Allergies - what they tell us about our immune system and how we can treat them

Special Journal Club series on animal science

Marc Emmenegger
Aguzzi lab
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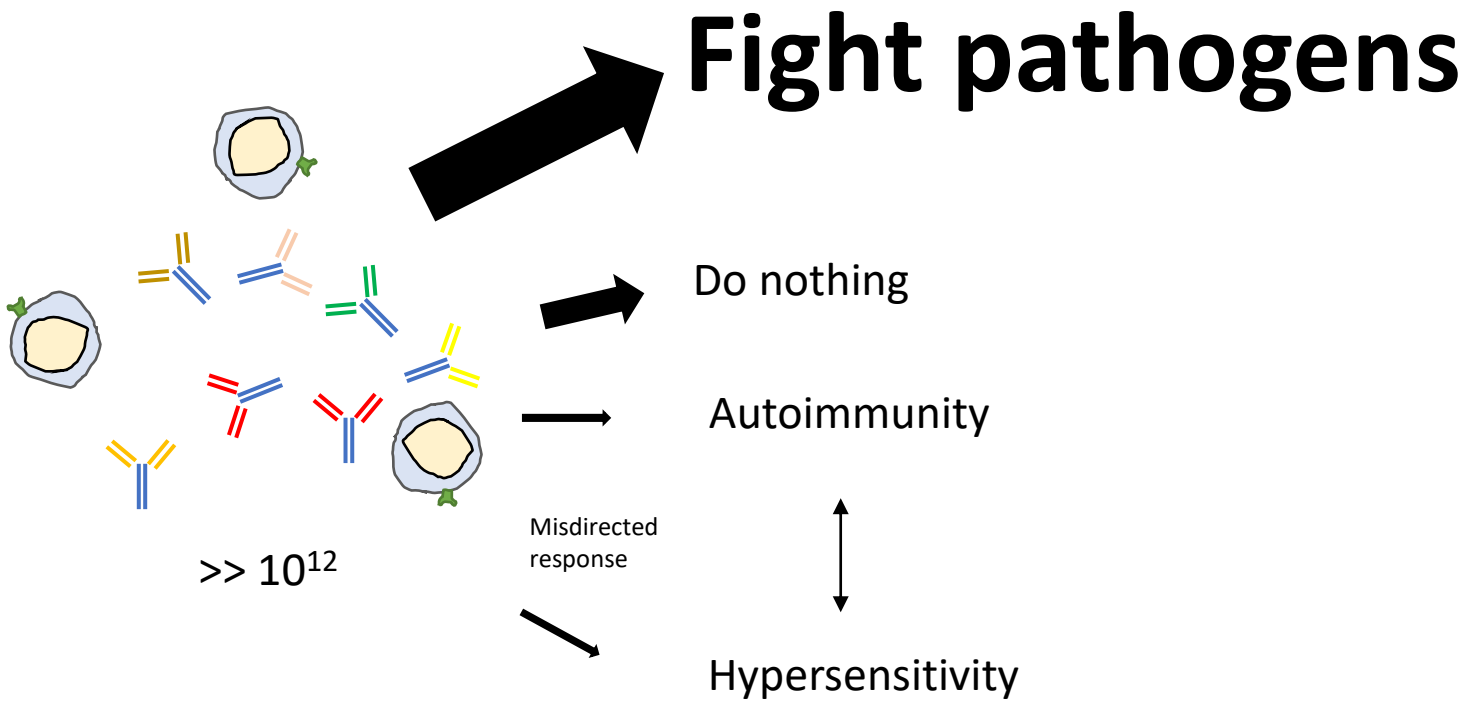
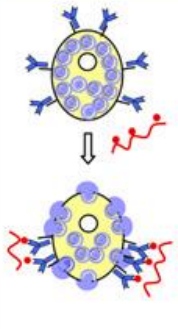
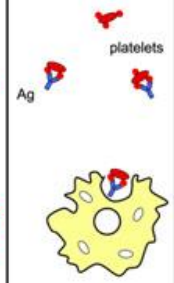
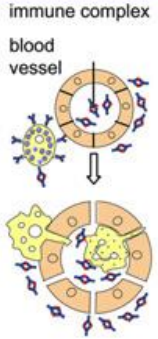
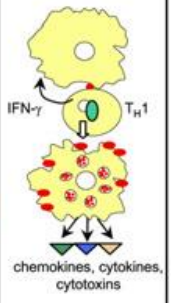
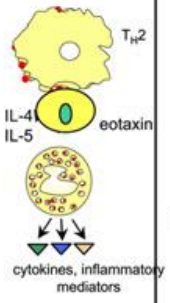
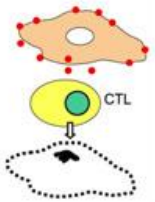
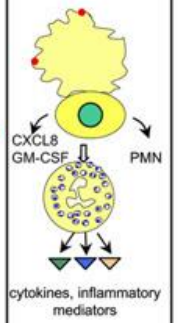
B and T cell diversity



Different forms of hypersensitivity

	Type I	Type II	Type III	Type IV a	Type IV b c	Type IV	Type IV d
Immune reactant	IgE	IgG	IgG	IIFNγ, TNFα (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8, IL-17 (?). GM-CSF (T-cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast-cell activation	FcR^+ cells (phagocytes, NK cells)	FcR^+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behçet disease

Pichter et al. 2010.

Allergies

Food

Insect/snake venom

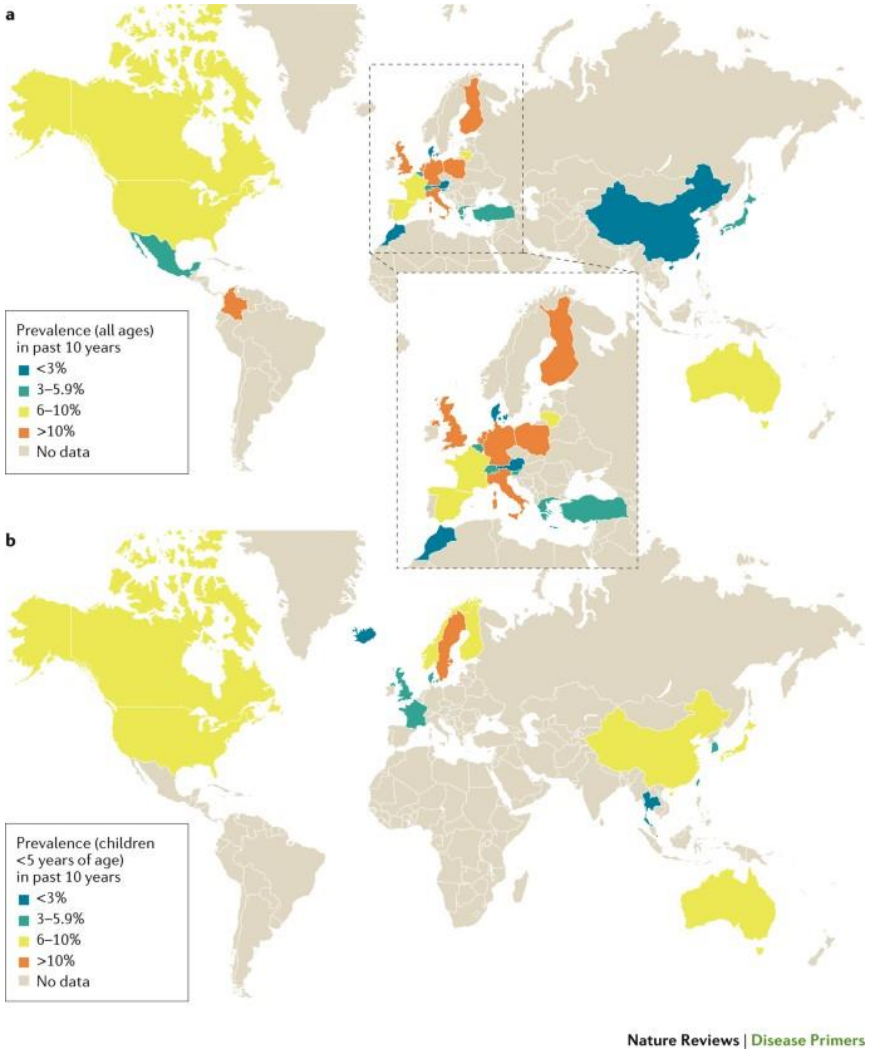
Pollen

Drugs

Animal

Food allergy

- **Is not intolerance** (does not arise from immune system dysregulation, e.g. lactase deficiency).
- Is quite prevalent, with an estimated 5-10% of US children under age 18.
- Approximately 40% of patients with food allergy have experienced a life-threatening allergic reaction.
- 30% of children with food allergy have multiple food allergies.
- **Can be very, very severe!**



Renz et al. 2018.

Classification of food allergies

- **IgE-mediated food allergies**
  - Risk of severe fatal reactions.
  - Cow milk, egg, wheat, soy seem to be outgrown, atopic responses to peanuts, tree nuts, and shellfish usually persist into adulthood.
  - Variation by region:
    - Children in Ghana: Pineapple, pawpaw, orange, mango, peanut.
    - North America: peanut, milk, egg, shellfish, soy.
    - Asia: shellfish; wheat allergy uncommon (except Japan and Korea: leading cause of anaphylaxis).
  - Following sensitisation, IgE-mediated degranulation of effector cells (mast cells, basophils), rapid manifestation of symptoms.
- **Mixed food allergies**
  - IgE-dependent and IgE-independent pathways.
  - Contribution of Th2 helper T cells.
  - Example: eosinophilic oesophagitis (EoE), not well studied.
- **Non-IgE-mediated food allergies**
  - Mostly directly affect the GI tract, rather than skin and respiratory tract.
  - E.g. food protein-induced enterocolitis syndrome, mostly in infants allergic to cow milk.

Allergen immunotherapy

Although mechanistically hardly understood, immunotherapy has been performed for more than 100 years.

One hundred years of allergen immunotherapy: Time to ring the changes

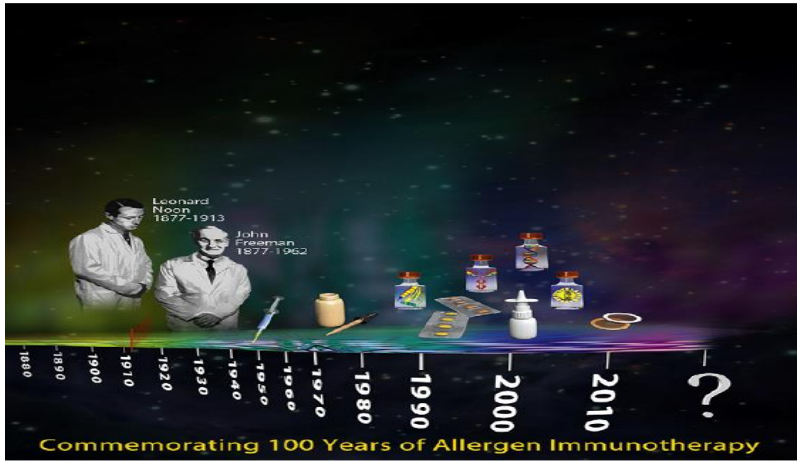
Stephen R. Durham, MD, FRCP,[a] and Donald Y. M. Leung, MD, PhD[b] *London, United Kingdom, and Denver, Colo*

