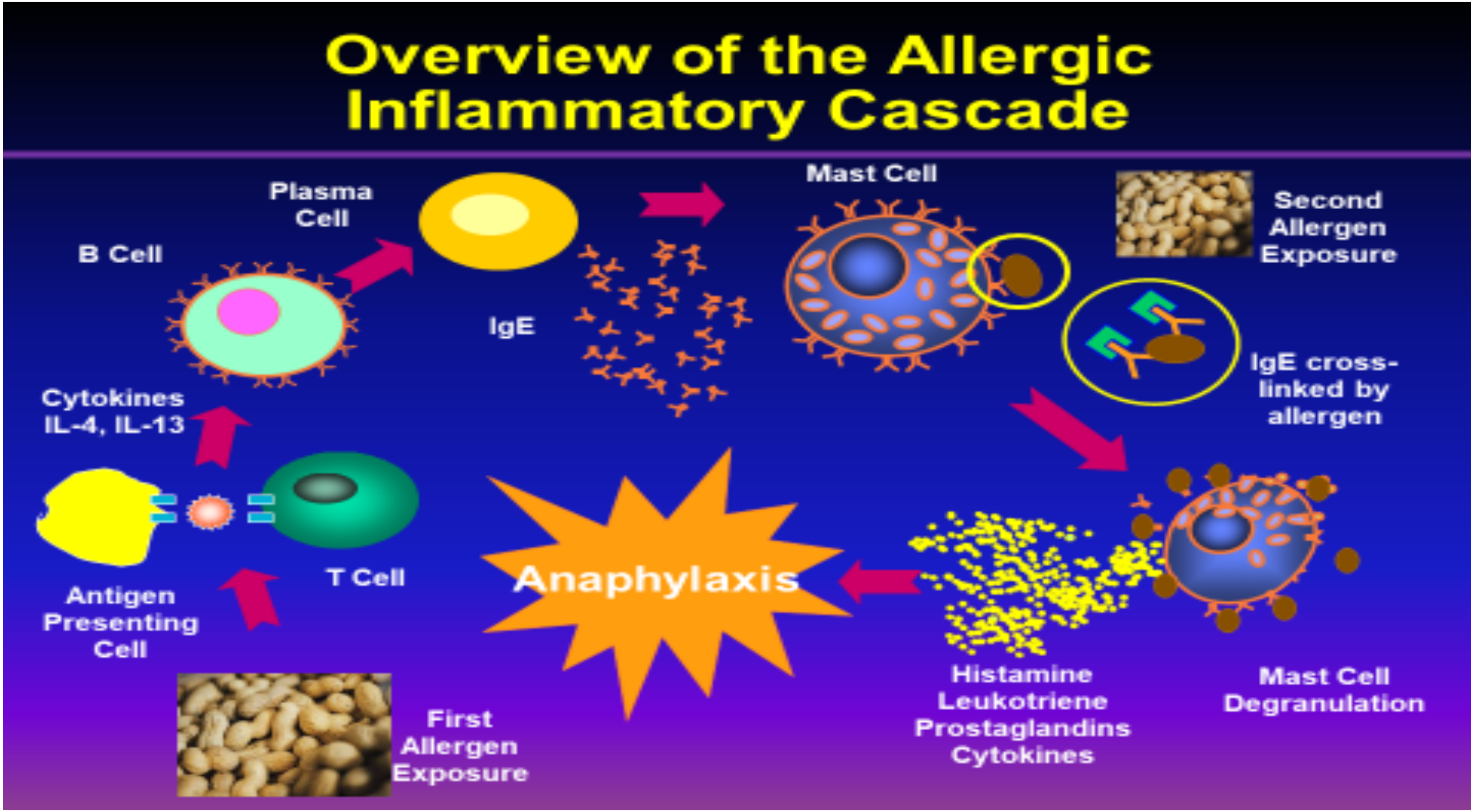


Biologics for Asthma and Non-Asthma Conditions

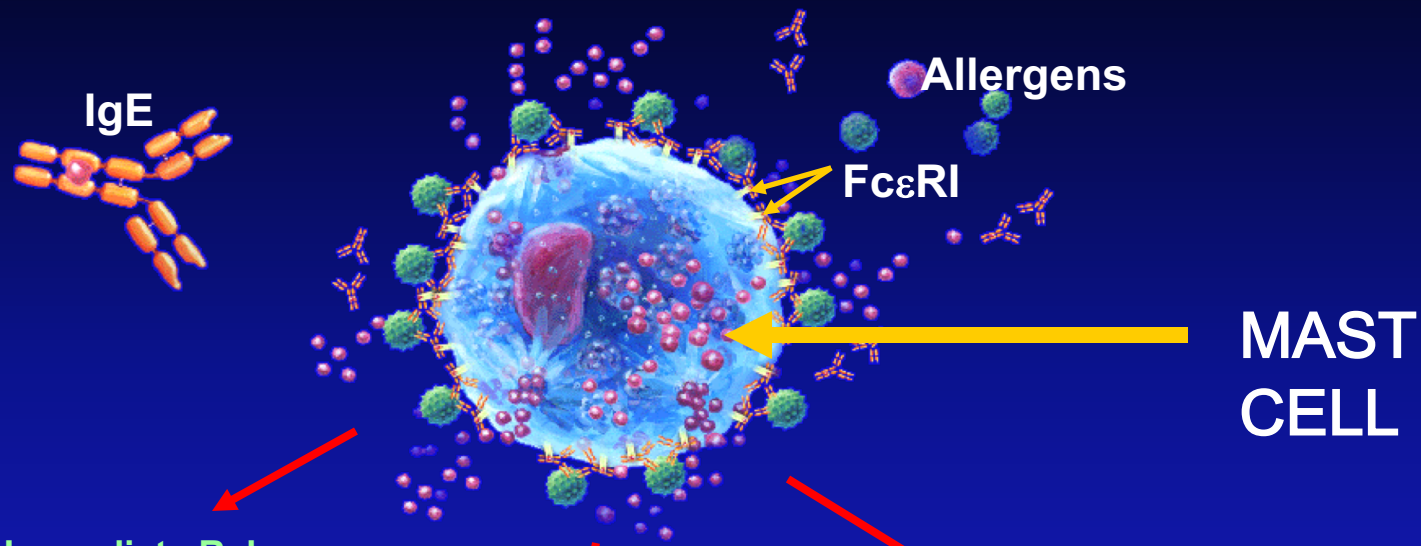
- **Approved Indications:**
  - **Asthma: omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab**
  - **Atopic dermatitis (eczema): dupilumab**
  - **Chronic rhinosinusitis with nasal polyps: dupilumab**
  - **Chronic spontaneous urticaria / chronic idiopathic urticaria (chronic hives with unknown cause): omalizumab**
  - **Eosinophilic granulomatosis with polyangiitis (vasculitis): mepolizumab**

- **Experimental/In Development**
  - ***Food allergy***
  - **Chronic obstructive pulmonary disease (COPD)**
  - **Allergic rhinoconjunctivitis/ allergic rhinitis**
  - **Allergic bronchopulmonary aspergillosis (ABPA)**
  - **Eosinophilic esophagitis**

Overview of the Allergic Inflammatory Cascade



IgE-Dependent Release of Inflammatory Mediators Leading to Early/Acute Allergic Symptoms



Immediate Release
Preformed Mediators:
Histamine, TNF-α,
Proteases, Hydrolases,
Proteoglycans(Heparin)

Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes
Thromboxanes

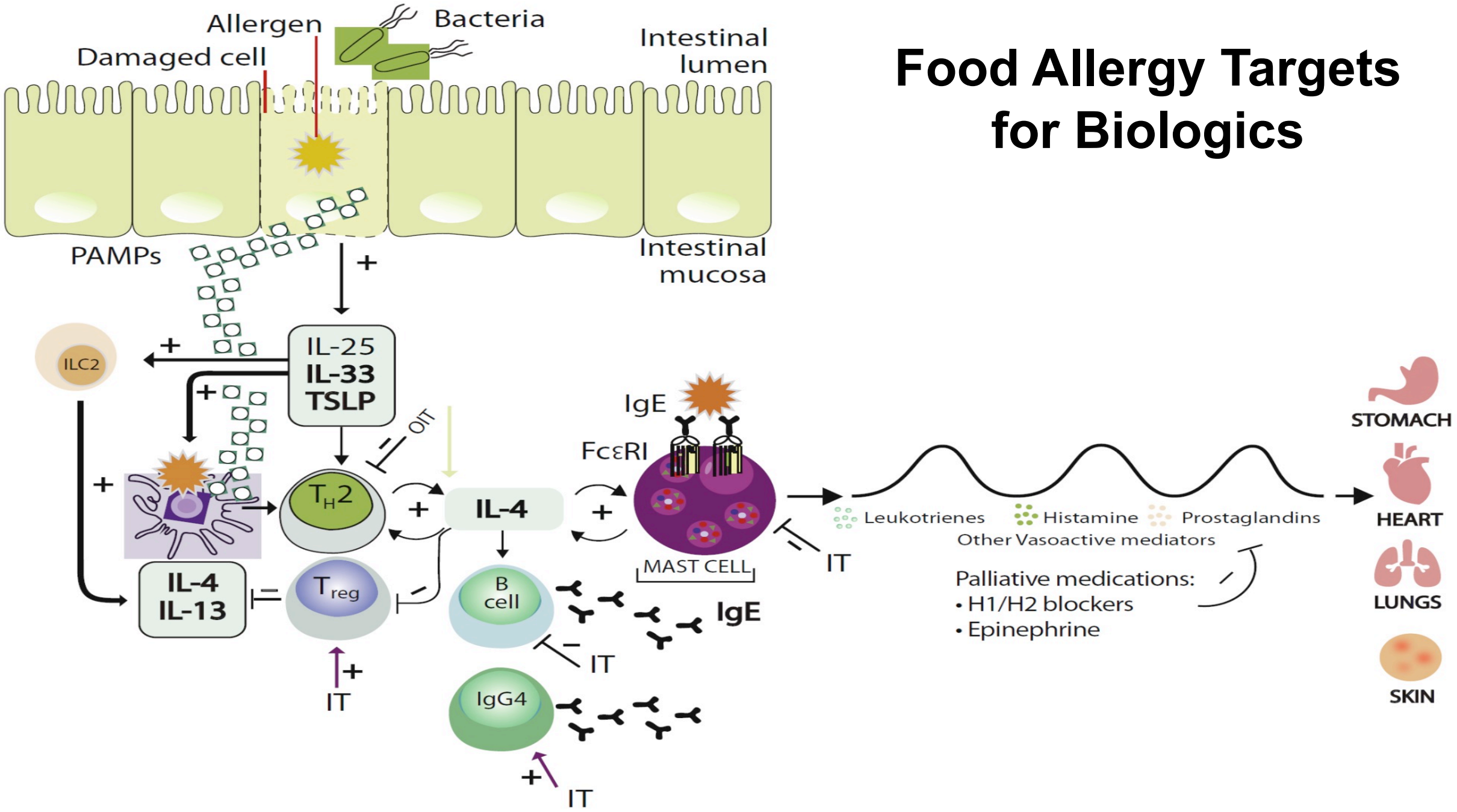
Over Hours
Cytokine production:
ILs-3,4, 5,6,8,9,11,13
TNF-α, MIP1, MCP