TABLE I. One hundred years of allergen immunotherapy

Author(s)	Milestone	Year
Noon[1]	First grass pollen subcutaneous immunotherapy trial	1911
Prausnitz and Küstner[2]	Passive serum transfer of immediate skin prick test reactivity "reagin"	1921
Freeman[21]	First grass pollen rush immunotherapy trial	1930
Cooke et al[3]	Concept of serum blocking antibodies	1935
Frankland and Augustin[22]	First double-blind, placebo-controlled, subcutaneous grass pollen immunotherapy trial	1954
Lowell and Franklin[24]	Grass pollen effective in multiallergen mix subcutaneous immunotherapy	1965
Ishizaka et al[4] and Johansson and Bennich[5]	Discovery of IgE antibody	1966
Johnstone and Dutton[27]	Long-term benefits of subcutaneous immunotherapy in children	1968
Hunt et al[31]	Efficacy of Hymenoptera venom vs whole-body extract subcutaneous immunotherapy	1978
Warner et al[10]	Suppression of late asthmatic responses after mite immunotherapy	1978
Rocklin et al[12]	Role of antigen-specific suppressor T cells in immunotherapy	1980
Gleich et al[6]	Early increase in IgE level after ragweed subcutaneous immunotherapy, blunting of seasonal IgE	1982
Scadding and Brostoff[55]	First double-blind trial of sublingual immunotherapy	1986
Creticos et al[8]	Inhibition of allergic inflammation in the target organ after ragweed immunotherapy	1989
Rak et al[11]	Inhibition of late asthmatic responses after birch immunotherapy in adults	1991
Norman et al[73]	First T-cell peptide subcutaneous immunotherapy trial in patients with cat allergy	1996
Akdis et al[13]	Role of IL-10 and regulatory T cells in venom immunotherapy	1998
Passalacqua et al[9]	House dust mite allergoid sublingual immunotherapy	1998
Durham et al[68]	Long-term clinical efficacy of grass pollen subcutaneous immunotherapy	1999
Niederberger et al[80]	First trial of recombinant allergen subcutaneous immunotherapy in patients with birch allergy	2004
Creticos et al[76]	Ragweed Toll-like receptor 9 agonist subcutaneous immunotherapy	2006
Jacobsen[28]	Prevention of asthma after pollen subcutaneous immunotherapy in children (the PAT study)	2007
Durham et al[70]	Long-term clinical efficacy of grass pollen sublingual immunotherapy	2010

Allergen immunotherapy - history

- **Leonard Noon (1911)**: prophylactic inoculation with grass pollen extract in patients with hay fever resulted in effective desensitisation.
- **Prausnitz and Kuestner (1921)**: Serum factor (called ‘reagin’) may transfer immediate allergen sensitivity as shown by ‘skin prick test’.
- **Cooke (1935)**: Serum contains factors that confer ‘immunity’ as well as ‘hypersensitivity’.
- **Ishizaka, Johansson, Bennich (1966)**: IgE antibodies = ‘reagins’.
- **Creticos (1989)**: Allergen-specific IgG ‘blocking’ antibodies.
- **Rocklin (1980)**: Association between T cell responses and immunotherapy with discovery of peripheral antigen-specific T suppressor cells after desensitisation.
- **Akdis (1998)**: Role of Tregs.
- More than 100 years later, whole allergen extracts administered through subcutaneous route is still usual practice.



Immune mechanisms of oral immunotherapy

Michael D. Kulis, PhD,[a]* Sarita U. Patil, MD,[b]* Erik Wambre, PhD,[c]* and Brian P. Vickery, MD[a] *Chapel Hill, NC, Boston, Mass, and Seattle, Wash*

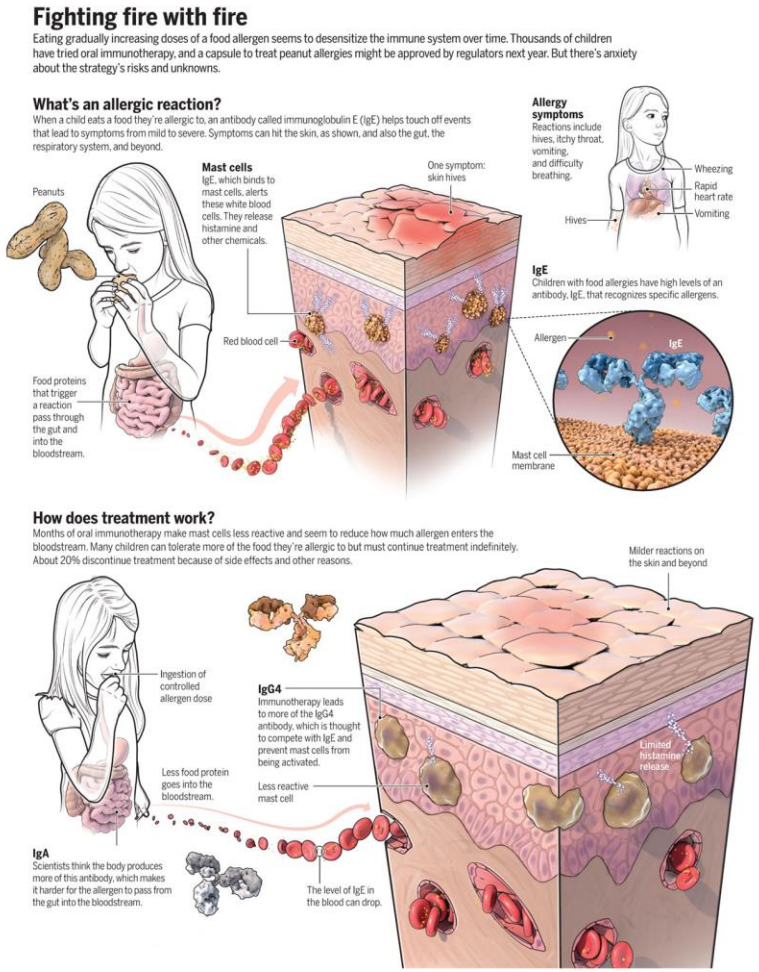
Immune mechanisms of OIT

- Oral administration of a protein to an animal, including humans, normally induces tolerance.
- However, it can lead to sensitisation and allergic disease.
- Several factors have been implicated to breaking tolerance:
  - Epithelial barrier damaging factors (alcohol, toxins, unknown ingredients).
  - Allergen type and exposure dose.
  - Type of adjuvants, microbial contamination.
  - Route of exposure. Perhaps, oral route less immunogenic.
  - Individual factors such as age and immune status, microbiome, barrier defects, diseases (e.g. atopy, dermatitis, rhinitis, immune deficiency).
- Mechanism of action poorly understood, **primarily studied on peripheral blood in human patients**.

Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Kulis et al. 2017.

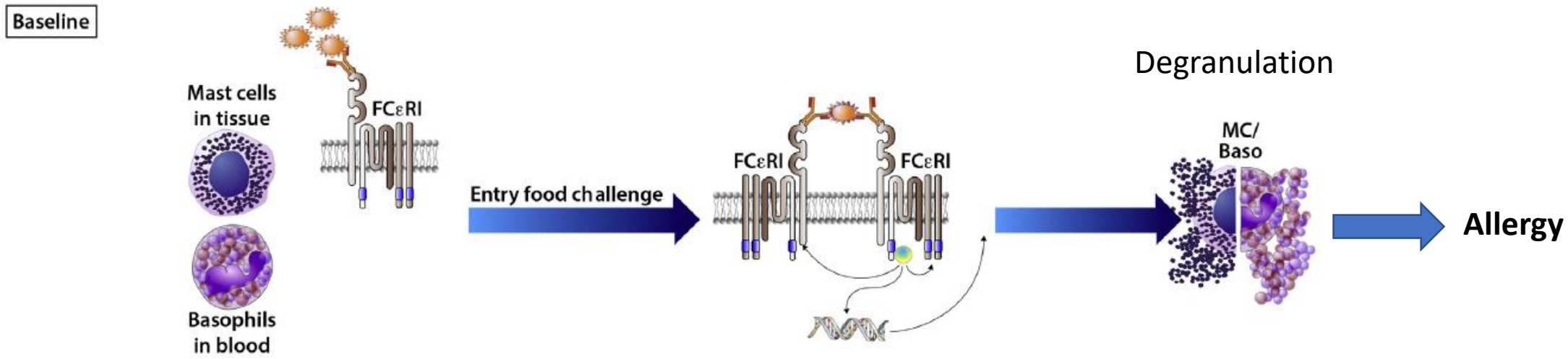
Immune mechanisms of OIT

- Primary clinical objective: induce a **desensitized state** defined as a temporary increase in threshold reactivity to the allergen.
- Continuous stimulation of immune system with subthreshold allergen doses, gradual increase.
- **Baseline** (untreated) – **Initiation** (dose escalation) – **Consolidation** (maintenance).



Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Kulis et al. 2017.
Couzin-Frankel, 2018.

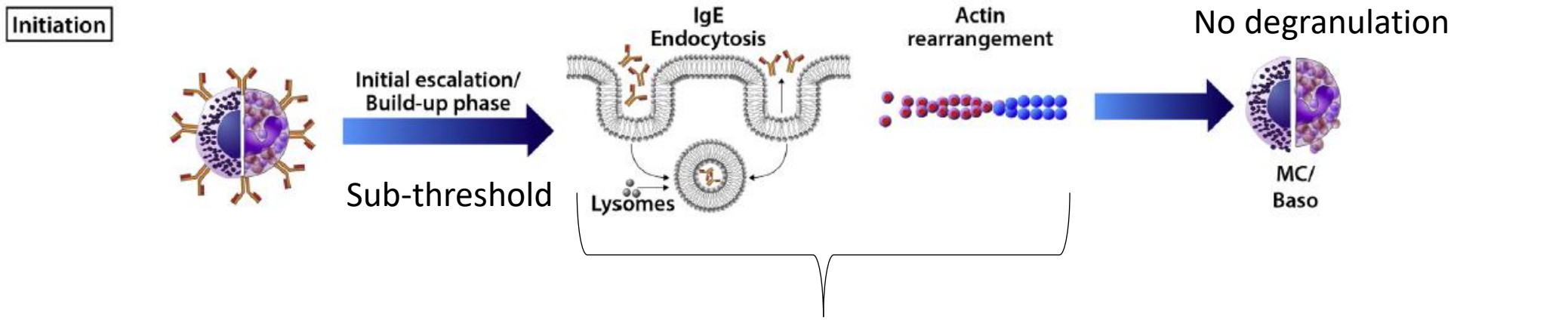
Immune mechanisms of OIT



- Basophils/mast cells express high-affinity FcεRI, primed with sIgE

Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Kulis et al. 2017.

Immune mechanisms of OIT



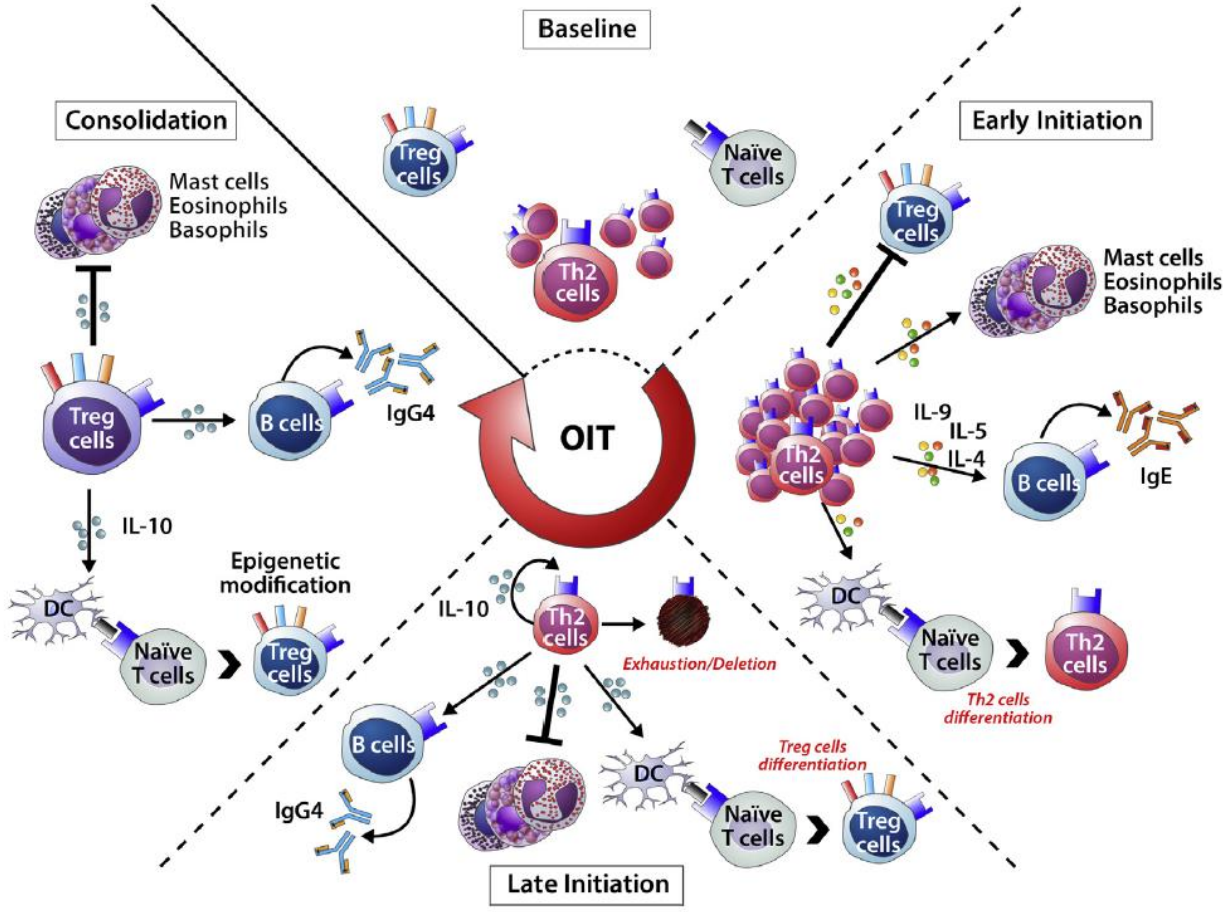
Down regulation of FcεRI on basophils/mast cells
Inhibition of calcium flux and actin remodelling

Short term desensitisation

- Decreased wheal size in skin prick test and basophil activation.
- **Suppression of effector cells as first effect**, in the absence of decreased sIgE levels.
- However, effect enhanced when depleting IgE populations (i.e. via omalizumab): more rapid escalation possible.
- Although specific allergens are used for OIT (e.g. peanut allergens), the **effect seems to be generic**, resulting in increased tolerance to other allergens not covered. This suggests that IgE signaling as such is targeted.

Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Kulis et al. 2017.

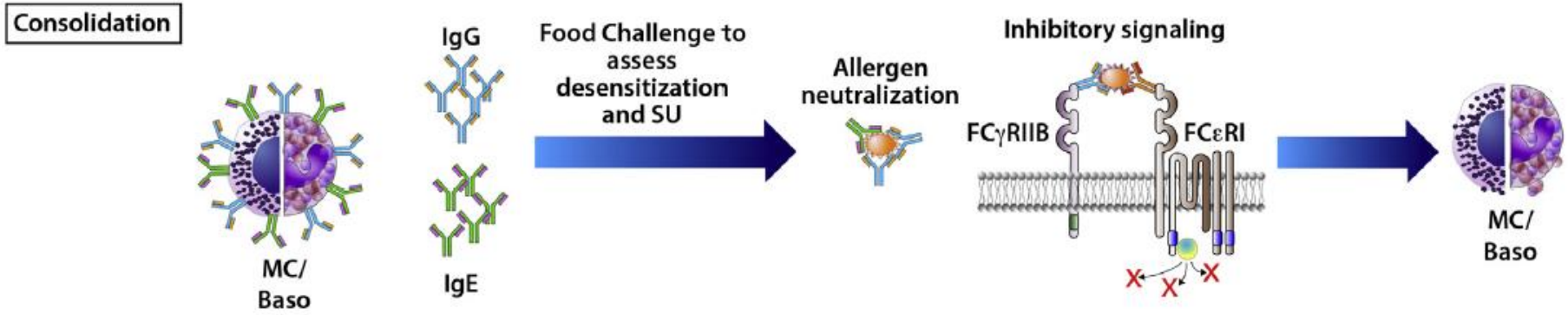
Immune mechanisms of OIT



- At baseline, atopic patients have a Th2-biased response.
- First doses (initiation):
  - Increased production of sIgE
  - Reinforcement of pathogenic Th2 cells
  - Creation of inhibitory milieu that hampers development of Treg response
- Escalation (late initiation):
  - Decrease in Th2 cell activity
  - IL-10-producing Th cells
  - Production of allergen-specific IgG4 antibodies
  - Overstimulation of Th2 cells may lead to their exhaustion and anergy.

Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Kulis et al. 2017.

Immune mechanisms of OIT

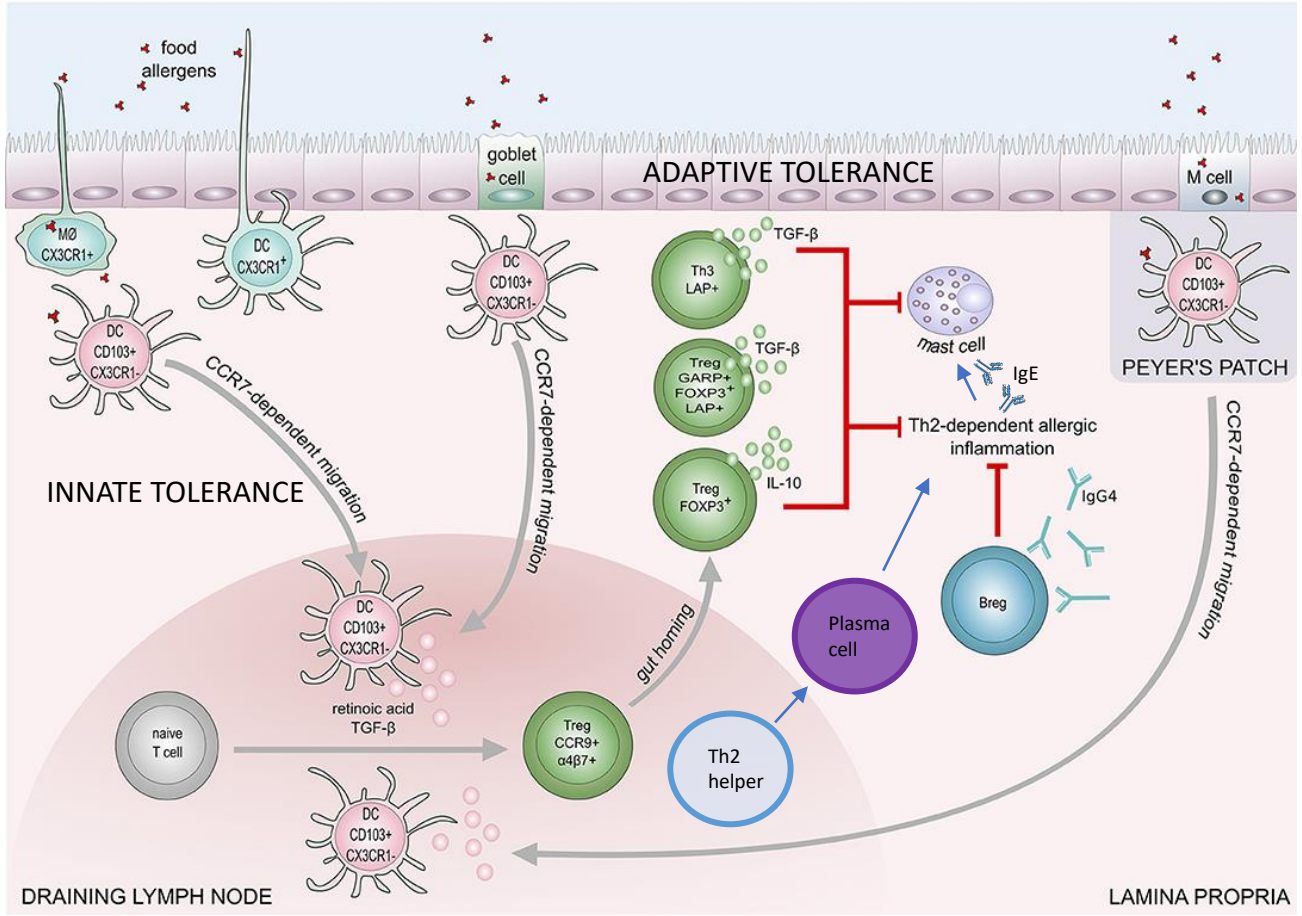


- Changes in antibody and effector cell responses are likely associated with changes at the T cell level.
- Increased IgG4 levels within few months: sequestration of allergen via IgA and IgG4.
- Negative signaling on basophil/mast cells via FcγRIIb.

Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Kulis et al. 2017.

Proposed immune mechanisms - summary

1. After ingestion, food proteins broken down by hydrolytic enzymes in the GI tract.
2. Remaining food proteins/peptides transported from lumen to mucosa via Goblet cells and M cells above Peyer's patches or direct sampling via mucosal dendritic cells extending into lumen.
3. In the mucosa, DCs internalise and process these proteins/peptides and move to T cell areas of draining lymph nodes.
4. DC interaction with naïve T cells in lymph nodes, antigen presentation via MHC II.
5. **Physiological response**: Induction of ADAPTIVE TOLERANCE via homing of T and B cell subsets.
6. **Pathophysiological response**: The naïve T cells differentiate into effector Th2 cells in the presence of IL-4, resulting in B cell differentiation into IgE-producing plasma cells.



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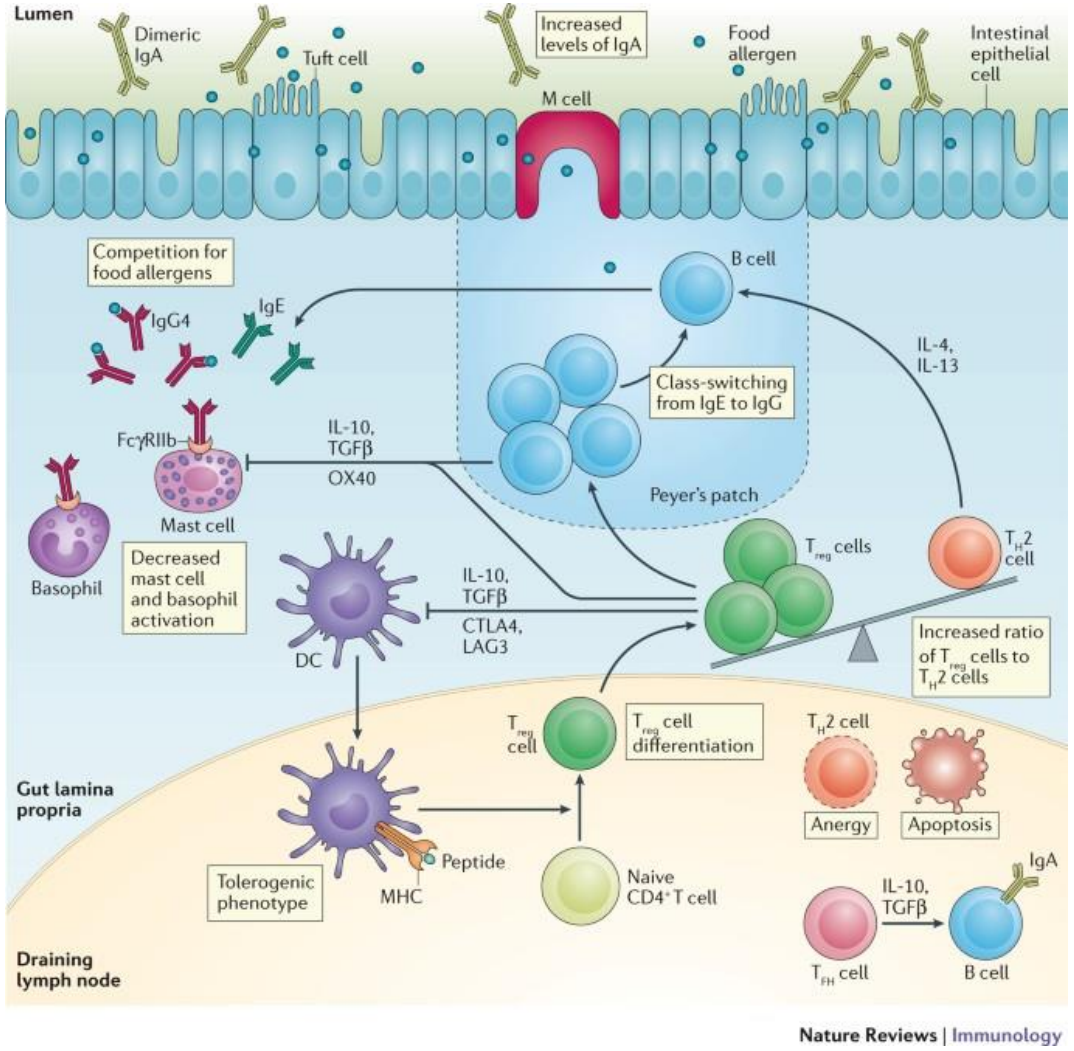
7. **OIT response**: Altered cytokine milieu leads to **Treg** instead of Th2 (anergy) homing, followed by B cell differentiation into **IgG4** instead of IgE-expressing B cells (**competition**), and a **decreased basophil/mast cell activation**.
8. **However, the mechanisms by which tolerance or allergy are induced are far from being understood.**



Satitsuksanoa et al. 2018.
Sampson et al. 2017.
Yu et al. 2016.