Mucus Production
Edema
Bronchoconstriction
Abdominal Distress
Cardiovascular Effects

Chronic Inflammation

Acute Symptoms

Food Allergy Targets for Biologics



Vickery et al, JACI IP, 02/2019

Biologic Clinical Trials Ongoing or Planned

- Omalizumab alone/adjunct to OIT
  - OUTMATCH: Omalizumab + Multi OIT
- Dupilumab alone/adjunct to OIT+/- Omalizumab
- Anti-IL-33 +/- OIT
- Anti-ST2+/- OIT
- Anti-IL-5
- Anti-IL-13
- Anti-TSLP
- DNA vaccines and novel allergen immunotherapy approaches

Omalizumab Mechanism in Relation to Food Allergy and Anaphylaxis

- Omalizumab binds to circulating IgE[1]:
  - ↓ amount of IgE available to interact with FcεRI on mast cells and basophils surfaces
  - ↓ IgE/FcεRI interactions results in a decreased expression of FcεRI
- As a result, mast cells and basophils exhibit reduced degranulation in response to an allergen

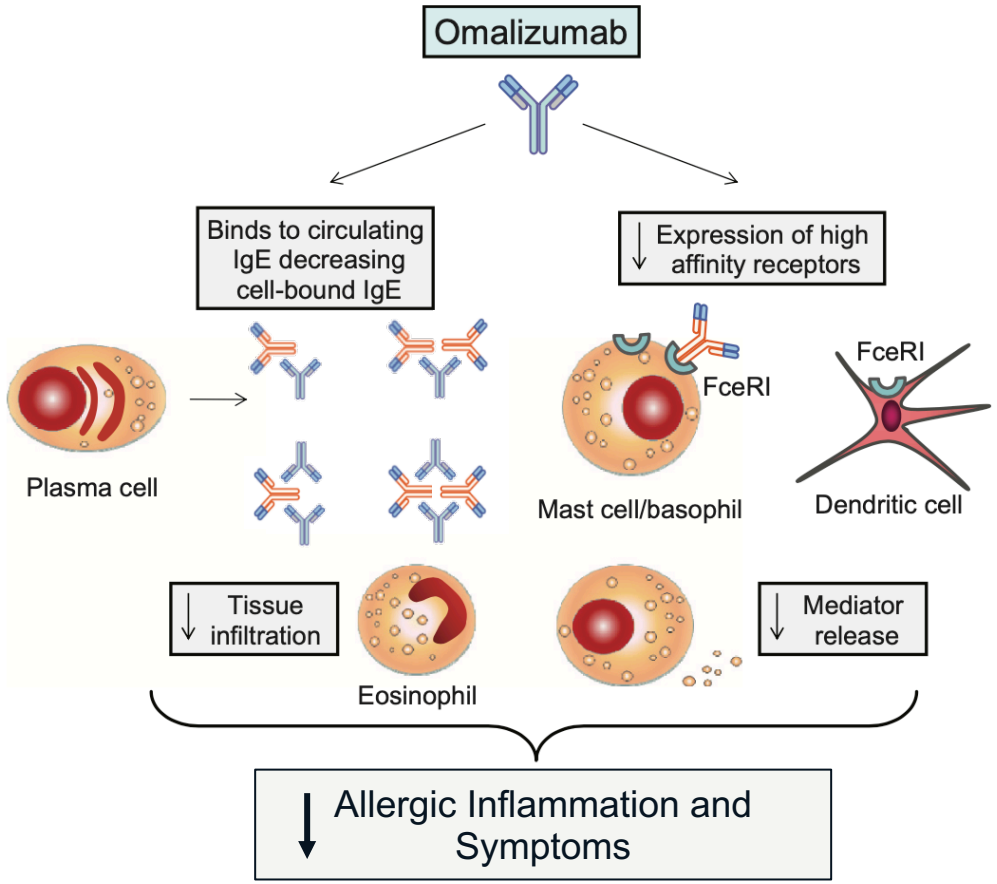
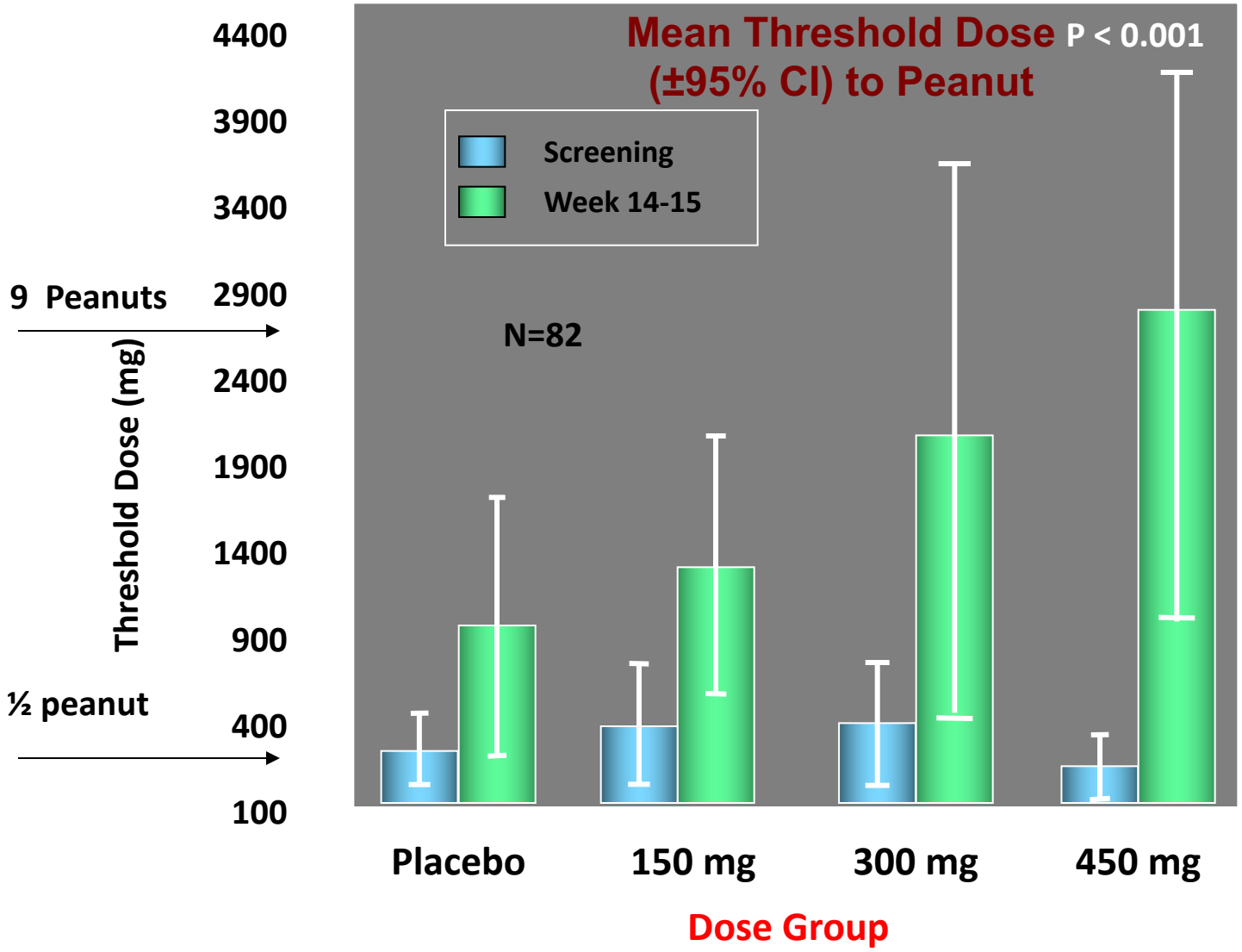


Figure adapted from:
Pelaia G et al. *J Asthma Allergy*. 2011;4:49-59;
D'Amato G et al. *Curr Drug Targets Inflamm Allergy*. 2004;3:227-229.

FcεRI=high affinity IgE receptor.
Lieberman J et al. *Curr Allergy Asthma Rep*. 2013;13(1):78-84.

Effects of TNX-901 on Peanut Allergy



~ 25% could ingest 8 gm

~25% were no better

- 450 mg dose group vs. placebo, $p<0.001$ (log_{10}-transformed data)

Leung, Sampson, et al.
NEJM 2003;348:986.