AR101 Oral Immunotherapy for Peanut Allergy

The PALISADE Group of Clinical Investigators*

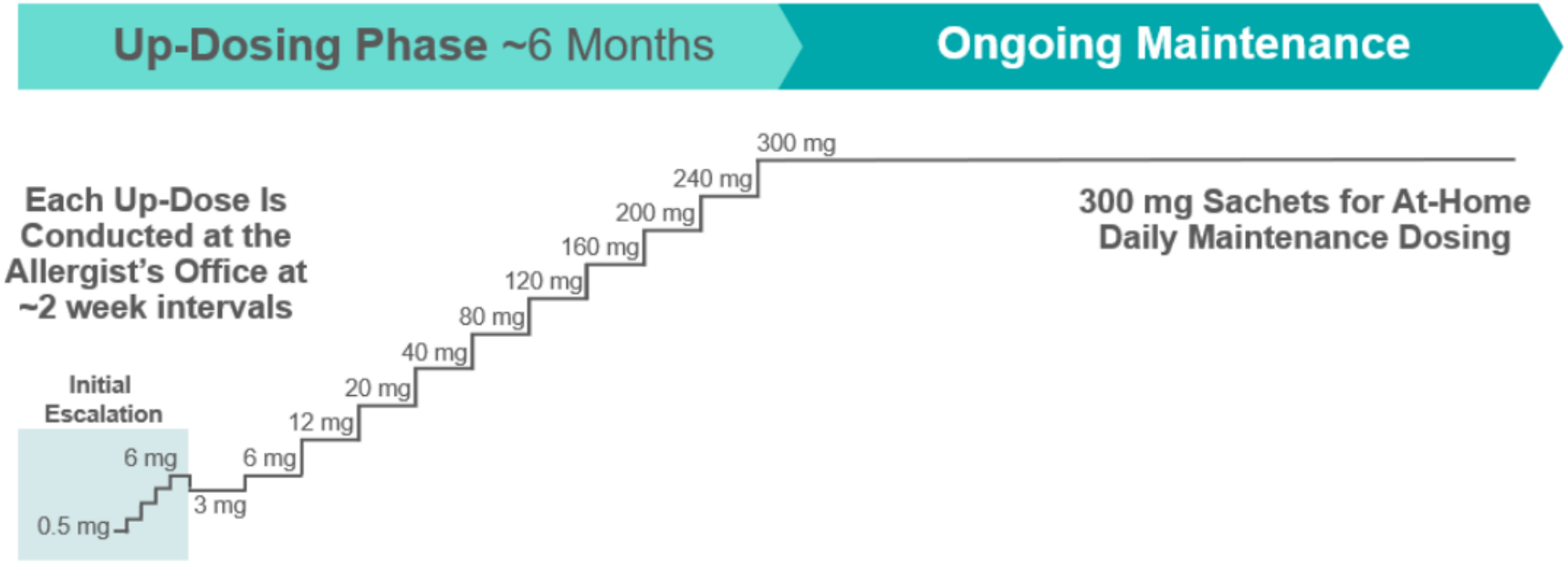
AR101 Oral Immunotherapy for Peanut allergy

- Peanut allergies are most severe form of allergy, persisting into adulthood and often life-threatening.
- Standard of care: Strict elimination diet, timely administration of rescue medication in case of allergic reaction on accidental exposure.
- However, exposure cannot always be avoided despite vigilance.
- Lifelong risk of reactions, in spite of being an otherwise healthy child/adult.
- AR101 is a peanut-derived oral biologic drug that delivers a target daily maintenance dose of 300 mg of peanut protein.

AR101 Oral Immunotherapy for Peanut allergy

- Multicenter, double-blind, placebo-controlled, phase 3 trial at 66 sites in 10 countries in North America and Europe.
- Persons 4 to 55 years of age who had a clinical history of peanut allergy and supportive test results were considered to be eligible for participation in the trial if
  - they had a serum peanut-specific IgE level of at least 0.35 kUA (allergen-specific unit) per liter according to ImmunoCAP (Thermo Fisher Scientific),
  - a mean wheal diameter that was at least 3 mm larger than the negative control on skin-prick testing for peanut,
  - or both.
- The baseline characteristics of the participants 4 to 17 years of age were consistent with peanut allergy and were well balanced between the two trial groups.
- A majority of participants had a history of peanut anaphylaxis (72%), asthma (53%), and multiple food allergies (66%).
- The median maximum tolerated dose of peanut protein at the initial screening food challenge was 10 mg.

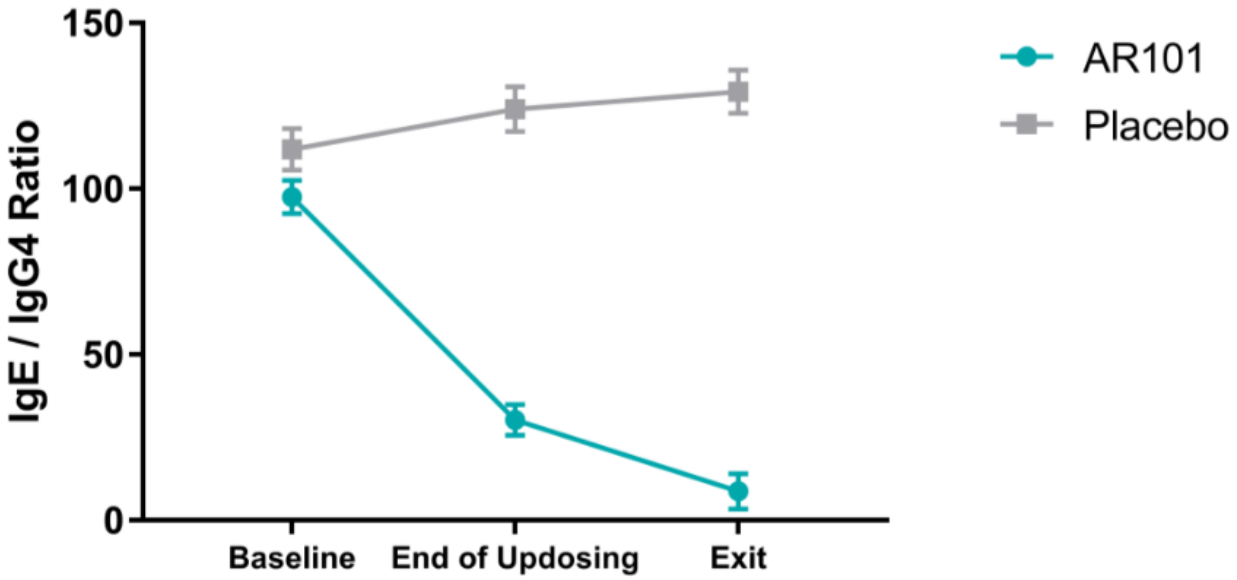
AR101 Oral Immunotherapy for Peanut allergy



Initial challenge

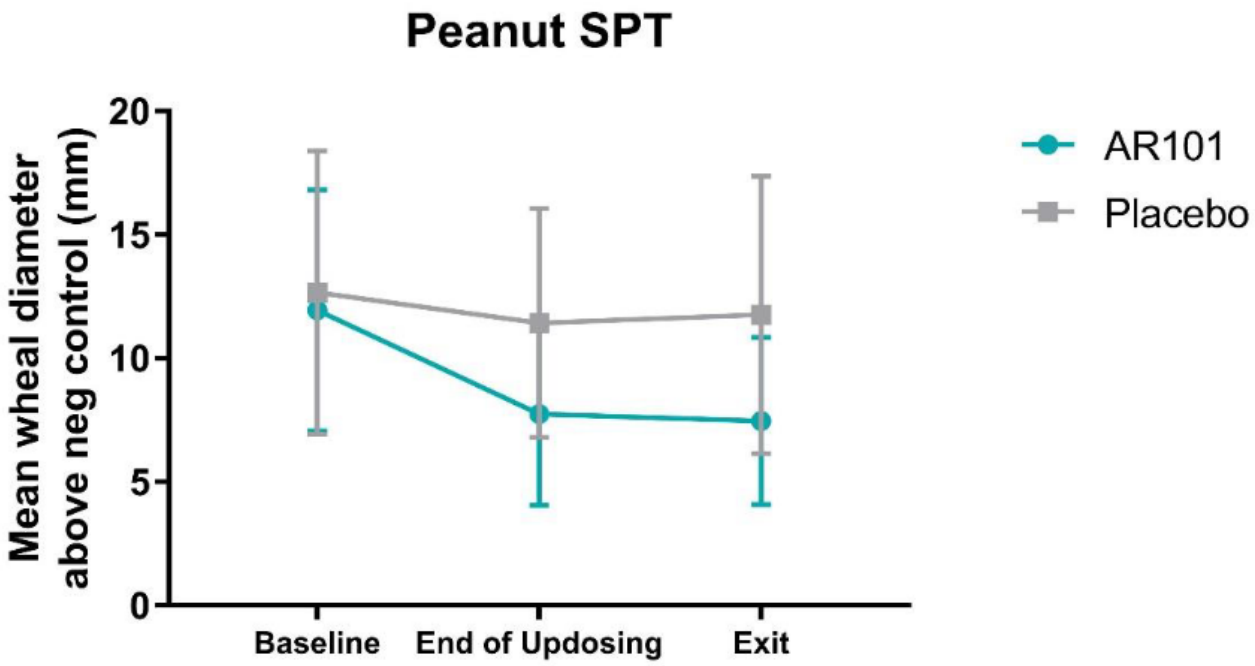
Exit challenge

AR101 Oral Immunotherapy for Peanut allergy



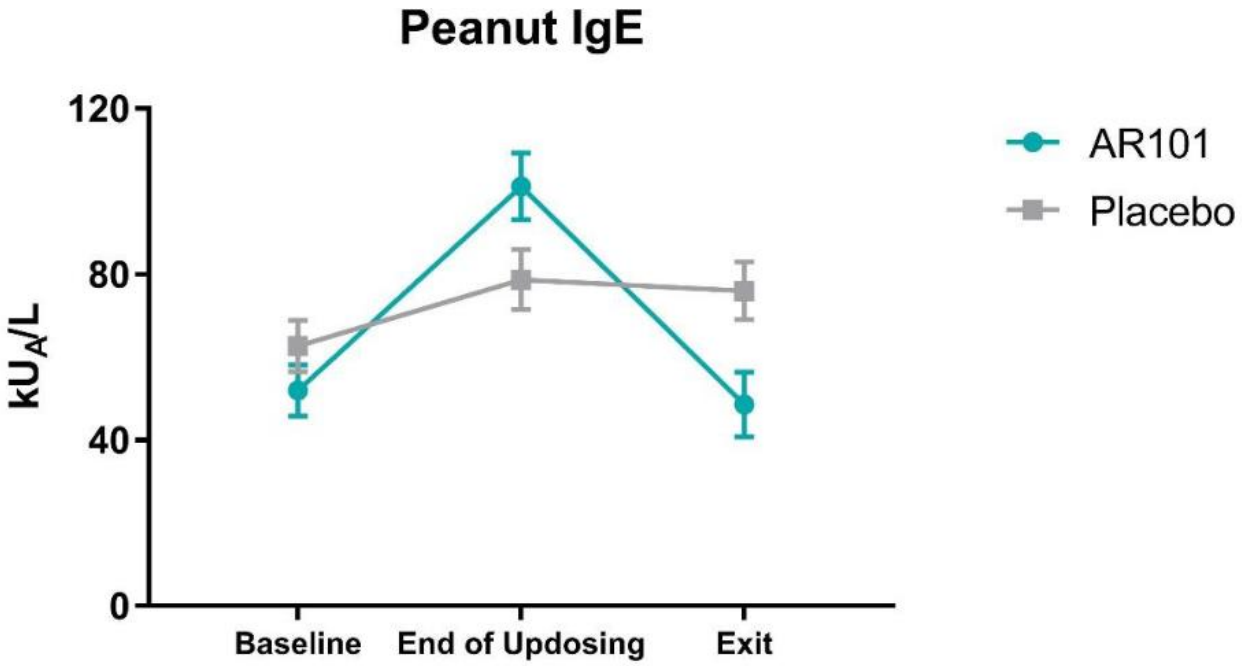
- Peanut-specific IgE to IgG4 in placebo and AR101-treated group.

AR101 Oral Immunotherapy for Peanut allergy



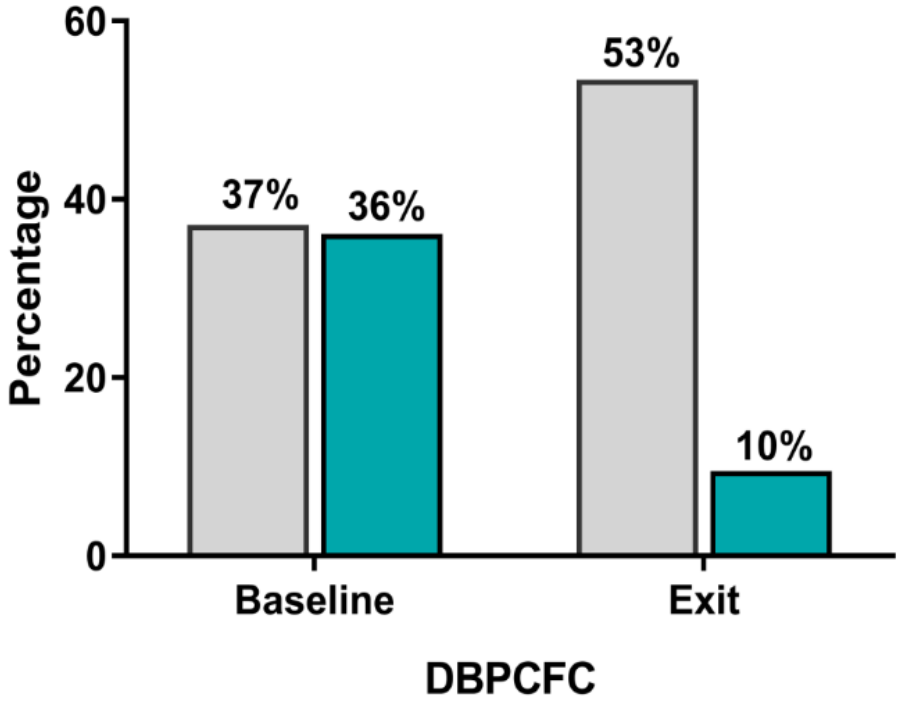
- Peanut-specific skin prick test diameter above negative control.
- Reduction already before maintenance.

AR101 Oral Immunotherapy for Peanut allergy



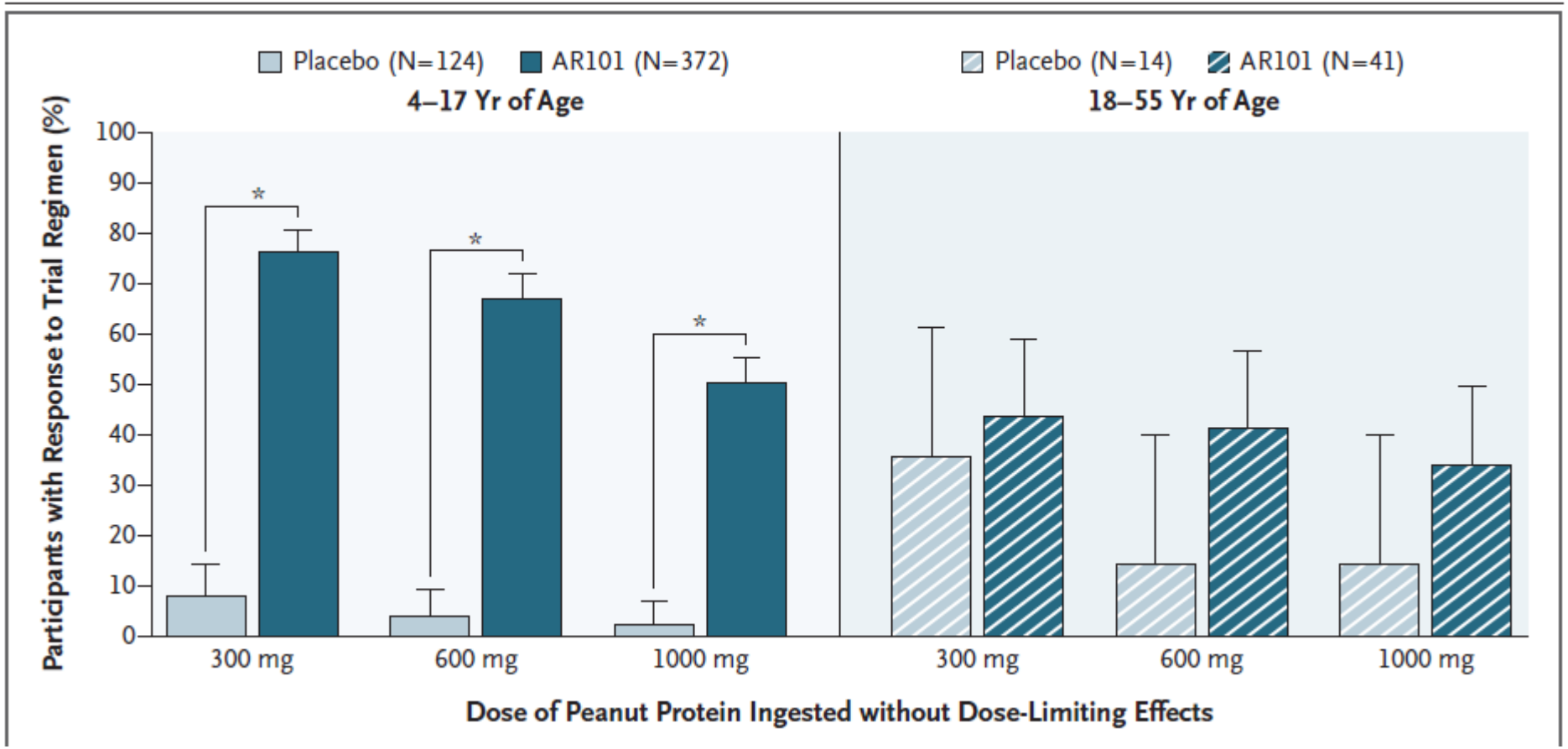
- Peanut-specific IgE levels first increase and decrease only during maintenance.

AR101 Oral Immunotherapy for Peanut allergy



- Utilisation of rescue epinephrine at baseline and exit.
- Clear reduction in AR101-treated versus placebo.

AR101 Oral Immunotherapy for Peanut allergy



AR101 Oral Immunotherapy for Peanut allergy

Efficiency

- Significant desensitisation in group 4-17 years but not in older group (18-55 years).
- 67% of participants in the age group 4-17 years could tolerate a single dose of at least 600 mg of peanut protein (two whole peanut kernels), while before treatment, they could tolerate no more than 30 mg (1/10 of a peanut kernel).
- Overall, the threshold dose of peanut exposure triggering the onset of clinically significant allergic symptoms could be raised and symptoms where attenuated when they occurred.

Safety

- Adverse events were common.
- Serious adverse events in 6% of participants in the active-drug group and 2% in placebo.

AR101 Oral Immunotherapy for Peanut allergy

Table 2. Adverse Events Affecting More Than 5% of the Participants 4 to 17 Years of Age in Either Group, According to Trial Phase.*

Event	Initial Dose-Escalation Phase		Increasing-Dose Phase		Maintenance Phase		Overall	
	AR101 (N=372)	Placebo (N=124)	AR101 (N=366)	Placebo (N=123)	AR101 (N=310)	Placebo (N=118)	AR101 (N=372)	Placebo (N=124)
	number of participants with event (percent)							
≥1 Adverse event	189 (50.8)	36 (29.0)	353 (96.4)	108 (87.8)	270 (87.1)	94 (79.7)	367 (98.7)	118 (95.2)
Abdominal pain	83 (22.3)	8 (6.5)	156 (42.6)	25 (20.3)	46 (14.8)	7 (5.9)	194 (52.2)	30 (24.2)
Vomiting	15 (4.0)	0	127 (34.7)	22 (17.9)	50 (16.1)	14 (11.9)	154 (41.4)	30 (24.2)
Upper abdominal pain	9 (2.4)	3 (2.4)	136 (37.2)	17 (13.8)	41 (13.2)	9 (7.6)	152 (40.9)	26 (21.0)
Oral pruritus	36 (9.7)	8 (6.5)	131 (35.8)	15 (12.2)	39 (12.6)	5 (4.2)	151 (40.6)	20 (16.1)
Nausea	31 (8.3)	1 (0.8)	128 (35.0)	22 (17.9)	45 (14.5)	8 (6.8)	146 (39.2)	29 (23.4)
Oral paresthesia	4 (1.1)	2 (1.6)	57 (15.6)	5 (4.1)	23 (7.4)	2 (1.7)	65 (17.5)	8 (6.5)
Lip swelling	2 (0.5)	0	25 (6.8)	3 (2.4)	13 (4.2)	2 (1.7)	38 (10.2)	5 (4.0)
Cough	10 (2.7)	0	117 (32.0)	30 (24.4)	61 (19.7)	22 (18.6)	152 (40.9)	42 (33.9)
Throat irritation	28 (7.5)	5 (4.0)	131 (35.8)	26 (21.1)	43 (13.9)	11 (9.3)	152 (40.9)	34 (27.4)
Rhinorrhea	6 (1.6)	1 (0.8)	82 (22.4)	25 (20.3)	46 (14.8)	9 (7.6)	113 (30.4)	28 (22.6)
Sneezing	16 (4.3)	3 (2.4)	76 (20.8)	15 (12.2)	33 (10.6)	5 (4.2)	98 (26.3)	18 (14.5)
Throat tightness	14 (3.8)	3 (2.4)	70 (19.1)	6 (4.9)	20 (6.5)	0	86 (23.1)	8 (6.5)
Dyspnea	2 (0.5)	1 (0.8)	32 (8.7)	3 (2.4)	17 (5.5)	1 (0.8)	44 (11.8)	5 (4.0)
Dysphonia	1 (0.3)	0	19 (5.2)	2 (1.6)	8 (2.6)	1 (0.8)	25 (6.7)	2 (1.6)
Pruritus	25 (6.7)	8 (6.5)	117 (32.0)	25 (20.3)	45 (14.5)	14 (11.9)	153 (41.1)	34 (27.4)
Urticaria	16 (4.3)	3 (2.4)	115 (31.4)	23 (18.7)	63 (20.3)	17 (14.4)	143 (38.4)	30 (24.2)
Rash	12 (3.2)	1 (0.8)	61 (16.7)	15 (12.2)	24 (7.7)	7 (5.9)	81 (21.8)	18 (14.5)
Chest discomfort	2 (0.5)	0	19 (5.2)	1 (0.8)	8 (2.6)	0	24 (6.5)	1 (0.8)
Systemic allergic reaction†	1 (0.3)	0	31 (8.5)	2 (1.6)	27 (8.7)	2 (1.7)	53 (14.2)	4 (3.2)
Ear pruritus	3 (0.8)	0	23 (6.3)	0	7 (2.3)	0	25 (6.7)	0

Including anaphylaxis →

* The data in the maintenance-phase and overall columns exclude symptoms that were recorded during the exit double-blind, placebo-controlled food challenge.
† Events of systemic allergic reaction included one case of severe anaphylaxis in the active-drug group during the maintenance phase.