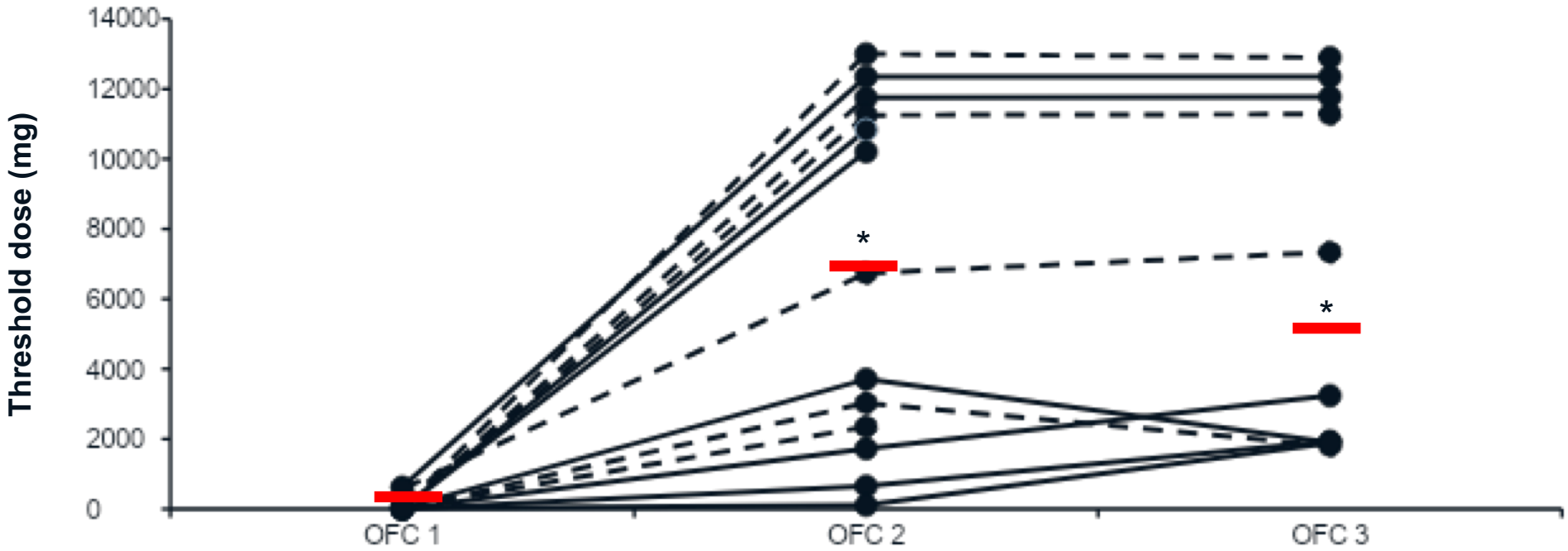
Omalizumab as Monotherapy

Reference/Age (median)	Patients	Treatment Regimen	Outcomes
Sampson et al 2011[1] 18–44 years (19)	▪ 14 peanut-allergic ▪ 9 treated, 5 placebo	▪ q2–4 weeks for 24 weeks vs placebo	▪ Increase threshold dose compared with baseline ▪ Study terminated due to 2 severe reactions during entry DBPCFC
Savage et al 2012[2] 18–44 years (23)	▪ 14 peanut-allergic ▪ All treat with OMA	▪ q2–4 weeks for 24 weeks	▪ Increased median tolerated dose from 80 mg to 6500 mg at week 5 ▪ 4/14 tolerated full 10,000 mg at week 24
Brandström et al 2017[3] 12–19 years (17)	▪ 23 peanut-allergic ▪ All treated with OMA	▪ q2–4 weeks for 1–4 8-week cycles ▪ Dose adjusted based on basophil activation test	▪ 15/23 (65%) were able to tolerate full dose (2800 mg) after OMA ▪ All ingested at least 840 mg
Fiocchi et al 2019[4] 8–23 years (12)	▪ 15 multi-food allergic (or single if failed OIT) ▪ All treated with OMA for asthma	▪ q2–4 weeks for 16 weeks	▪ Mean increase in threshold from 1013 mg to 8727 mg (milk, egg, wheat, hazelnut) ▪ 70% tolerated complete OFC dose and able to reintroduce into diet without OIT

Content courtesy of Dr. David Fleischer. University of Colorado Denver School of Medicine Aurora, CO.
DBPCFC=double-blind, placebo-controlled food challenge; OFC=oral food challenge; OMA=omalizumab; q=every.
1. Sampson HA et al. *J Allergy Clin Immunol.* 2011;127(5):1309-1310; 2. Savage JH et al. *J Allergy Clin Immunol*. 2012;130(5):1123-1129; 3. Brandström J et al. *Clin Exp Allergy*. 2017;47:540-550;
4. Fiocchi A et al. *J Allergy Clin Immunol Pract*. 2019;7:1901-1909.

Omalizumab Monotherapy: Savage et al., 2012

- Omalizumab increased the median tolerated threshold dose of peanut protein from 80 mg at baseline to 6500 mg at week 5 (*P*=0.002) and 5080 mg at week 24 (*P*=0.005)
- 4 patients were able to tolerate the full 10,000 mg peanut protein challenge dose at weeks 5 and 24
- Symptoms recorded during OFCs did not appear to change during treatment, although it took a higher oral dose of allergen to elicit gastrointestinal (local) and nongastrointestinal (systemic) symptoms during OFC 2



These are results for all patients.

The median threshold dose for each time point is indicated by a red bar.
*P<0.05

Dashed lines indicate group A patients

Solid lines indicate group B patients

Savage JH et al. *J Allergy Clin Immunol*. 2012;130(5):1123-1129.

Omalizumab Monotherapy: Fiocchi et al., 2019

Food allergen	Multiple (milk, egg, hazelnut, wheat)
Study design	Observational, real-life, efficacy study ▪ In patients with severe asthma (n=15), food allergen thresholds (2+ foods) were evaluated before and after a 4-month treatment with omalizumab ▪ Control of asthma and patient quality of life (PedsQL) were also evaluated
Patient population	▪ Median age: 12 years ▪ Total IgE: 208–1491 kU/L ▪ Median (range) ACT: 16 (9–19) ▪ Baseline PedsQL (median): Parent, 61; Patient, 65
Primary endpoints	▪ Tolerance threshold to foods (TTF); full TTF defined as: • Cow's milk: 144.4 mL (4700 mg of protein) • Baked milk: 80 g (6960 mg of protein) • Hen's egg: two 45 g eggs (11,160 mg of protein) • Baked egg: 80 g (9520 mg of protein) • Hazelnut: 64 g (8847.5 mg of proteins) • Wheat: 220 g (10,060 mg of protein)

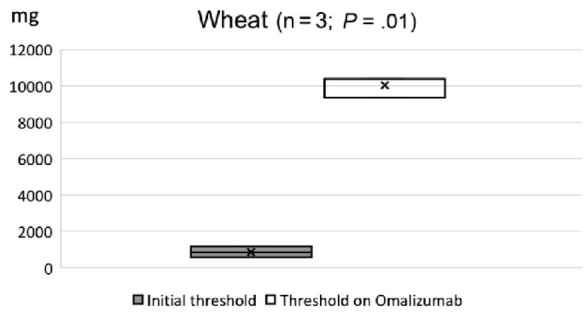
ACT=Asthma Control Test; PedsQL=Pediatric Quality of Life Inventory.

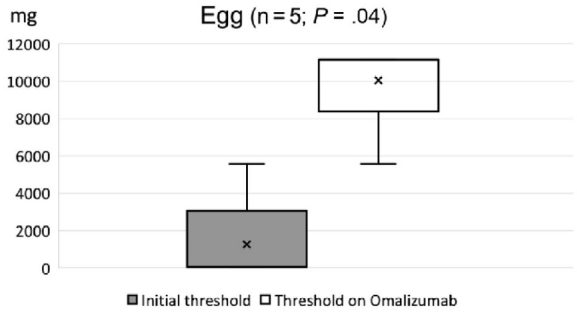
Fiocchi A et al. *J Allergy Clin Immunol Pract*. 2019;7:1901-1909.

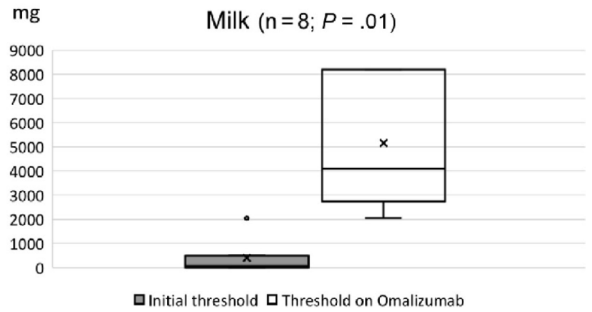
Omalizumab Monotherapy: Fiocchi et al 2019

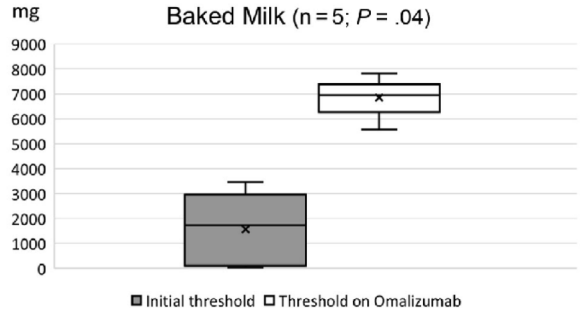
- Omalizumab induced an increase in the allergen threshold for milk, egg, wheat, and hazelnut from a mean of 1012.6 ±1464.5 mg protein to 8727 ± 6463.3 mg protein (8.6-fold increase; *P*<0.001)
- A total of 70.4% of patients tolerated the complete challenge dose after 4 months of treatment with omalizumab
  - These foods were reintroduced in the patients' diet without the need for any oral immunotherapy procedures
  - The remaining foods were partially tolerated
  - The number of reactions to the unintended ingestion of allergenic foods over 4 months dropped from 47 to 2
- PedsQL increased from 61±5.32 to 87±7.33 (parent; *P*<0.001) and from 65±7.39 to 90±4.54 (patients; *P*<0.001)

Initial Threshold (mg) and Threshold After 4 Months of Omalizumab Treatment (4 foods*)