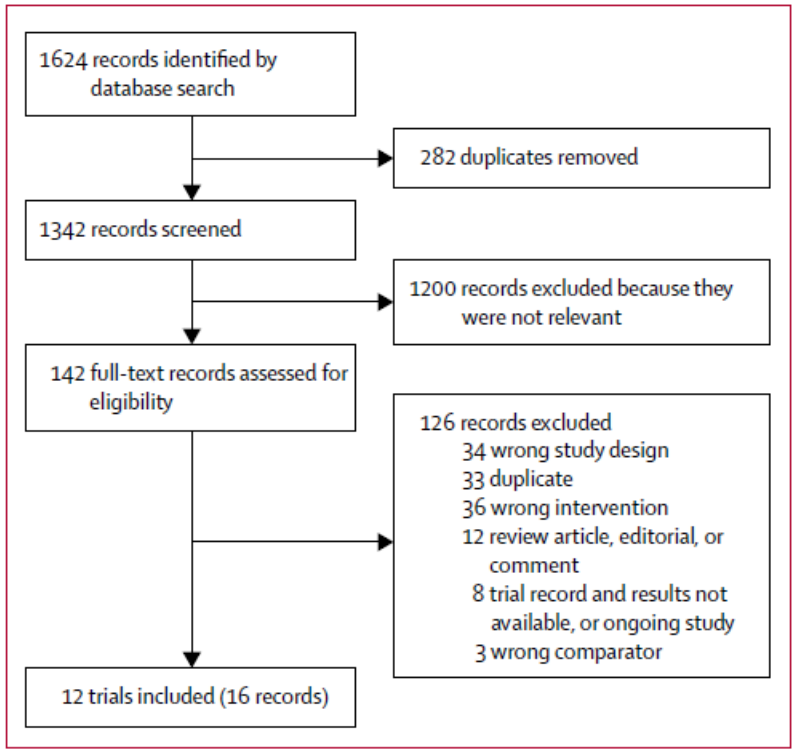
Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety

Derek K Chu, Robert A Wood, Shannon French, Alessandro Fiocchi, Manel Jordana, Susan Waserman, Jan L Brożek, Holger J Schünemann

PACE - introduction

- Without any other treatment options, there is a growing public, medical, and commercial interest in the therapeutic potential of oral immunotherapy for food allergies.
- Allergen immunotherapy was first established in 1911 by Noon and Freeman who used grass pollen extracts to treat hay fever.
- Repeated exposure over time to incrementally increasing doses of the allergen to which the patient is allergic.
- Principal aim of immunotherapy is to reduce disease-related allergic reactions.
- For **inhalant allergies**, this reduction entails less nasal congestion and rhinorrhoea in allergic rhinoconjunctivitis, or fewer exacerbations in asthma.
- Randomised-controlled trials (**RCTs**) and meta-analyses **support the safety and efficacy** of sublingual and subcutaneous immunotherapy **for these respiratory allergic conditions**.
- **In contrast, narrative reviews, observational studies, and a historical lack of randomized trials** drive the debate on whether oral **immunotherapy for food allergy** is ready for routine and widespread clinical use, or whether it should remain an investigational therapy (ie, more research is needed).

PACE



	Country	Setting		Intervention and comparator assignments						Restrictions		Participants		
		Entry OFC	Median follow-up, years	OIT group	Proprietary	No OIT group	Starting dose (mg)	Target dose (mg)	Time to achieve maintenance (weeks), median	Strictly avoid peanut?	Other restrictions	Sample size, n	Median age, years	Women, n (%)
Varshney et al (2011)[23]	USA	No	1·00	OIT	No	Placebo	0·1	4000	50	Yes	No dose if fever, infection, or otherwise feeling ill; dose on full stomach	28	5·75	10 (36%)
STOP II (2014)[24]	UK	Yes	0·50	OIT	Yes	Avoidance	2	800	26	No mention	Dose with food; no exercise for 2 h after dose	99	12·4	29 (29%)
PPOIT (2015)[25–27]	Australia	No	5·80	OIT and probiotic	Yes	Placebo	0·1	2000	36	Yes	-	62	5·95	25 (40%)
Narisety et al (2015)[28]	USA	Yes	1·33	OIT	No	Sublingual immunotherapy	0·1	2000	16	Yes	No exercise for 2 h after dose; call for individualised instructions during fever, and either full dose or skip dose	21	11·1	10 (48%)
ARC001 (2017)[29]	USA	Yes	0·42	OIT	Yes	Placebo	0·5	300	22	Yes	No exercising, or taking hot showers or baths within 4 h; dose reduction during menstrual period	55	7·5	19 (35%)
PMIT (NCT00597675; 2017)	USA	No	1·00	OIT	No	Placebo	2	4000	..	No mention	..	10	5·4	3 (30%)
PnOIT3 (NCT00815035; 2017)	USA	No	0·85	OIT	No	Placebo	..	4000	..	No mention	..	16	5	10 (63%)
PNOIT (NCT01324401; 2018)	USA	No	1·08	OIT	No	Avoidance	..	4000	44	No mention	..	30	9	12 (40%)
Blumchen et al (2018)[30]	Germany	Yes	1·33	OIT	No	Placebo	0·5	125–250	56	Yes	No exercise activity for 2 h	62	6·8	24 (39%)
PALISADE (2018)[31–33]	North America and Europe	Yes	1·00	OIT	Yes	Placebo	0·5	300	26	Yes	No exercise, or showering or bathing within 3 h; dose reduction during menstrual period; no dose within 2 h of bedtime; no dose without food; must dose daily	551	11·3	236 (43%)
PITA (2018)[35]	France	Yes	0·46	OIT	No	Placebo	2	400	24	Yes	No sports for 2 h after dose nor any condition of stress likely to be induced either by effort or sun exposure	30	14·75	8 (27%)
TAKE-AWAY (2018)[34,36]	Norway	Yes	1·07	OIT	No	Avoidance	1	5000	56	Yes	No exercise within 2 h after dose; monitor during menses; no dose if ongoing infections, asthma exacerbations, excessive tiredness, or vaccinations	77	9·5	33 (43%)

OFC=oral food challenge. OIT=oral immunotherapy.

Table 1: Characteristics of included oral immunotherapy studies

PACE – meta-analysis on twelve studies

- 1041 participants in total with OIT/placebo/avoidance, median of median age 8.7 (5.9-11.2) years, 39% female, 61% male.
- In all trials, both groups were instructed to strictly avoid peanut consumption other than that provided in the study.
- Across all trials, median starting dose was 0·5 mg (IQR 0·2–1·75).

PACE

	Sample size	Risk ratio* (95% CI)	Anticipated absolute effects (95% CI) per 1000 individuals			Grades of evidence	Main findings†‡§
			No OIT	OIT	Risk difference		
Anaphylaxis	9 RCTs; 891 participants	3·12 (1·76–5·55)	71¶	222 (125–394)	151 (54–323)	High	Peanut OIT results in large increase in anaphylaxis; NNT_H 7 (3–19); IRR 2·72 (1·57–4·72)
Epinephrine use‡	9 RCTs; 984 participants	2·21 (1·27–3·83)	37	82 (47 to 142)	45 (10–105)	High	Peanut OIT results in large increase in epinephrine use; NNT_H 22 (10–100); IRR 2·87 (1·70–4·85)
Serious adverse events	12 RCTs; 1041 participants	1·92 (1·00–3·66)	62‖	119 (62–227)	57 (0–165)	Moderate**	Peanut OIT probably increases serious adverse events (death, life threatening, disability, or requiring urgent medical intervention or hospitalisation to prevent these events); NNT_H 18 (6–5376)
Vomiting, representative of gastrointestinal reactions††	6 RCTs; 755 participants	1·79 (1·35–2·38)	186	334 (252–444)	147 (65 to 257 more)	High	Peanut OIT results in large increase in vomiting frequency; NNT_H 6 (4–14); IRR 2·11 (1·54–2·89)
Angioedema, representative of mucocutaneous reactions‡‡	5 RCTs; 694 participants	2·25 (1·13–4·47)	39	88 (44–174)	49 (5 to 135 more)	High§§	Peanut OIT increases angioedema; NNT_H 20 (7–200); IRR 2·51 (1·79–3·51)
Nasal congestion or blockage, representative of respiratory reactions§§	6 RCTs; 724 participants	1·36 (1·02–1·81)	178	241 (181–321)	64 (4 to 144 more)	Moderate¶¶	Peanut OIT probably increases nasal congestion or blockage (rhinitis); NNT_H 16 (7–250); IRR 1·48 (1·04–2·10)
Surrogate for exposure to peanut outside of clinic without a reaction: passing a supervised food challenge in-clinic	9 RCTs; 917 participants	12·42 (6·82–22·61)	32	397 (218–723)	365 (186 to 691 more)	High‖‖	Peanut OIT results in large increase in completing a supervised oral food challenge without an allergic reaction, but this does not translate into less reactions outside of clinic; for every gram increase in total cumulative challenge dose, the chance of passing decreases by 26%; NNT 3 (1–5)

PACE - conclusions

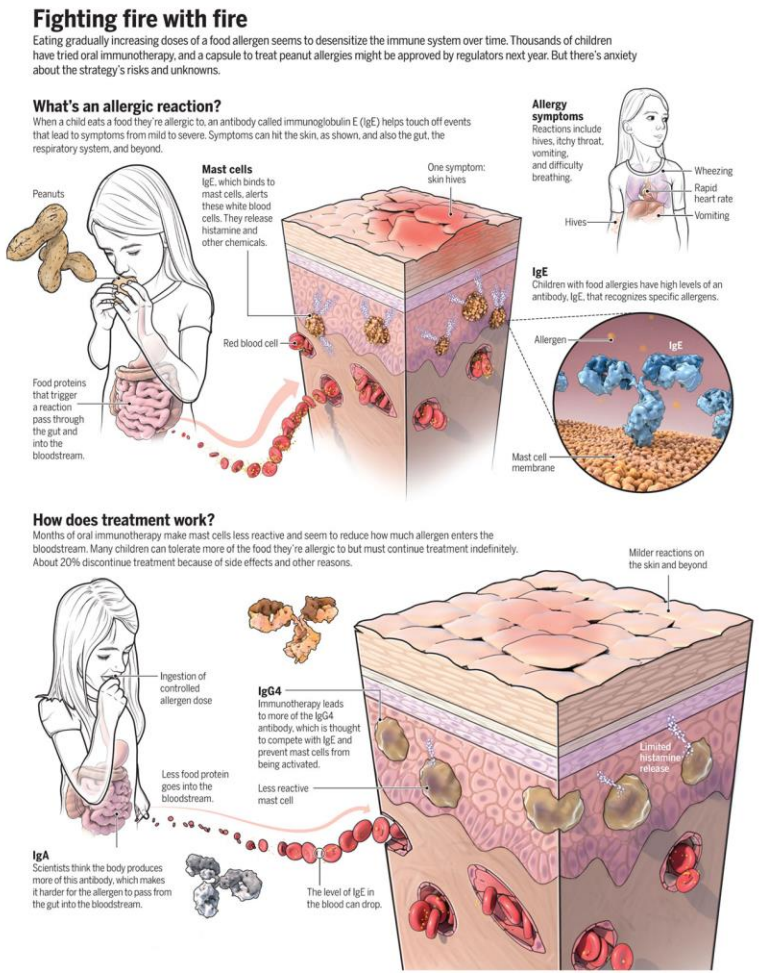
- Current peanut oral immunotherapy approaches **increase the chance and frequency of allergic reactions**, including
  - anaphylaxis,
  - need of epinephrine,
  - and serious adverse events.
- This is **despite oral immunotherapy being efficacious** in increasing in-clinic supervised food challenge thresholds (ie, desensitisation).
- These data question the **utility of in-clinic oral food challenges** as a primary (surrogate) measure of treatment efficacy in peanut allergy research.
- An equally limited surrogate outcome is the severity of reaction elicited during oral food challenge because several studies have shown that the **severity of one food allergic reaction does not predict the severity of the next**.
- In turn, for future studies, the primary measures to estimate health benefits and harms of interventions for IgE-mediated food allergies should be patient-centred outcomes, such as a risk and rate of allergic and anaphylactic reactions.
- **Clinically defined severe adverse events** (causing death, a life-threatening state, hospitalisation, disablility, congenital abnormality, or an event that necessitates intervention to prevent permanent impairment or damage) **are not what families may consider a severe adverse event**.

My conclusions

If a treatment causes more harm than no treatment, it is probably a bad treatment.