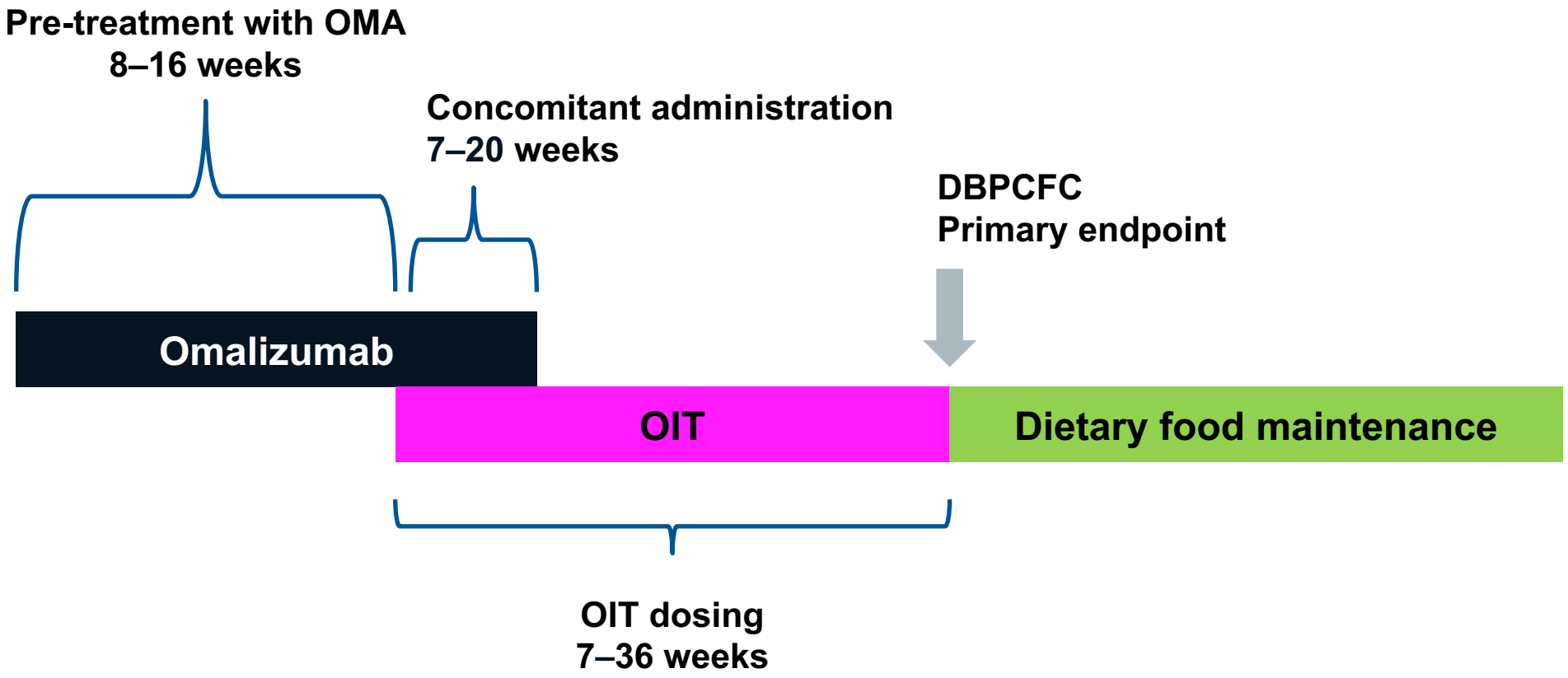




*Hazelnut data not provided.

Fiocchi A et al. *J Allergy Clin Immunol Pract*. 2019;7:1901-1909.

Omalizumab as Adjunct to Food OIT: General Study Design



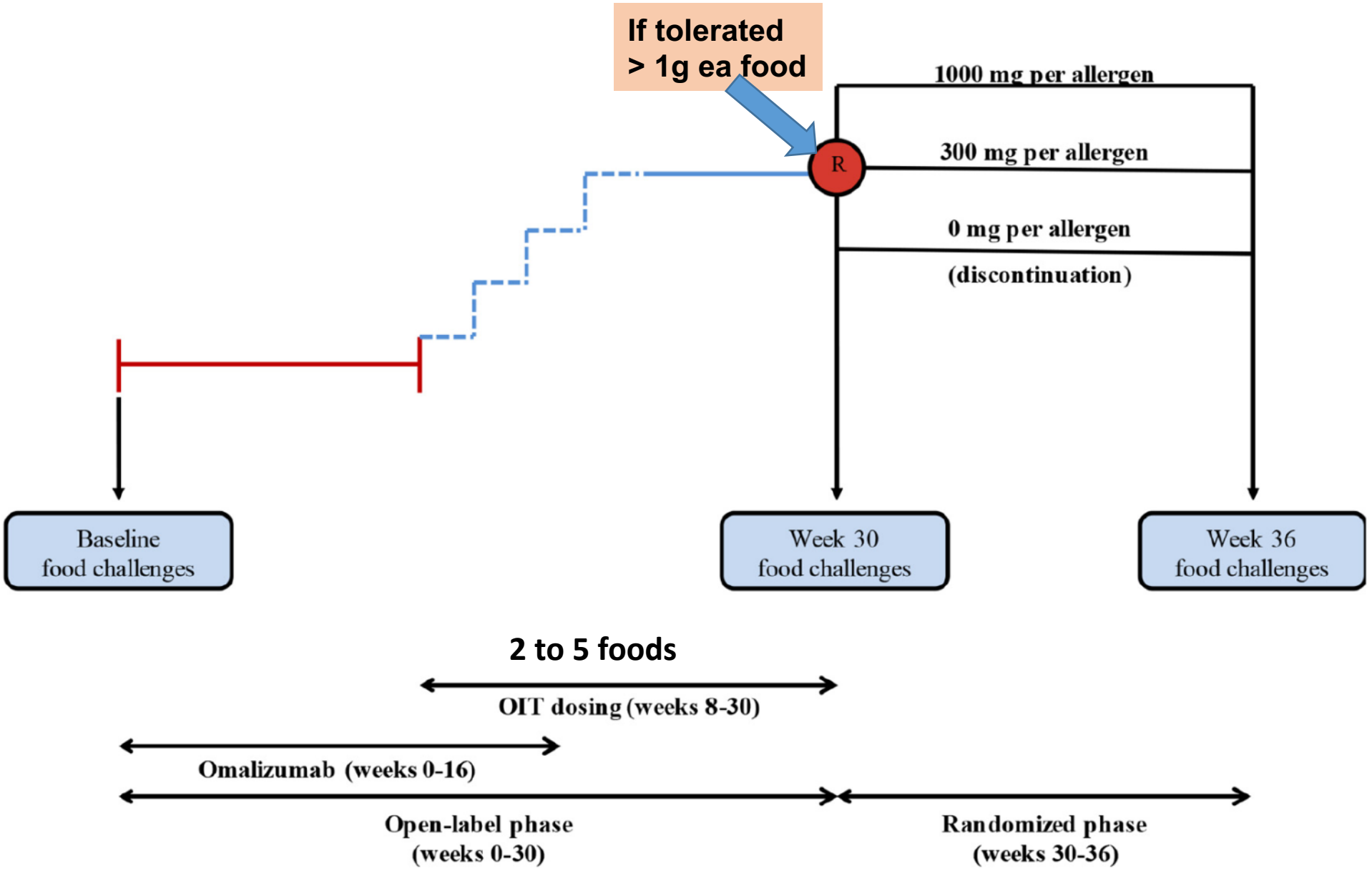
Randomized DBPC Studies: Omalizumab + OIT

Reference/Age (median)	Patients	Treatment Regimen	Outcomes
Wood (2016)[1] 7–32 years	▪ 57 milk-allergic ▪ 28 OMA, 29 placebo	▪ q2–4 weeks for 16 weeks vs placebo; OMA group continued until month 28 ▪ Open-label OIT started at 18 weeks to goal of 3.8 g	▪ 88.9% (OMA) vs 71.4% (P) passed 10 g desensitization OFC at month 28 (P=0.18) ▪ At month 32 (16 weeks off OMA and 8 weeks of OIT), 48.1% (OMA) vs 35.7% (P) had SU (P=0.42) ▪ Safety: 2.1% (OMA) vs 16.1% (P) doses/subject provoked symptoms in escalation (P<0.001); dose-related reactions requiring treatment (0.0% vs 3.8%, P<0.001)
MacGinnitie (2017)[2] 7–19 years	▪ 37 peanut-allergic ▪ 29 OMA, 8 placebo	▪ q2–4 weeks for 12 weeks; OMA group continued through 18 weeks ▪ Peanut OIT started week 12 to goal of 2 g	▪ 23 patients (79.3%, OMA) vs 1 (12.5%; P<0.01) were able to tolerate 2000 mg 6 weeks off OMA ▪ 22 patients (75.9%, OMA) vs 1 (12.5%; P=0.002) were able to tolerate 4000 mg peanut protein 12 weeks off OMA ▪ Safety: reactions rates to OIT were not significantly different, but OMA-treated patients were exposed to higher peanut protein doses
Andorf (2018)[3] 4–15 years	▪ 48 multi-food allergic ▪ 36 OMA, 12 placebo	▪ q2–4 weeks for 16 weeks ▪ Multi-food OIT started at week 8 for 2–4 foods with goal maintenance of 2 g per food	▪ At 36 weeks, 30 patients (83%, OMA) vs 4 (33%; P=0.0044) tolerated 2 g of ≥2 foods ▪ Patients in OMA group had significantly lower median per-subject percentage of OIT doses associated with adverse events: 27% (OMA) vs 68% (P); P=0.0082

DBPC=double-blind, placebo-controlled; P=placebo; SU=sustained unresponsiveness.

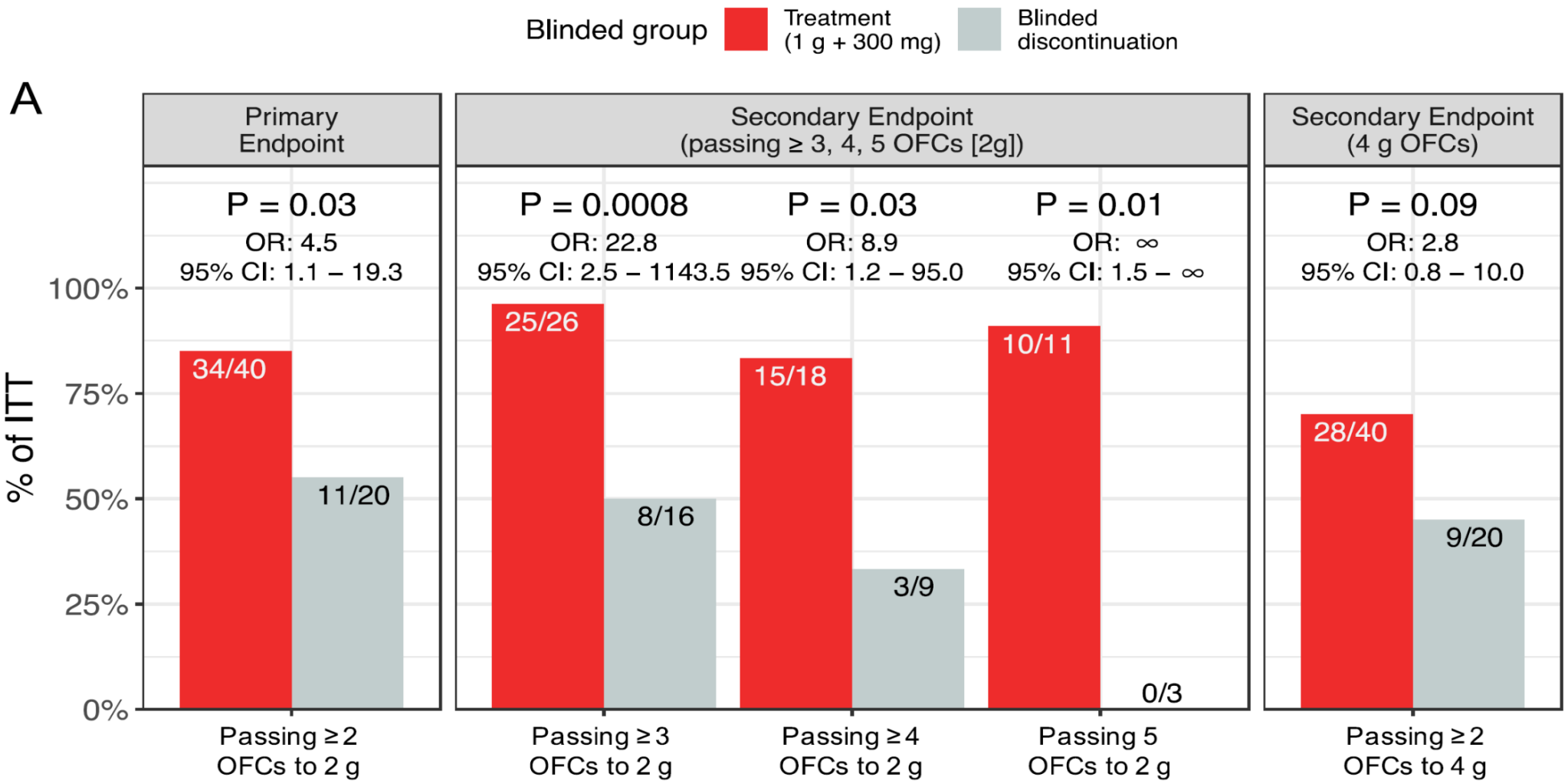
Content courtesy of Dr. David Fleischer. University of Colorado Denver School of Medicine Aurora, CO.

1. Wood RA et al. *J Allergy Clin Immunol*. 2016;137(4):1103-1110.e11; 2. MacGinnitie AJ et al. *J Allergy Clin Immunol*. 2017;139(3):873-881.e8;
3. Andorf S et al. *Lancet Gastroenterol Hepatol*. 2018;3(2):85-94.



S Andorf et al, EClinMED, 2019

% intent-to-treat in pooled treatment arm (1 g + 300 mg) and discontinued arm (0 mg) who passed food challenge to 2 g to at least 2 foods (primary endpoint), and to at least 3, 4, or 5 foods or at least 2 food challenges to 4 g (secondary endpoint) at week 36.



S Andorf et al., EClinMED, 2019

Clinical Evidence for the Use of Omalizumab in Food-Allergic Patients

Multiple clinical studies have evaluated the efficacy of omalizumab as monotherapy and in combination with OIT for decreasing sensitivity to food allergens

The results from these studies suggest:

- Omalizumab is potentially effective in treating multi-food allergies in patients allergic to ≥1 food
- As a monotherapy, omalizumab may increase the threshold dose for inducing allergic symptoms following food exposure
- In conjunction with OIT, omalizumab may increase OIT efficacy and enable safe and rapid desensitization

However, differing endpoints and OIT treatment regimens make cross-study comparisons challenging

OUtMATCH Study Overview

This study is designed to evaluate omalizumab efficacy in 3 stages

Stage 1

Omalizumab monotherapy
vs
placebo

Primary objective is to compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab or placebo for omalizumab.

Stage 2

Omalizumab-facilitated OIT
vs
Omalizumab + placebo OIT

Secondary objective* is to compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.

Stage 3

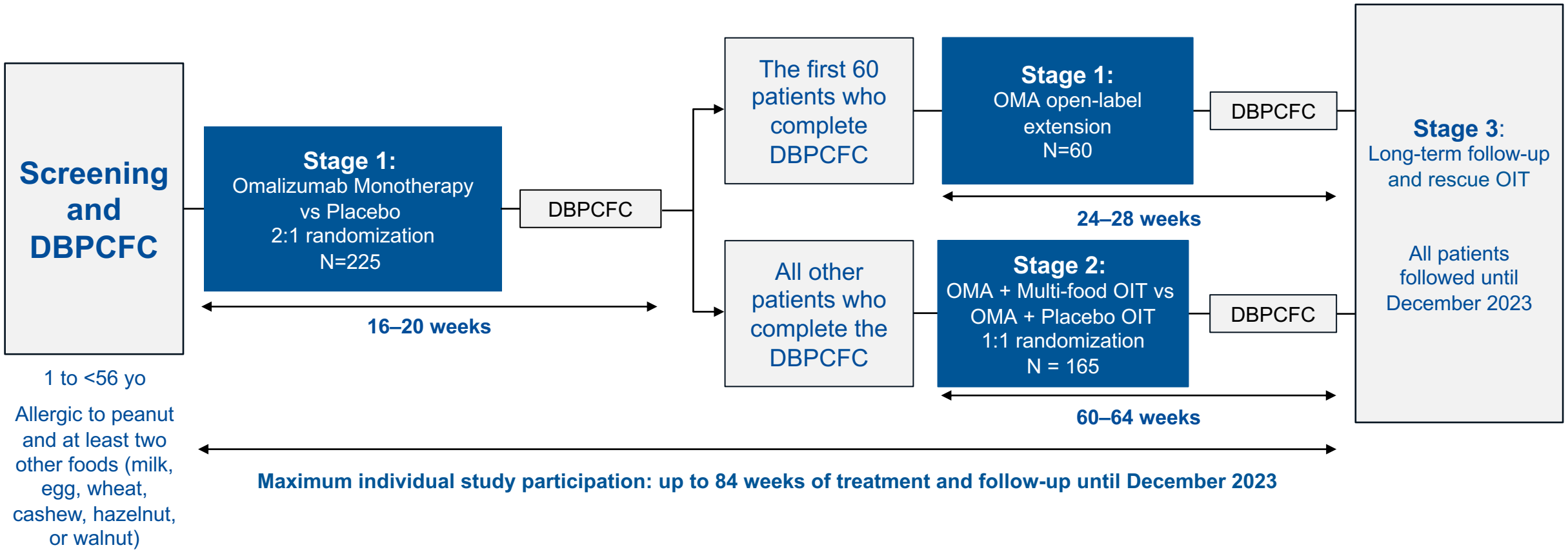
Long-term follow-up

Secondary objective is to compare dietary consumption of foods after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.

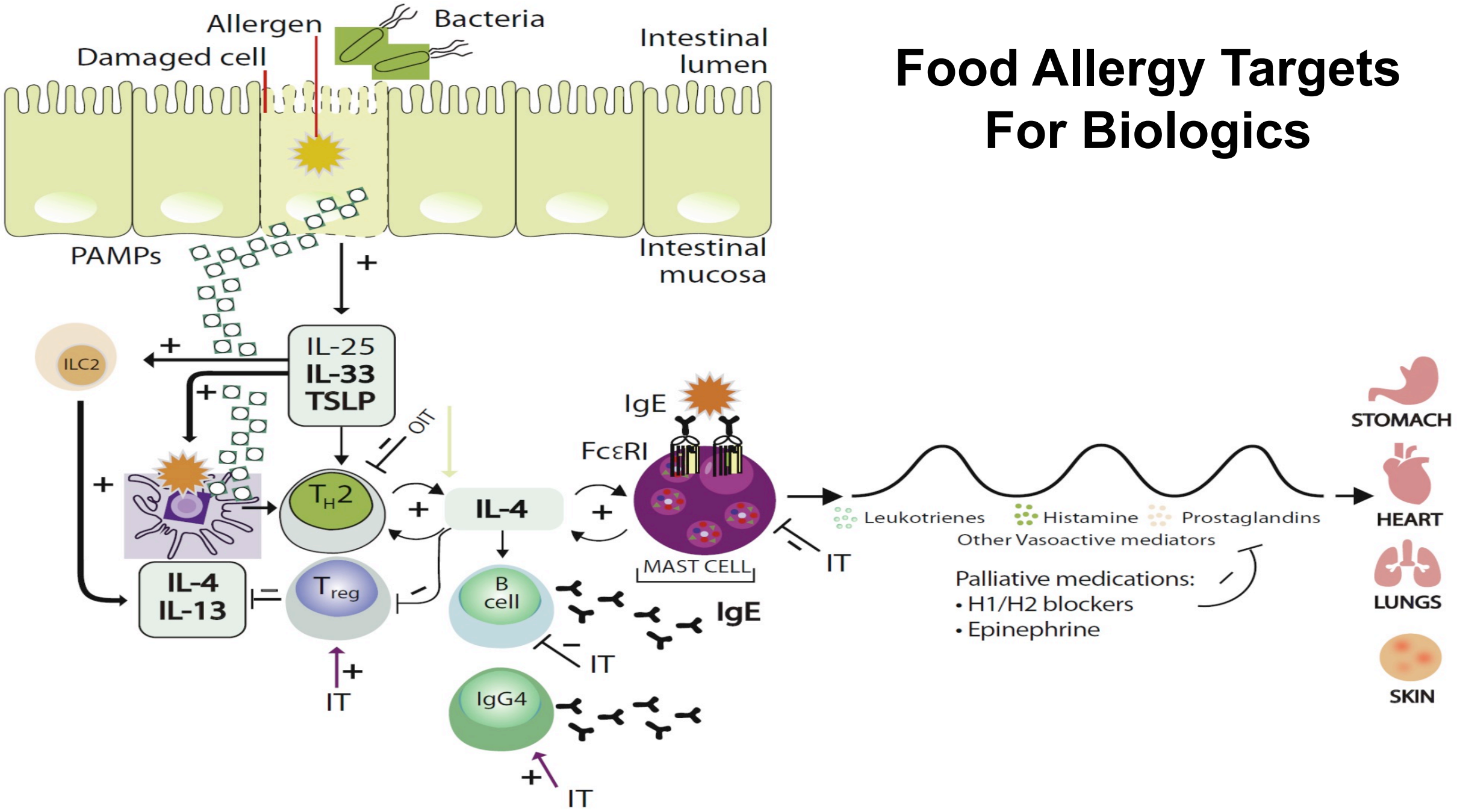
*Primary objective for stage 2.