More research as well as alternative therapeutic strategies may be needed?

Large patient-based trials may include more molecular analyses?



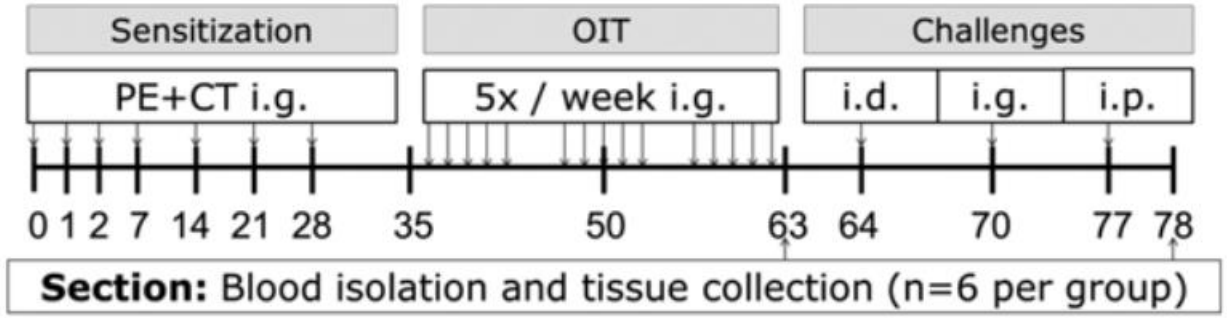
Mouse strain differences in response to oral immunotherapy for peanut allergy

Laura Wagenaar[1] | **Marianne W.H.C. Bol-Schoenmakers**[1] | **Giulio Giustarini**[1] | **Johan Garssen**[2,3] | **Joost J. Smit**[1] | **Raymond H.H. Pieters**[1]

Mouse strain differences

- Animal models have highly contributed to the insight in mechanisms of food sensitization.
- Mechanisms involved in AIT and OIT have been investigated.
- In most models, C3H/HeOuJ or C3H/HeJ (C3H) mice or BALB/c mice are used, but differences in allergic manifestations exist between both strains.

1. Intragastric sensitisation to PE using cholera toxin (CT) as adjuvant – sham only CT without PE.
2. Day 42, begin of OIT or sham treatment, for three weeks.
3. Day 64, measuring of ear swelling for acute allergic response.
4. Day 70, blood collection to measure mast cell degranulation.
5. Day 77, anaphylactic shock symptom scores and body temperatures were measured after i.p.



Groups	Strain	Number	Sensitization	Therapy
A	BALB/c	n=6	PBS sensitization	Sham therapy
B	BALB/c	n=6	PE sensitization	Sham therapy
C	BALB/c	n=6	PE sensitization	15 mg OIT
D	C3H/HeOuJ	n=6	PBS sensitization	Sham therapy
E	C3H/HeOuJ	n=6	PE sensitization	Sham therapy
F	C3H/HeOuJ	n=6	PE sensitization	15 mg OIT

Divergent T follicular helper cell requirement for IgA and IgE production to peanut during allergic sensitization

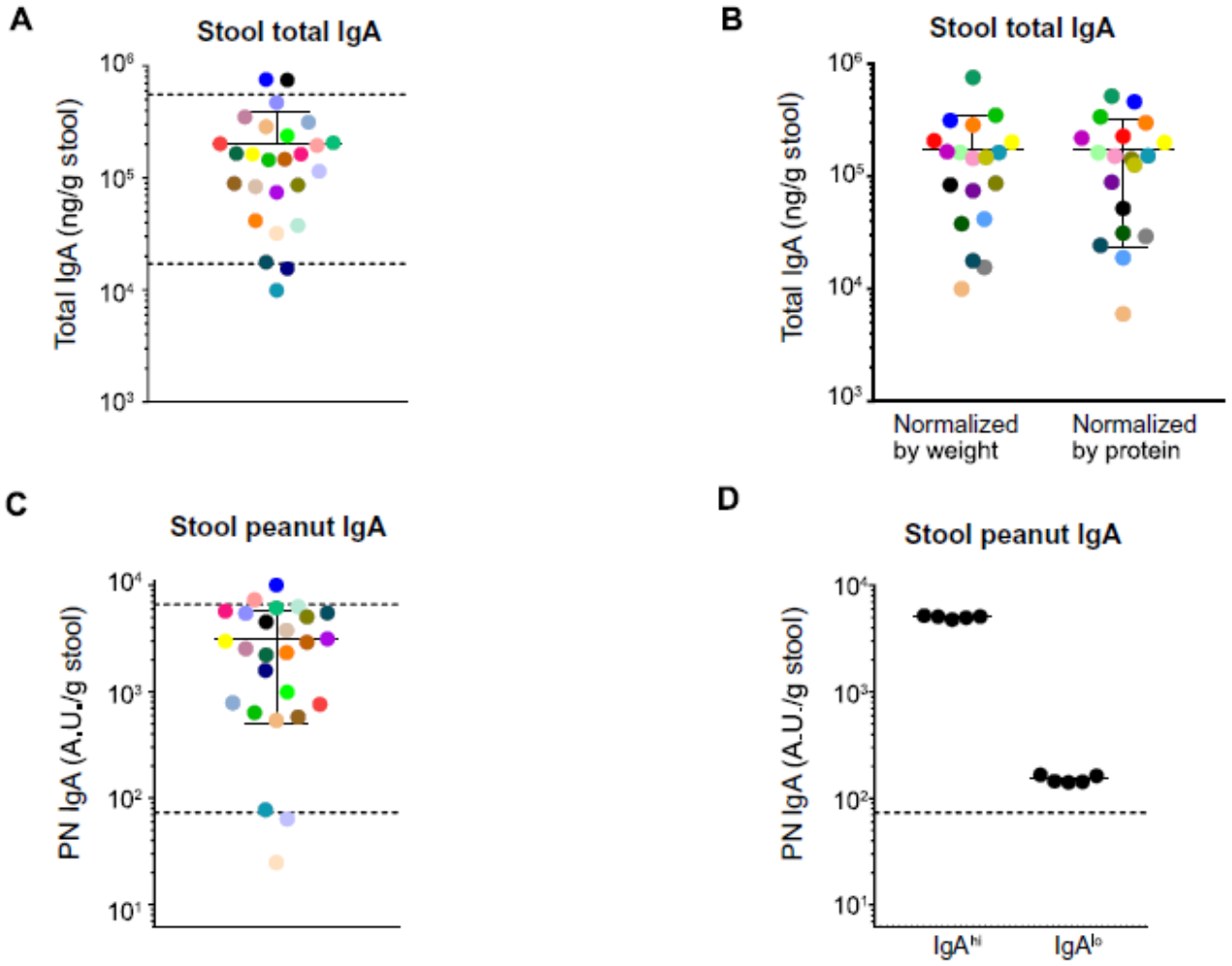
Biyan Zhang[1,2], Elise Liu[1,2,3], Jake A. Gertie[1,2], Julie Joseph[1], Lan Xu[1,2], Elisha Y. Pinker[1,4], Daniel A. Waizman[2], Jason Catanzaro[5,6], Kedir Hussen Hamza[7], Katharina Lahl[7,8], Uthaman Gowthaman[1,2], Stephanie C. Eisenbarth[1,2,3]*

Mouse allergic sensitisation - introduction

- The gut faces a daily challenge of maintaining tolerance to commensals and dietary antigens while protecting the body from pathogens and toxins.
- Orally delivered antigens: oral tolerance, or active suppression of specific immune responses.
- Loss of oral tolerance: inflammatory type 2 immune responses to dietary antigens, i.e. food allergy.
- Cellular immune response carried out by Tregs. Contribution of humoral immunity underexplored.
- IgA constitutes about 80% of all antibodies in the gut – regulation of composition of gut commensal microbiota, prevention of invasion of pathogens and toxins into mucosa.
- Role of dietary antigen-specific IgA is unclear.

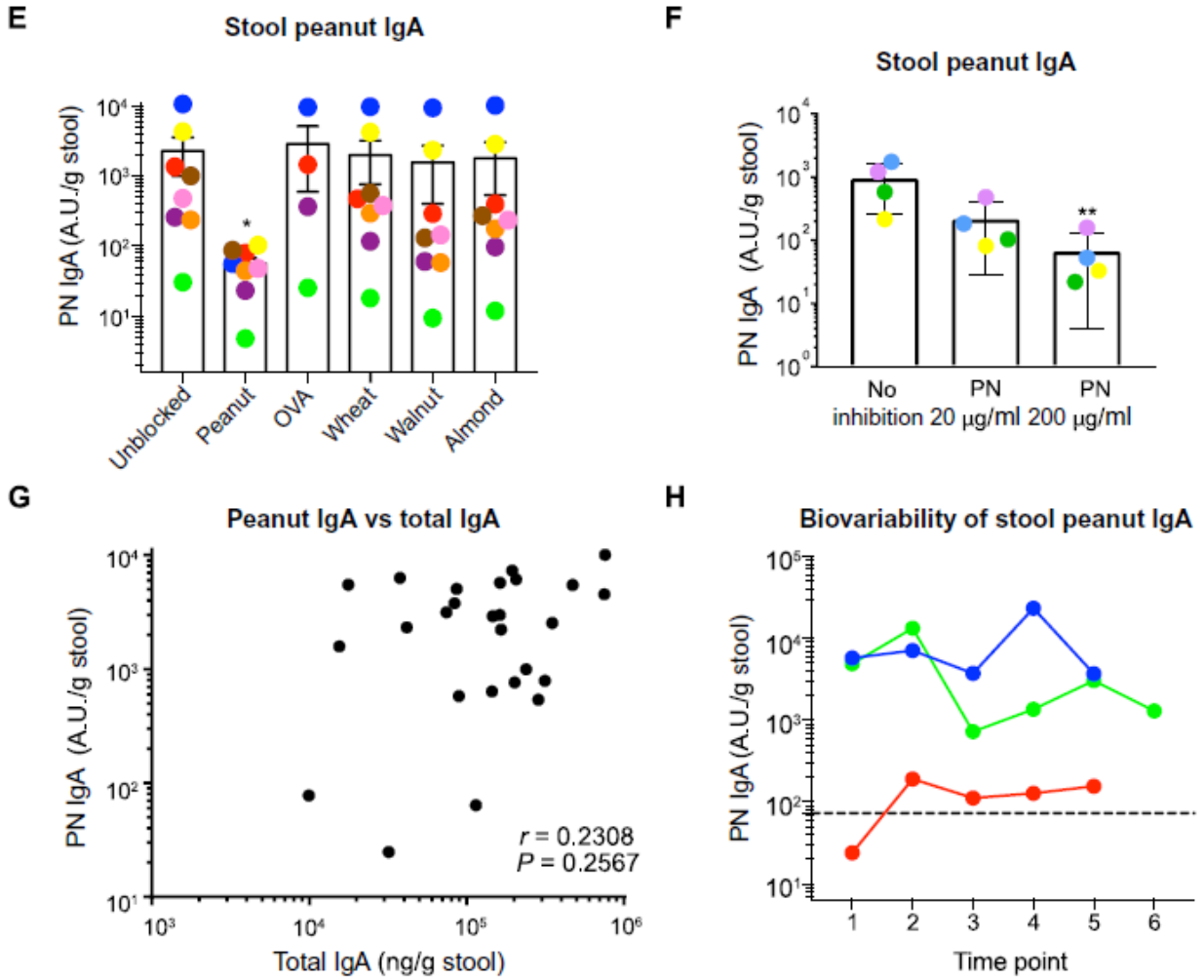
Mouse allergic sensitisation – IgA in healthy human adults

- Measuring total IgA in human feces (A), using normalisation (B).
- Peanut-specific IgA (C), reproducibility in two individuals (D).