General Study Overview

- **Multi-center, randomized, double-blind, placebo-controlled trial**



Food Allergy Targets For Biologics



Vickery et al, JACI IP, 02/2019

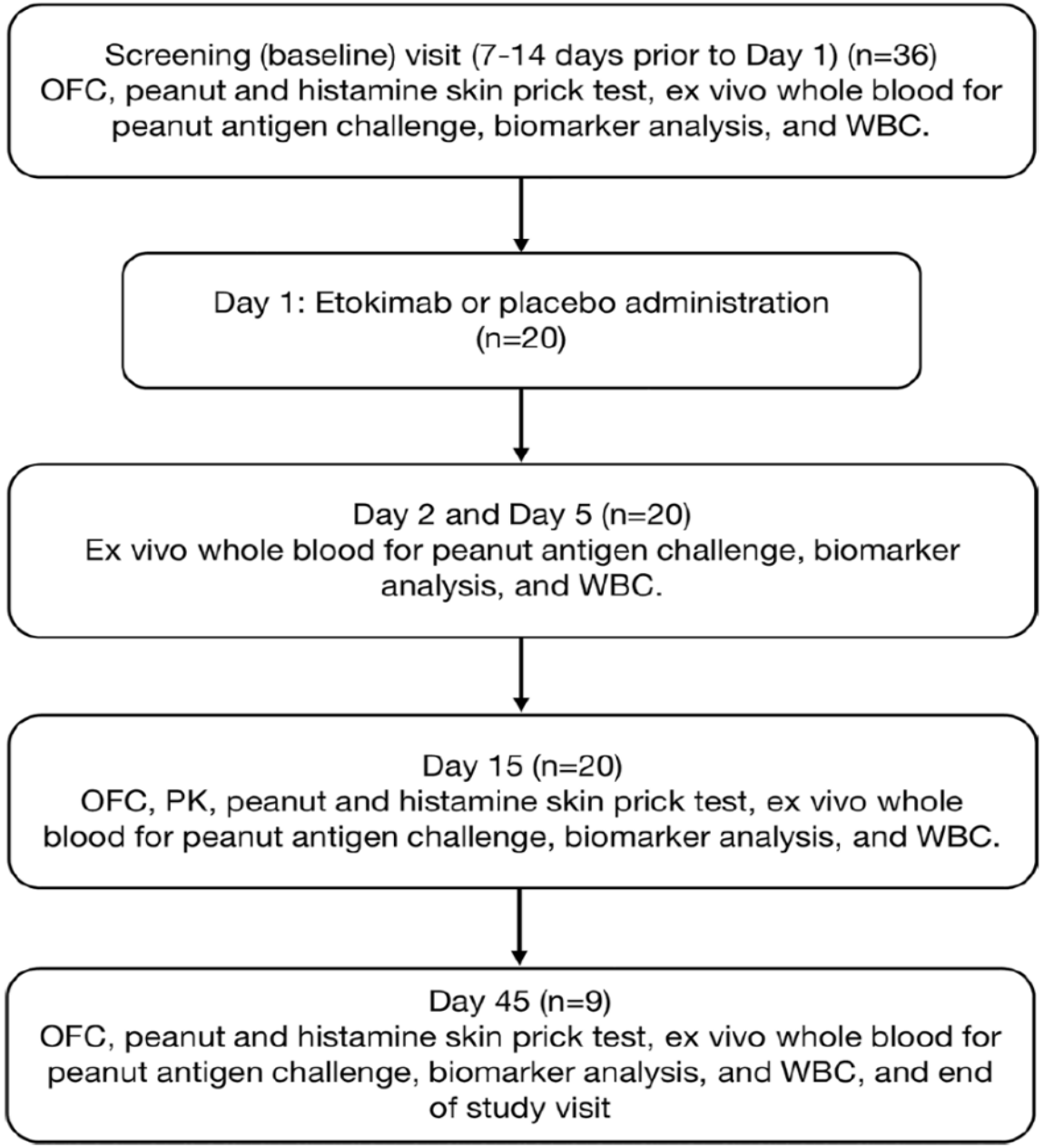
JCI insight

Phase 2a randomized, placebo-controlled study of anti–IL-33 in peanut allergy

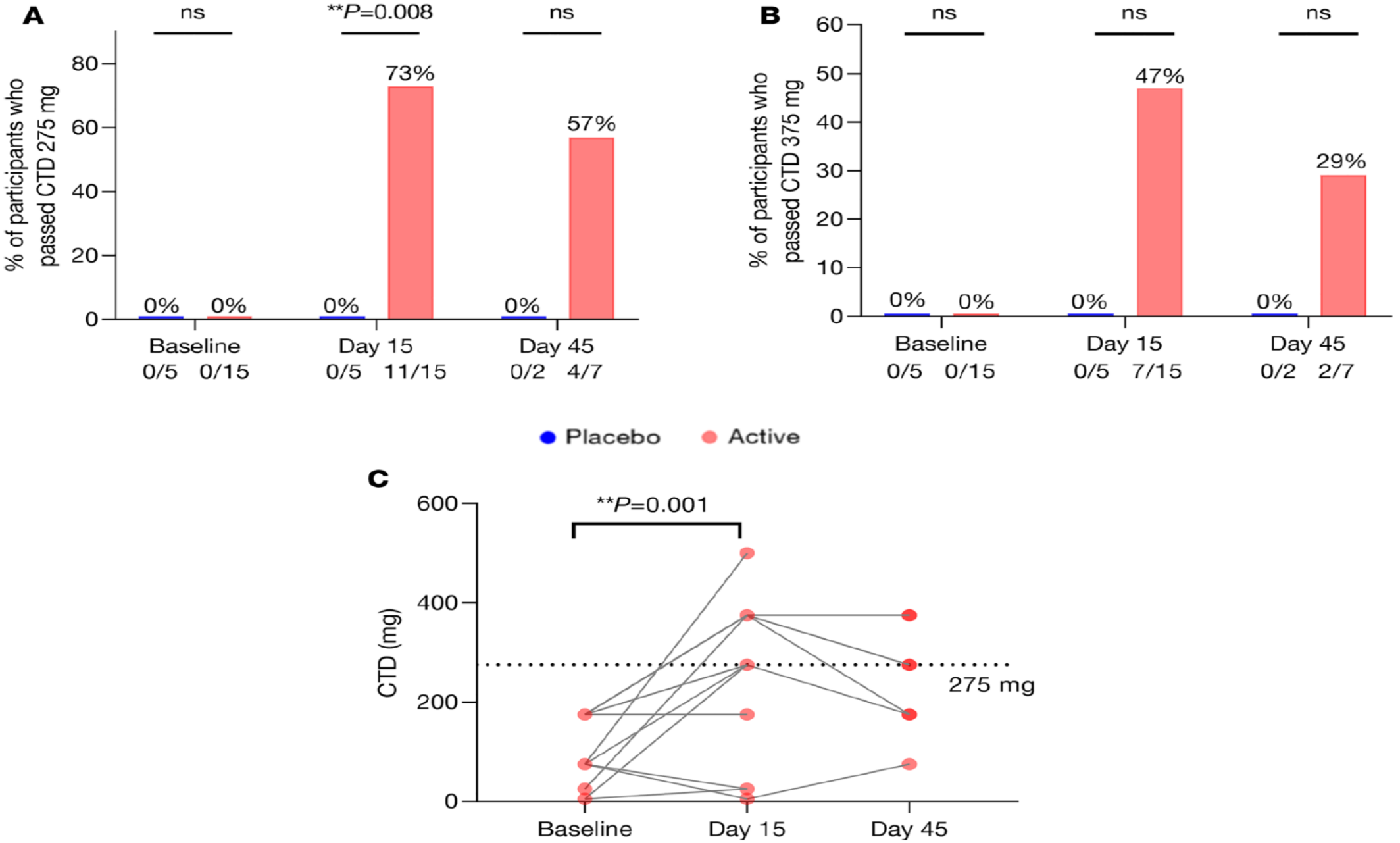
Sharon Chinthrajah, … , Marco Londei, Kari C. Nadeau

JCI Insight. 2019;4(22):e131347. https://doi.org/10.1172/jci.insight.131347.

Study Design



Results


A
ns
**P=0.008
ns
% of participants who passed CTD 275 mg
80
60
40
20
0
73%
57%
0%
0%
0%
0%
Baseline
0/5 0/15
Day 15
0/5 11/15
Day 45
0/2 4/7
B
ns
ns
ns
% of participants who passed CTD 375 mg
60
50
40
30
20
10
0
47%
29%
0%
0%
0%
0%
Baseline
0/5 0/15
Day 15
0/5 7/15
Day 45
0/2 2/7
Placebo
Active
C
**P=0.001
CTD (mg)
600
400
200
0
275 mg
Baseline
Day 15
Day 45

Dupilumab Monotherapy for Peanut Allergy Study Information

Study Type	Interventional (Clinical Trial)
Estimated Enrollment	48 participants
Allocation	Randomized
Intervention Model	Parallel Assignment
Masking	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose	Treatment
Official Title	A Study to Evaluate the Efficacy and Safety of Dupilumab Monotherapy in Pediatric Patients with Peanut Allergy
Actual Study Start Date	March 12, 2019
Estimated Primary Completion Date	August 13, 2020
Estimated Study Completion Date	November 10, 2020

https://clinicaltrials.gov/ct2/show/NCT03793608. Accessed November 2019.

Dupilumab as Adjunct to AR101 Study Information

Study Type	Interventional (Clinical Trial)
Estimated Enrollment	156 participants
Allocation	Randomized
Intervention Model	Parallel Assignment
Masking	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose	Treatment
Official Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Study in Pediatric patients with Peanut Allergy to Evaluate the Efficacy and Safety of Dupilumab as Adjunct to AR101 (Peanut Oral Immunotherapy)
Actual Study Start Date	October 3, 2018
Estimated Primary Completion Date	June 1, 2020
Estimated Study Completion Date	March 10, 2021

https://clinicaltrials.gov/ct2/show/NCT03682770. Accessed November 2019.

Efficacy, Safety, and Practicality of Emerging Treatment Modalities

	Efficacy	Safety	Practicality
Omalizumab	✓✓✓✓	✓✓✓✓	✓✓✓✓
Palforzia (OIT)	✓✓✓	✓✓	✓
Viaskin (EPIT)	✓✓	✓✓✓	✓✓
SLIT	✓✓✓	✓✓✓	✓✓
Dupilumab	✓	✓✓✓	✓✓✓
Office-based OIT	✓✓	✓✓	✓✓

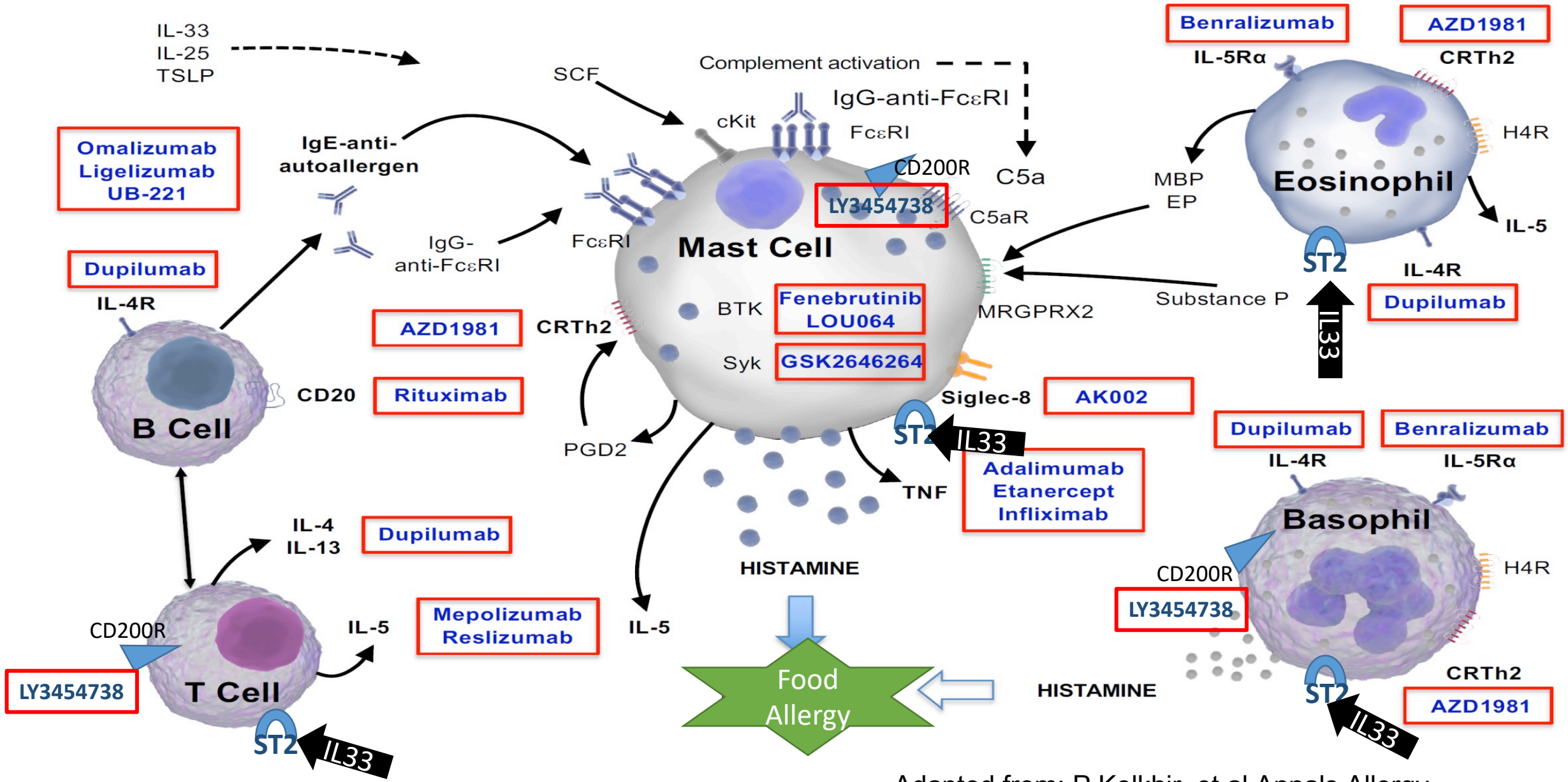
Biologics and Novel Modalities Presently Active in Clinical Trials

Subcutaneous immunotherapy (SCIT)[1] **(eg, HAL-MPE1)**	**Cytokine antibodies[2,3]** **(eg, Anti-TSLP, Anti-IL-33)**	**Vaccine[4,5]** **(eg, SPP0892*, BCG immunization)**
Intralymphatic immunotherapy[6]	**Bacteria[7]** **(eg, VE416†)**	**Microbiota Transplant[8,9]** **(eg, fecal matter capsule, vaginal seeding)**
Skin Barrier Protection[10] **(eg, EpiCeram)**	**Vitamin D[11]**	**Traditional Chinese Medicine[12]** **(eg, Chinese Herbal Formula-X [CHFX])**

*A single multivalent peanut (Ara h1, h2, h3) lysosomal associated membrane protein DNA plasmid vaccine; †dormant [inactive] bacteria that is reactivated once reaching the intestines.
BCG=Bacille Calmette Guérin; IL=interleukin; TSLP=thymic stromal lymphopoietin.

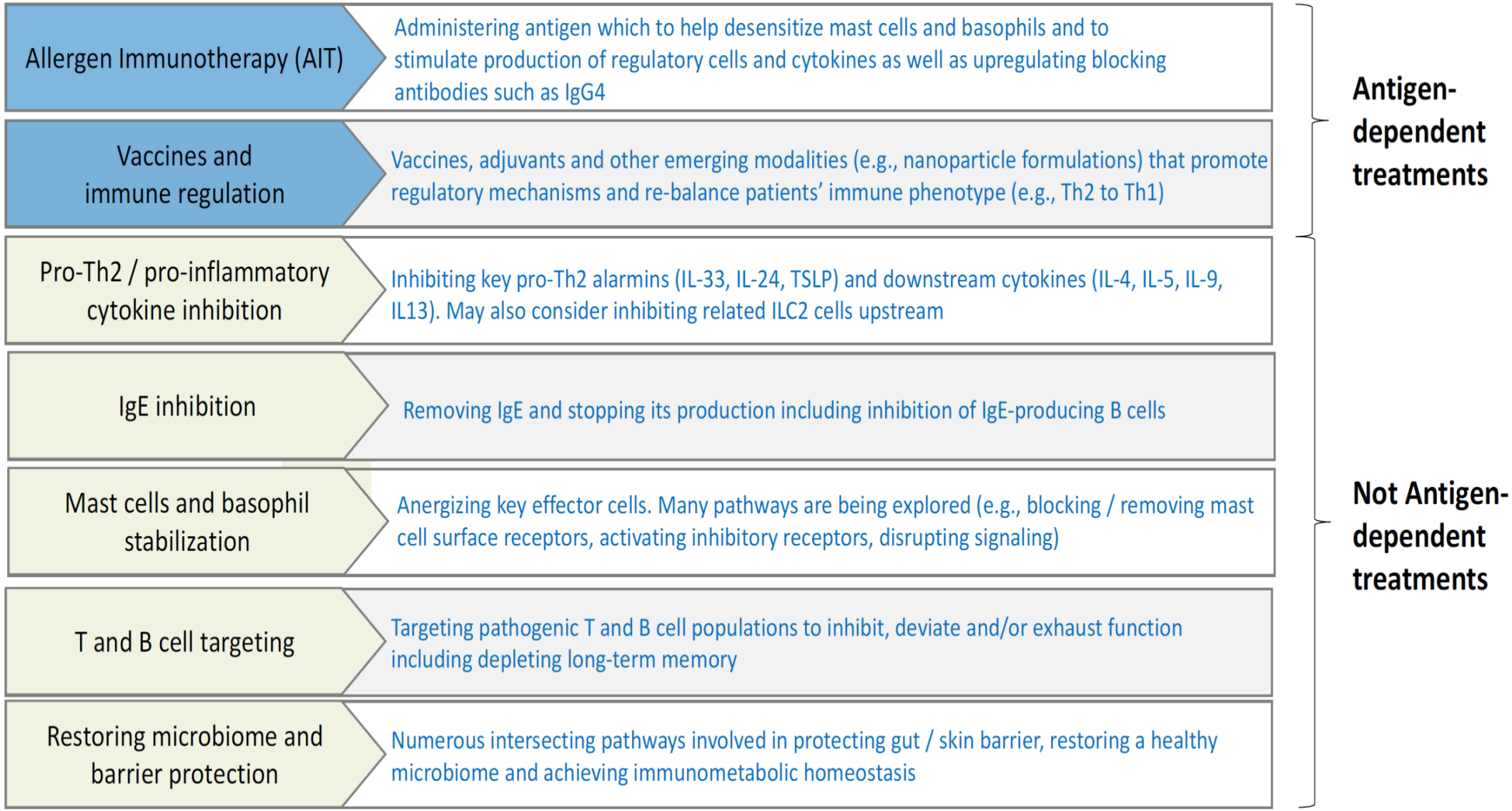
1. https://clinicaltrials.gov/ct2/show/NCT02163018; 2. https://clinicaltrials.gov/ct2/show/NCT02237196; 3. https://clinicaltrials.gov/ct2/show/NCT02920021;
4. https://clinicaltrials.gov/ct2/show/NCT03755713; 5. https://clinicaltrials.gov/ct2/show/NCT01906853; 6. https://clinicaltrials.gov/ct2/show/NCT03394508;
7. https://clinicaltrials.gov/ct2/show/NCT03936998; 8. https://clinicaltrials.gov/ct2/show/NCT02960074; 9. https://clinicaltrials.gov/ct2/show/NCT03567707
10. https://clinicaltrials.gov/ct2/show/NCT03667651; 11. https://clinicaltrials.gov/ct2/show/NCT02112734; 12. https://clinicaltrials.gov/ct2/show/NCT02490813. Alll sites accessed November 2019.

Potential Biologics for Food Allergy

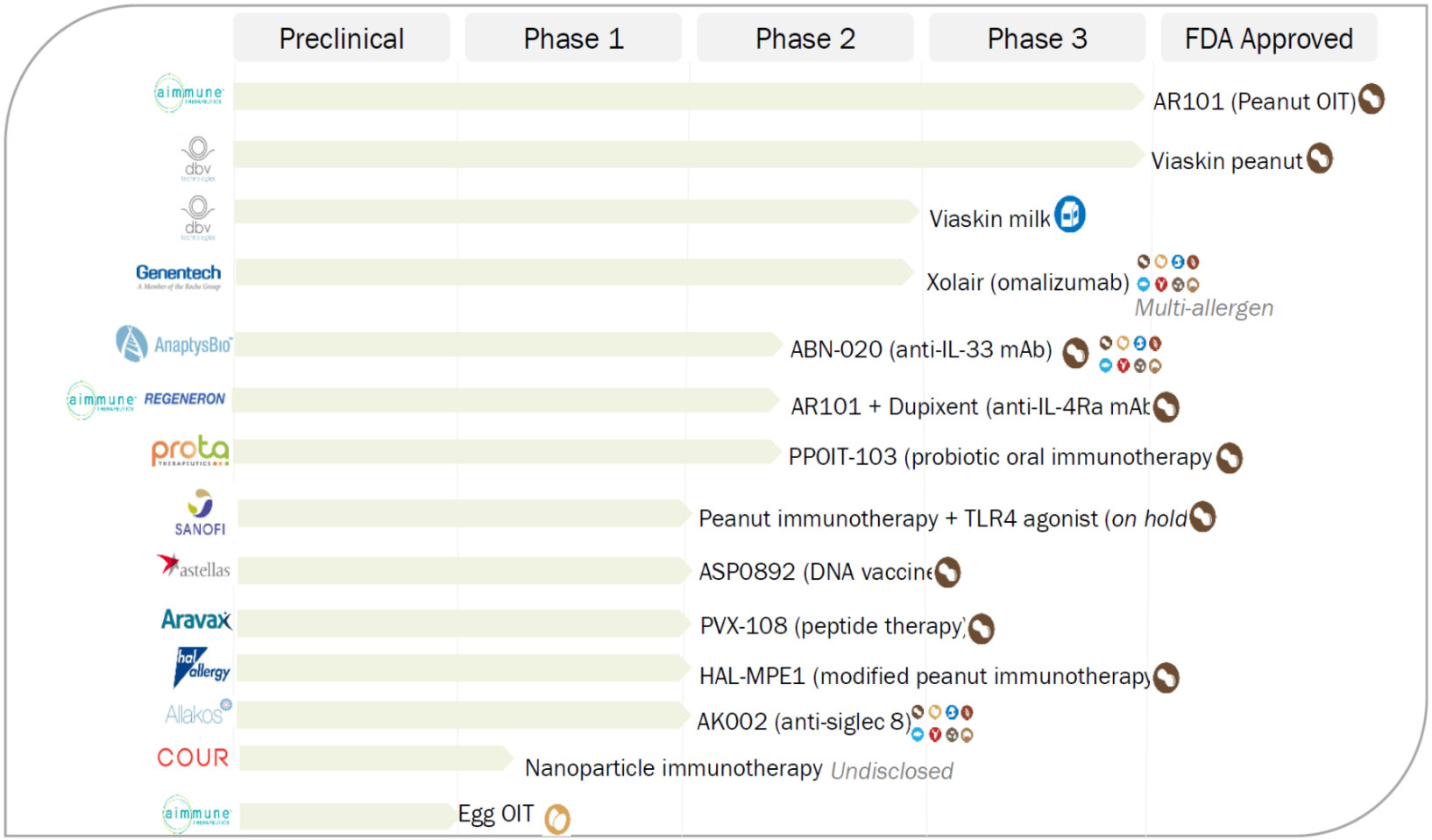


Adapted from: P Kolkhir, et al Annals Allergy

Novel Future Approaches to Food Allergy



FOOD ALLERGY DRUG PIPELINE



- A food allergy pipeline has begun to take shape with growing interest from biopharma
- Current efforts are still mostly targeted towards peanut, milk and egg allergy using allergen-specific immunotherapy
- Novel non-antigen-based therapies are also emerging, however, are still limited in total number

Source: Company websites and press releases, AAAAI abstracts and presentations, N Ventures and Advisory research and analysis

Points for Consideration

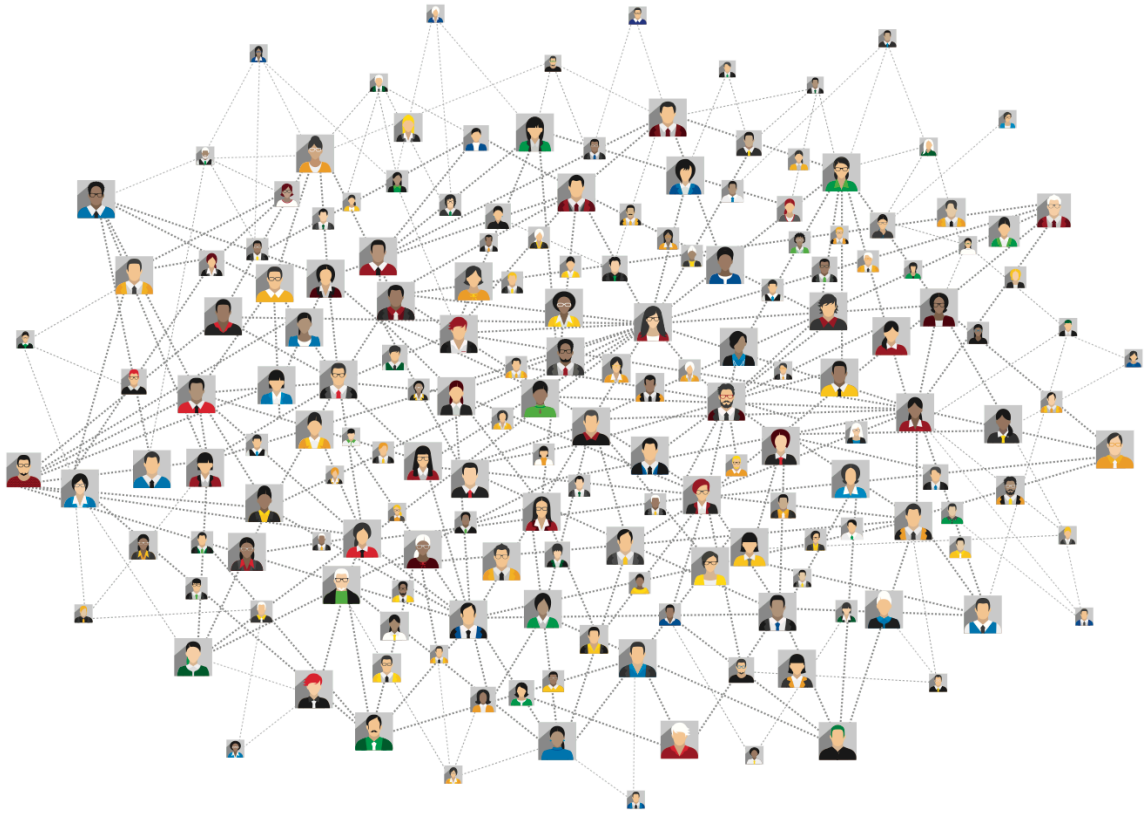
- Will a biologic prevent accidental exposure-induced allergic reactions (e.g., tolerate 300 to 600 mg peanut protein)?
- Will a biologic allow you to eat the food you are allergic to (e.g., a peanut butter sandwich)?
- Will a biologic drug change the immune system so you can achieve tolerance off therapy?
- With a projected 32 million food allergy patients in the U.S. and an average annual cost of $20,000 to 50,000 to treat each patient, how can the health care system afford this?
  - If everyone was treated: ***~$1 Trillion/year!***

Concluding Comments

Questions?

YOUR Food Allergy Story Drives Research Forward

FARE Patient Registry®



The FARE Patient Registry connects people living with food allergies to researchers seeking answers.

1. Enroll for free
2. Create your confidential patient profile
3. Take our surveys

FoodAllergyPatientRegistry.org

Thank you!