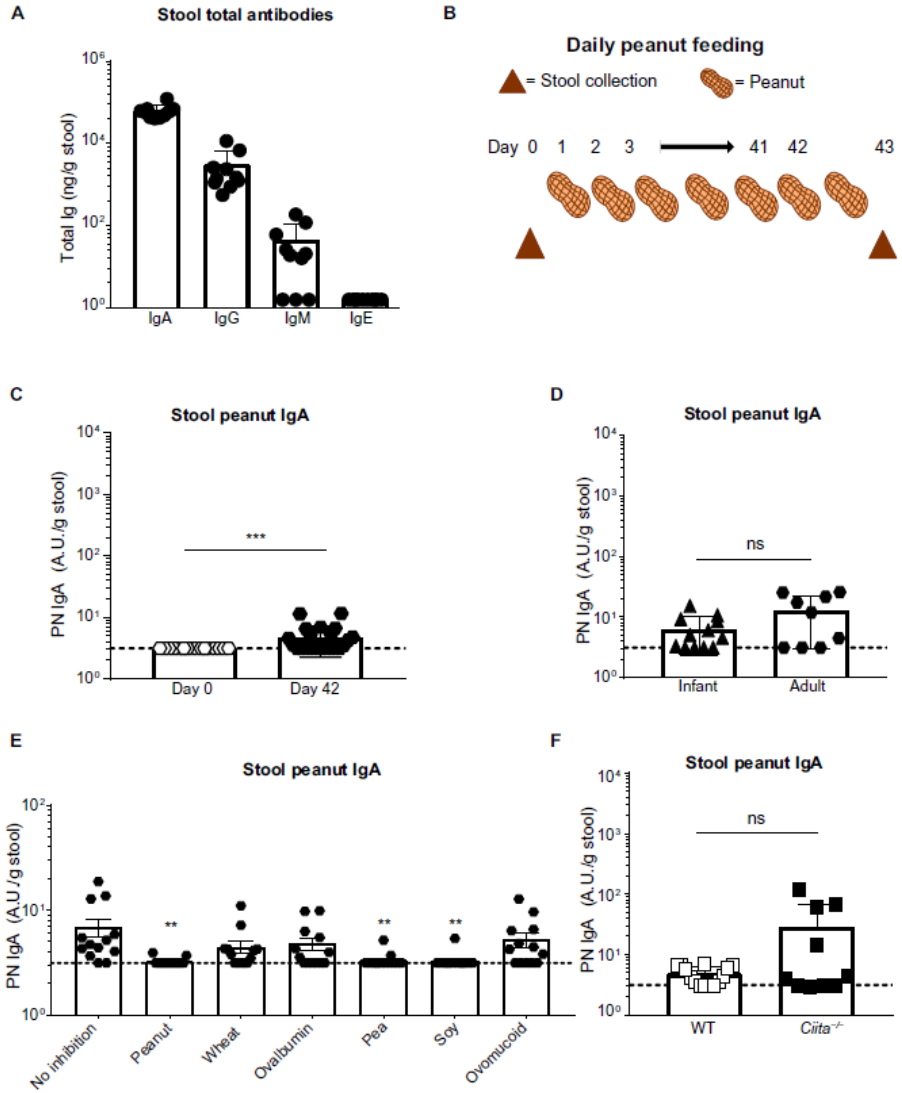
Mouse allergic sensitisation – IgA in healthy human adults

- Pre-incubation of fecal samples with with various food antigens only lowered peanut-specific IgA levels when pre-incubated with peanut, indicating specific finding (E).
- Dose-dependency of inhibition with peanut (F).
- No correlation between fecal peanut IgA and total IgA (G).
- Fluctuation of peanut-specific IgA per individual.
- Conclusion: **Most healthy adults seem to be peanut-specific IgA antibodies in stool samples**.



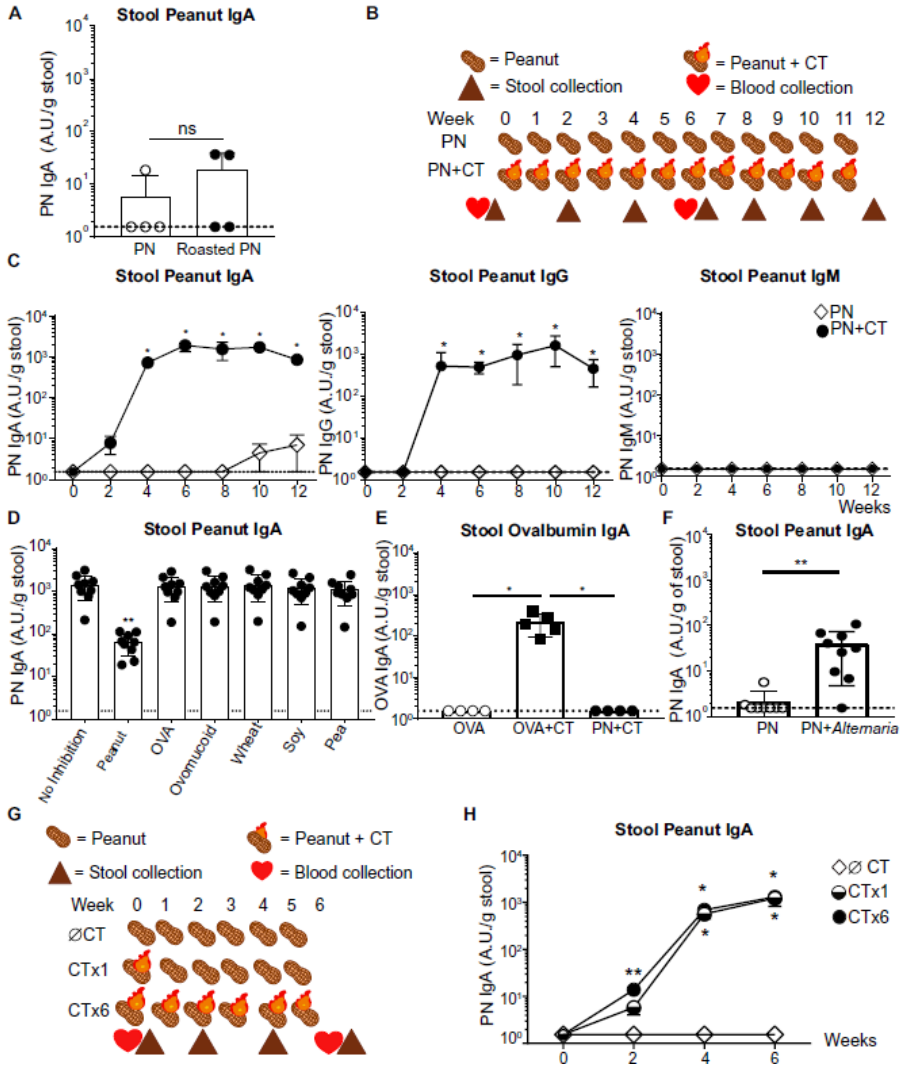
Mouse allergic sensitisation

- The high rate of peanut IgA–positive samples from our human cohort are consistent with the prevailing notion that gut IgA responses to food antigens are a tolerogenic response induced after any dietary exposure.
- This model predicts that a **nonallergic individual should produce IgA to every encountered dietary antigen**.
- However, these predictions have not been experimentally demonstrated.
- Free fecal total IgA is the most abundant antibody isotype in stool followed by IgG (A).
- Is food-specific IgA is produced in mice? Introduction of peanut into the peanut-free mouse chow diet (B). After 6 weeks of peanut feeding, a minority of the mice made IgA to peanut at low levels (C).
- Infants instead of adults were subjected to the same regimen (D).
- Inhibition assay points to cross-reactive/unspecific antibodies (E).
- MHC II transactivator KO mice show similar titers (F): low-titer cross reactive IgA can be produced in a T-cell-independent manner.



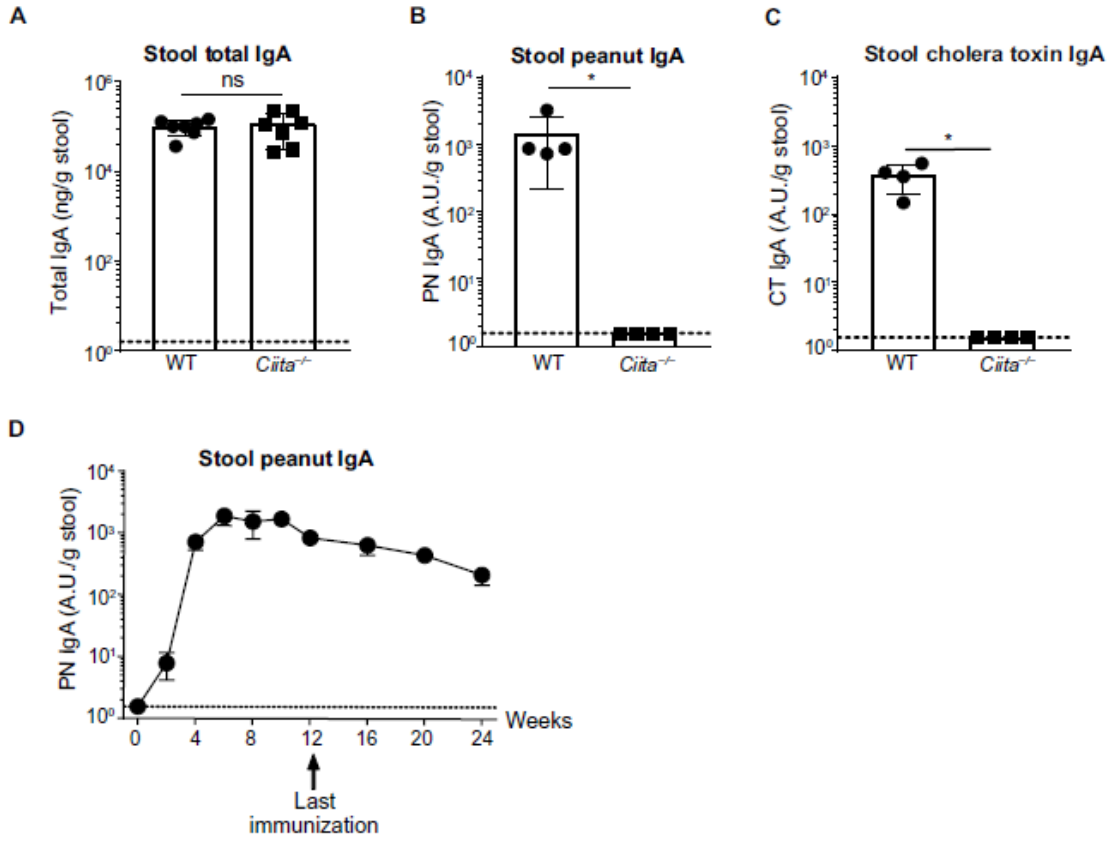
Mouse allergic sensitisation

- Probably, immunogenic adjuvant is required to trigger higher titers.
- Intragastric peanut exposure leads to poor induction of IgA (A).
- Peanut + cholera toxin (B).
- Robust production of peanut-specific IgA and IgG but not IgM in feces (C), selectively inhibited by pre-incubation with peanuts (D), and the same happens when regimen is changed to alternative antigen (OVA) (E).
- Peanut + Alternaria alternata (instead of CT) induced a gut IgA response.
- Indeed, CT is only required during the first peanut exposure (G and H): activation of DC used to prime T cells and enable T-B cell interactions.
- **High-affinity abs are produced in T-dependent manner**.



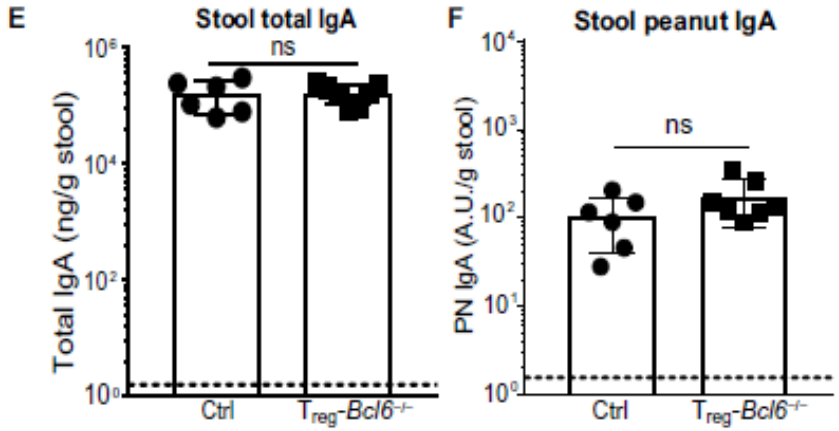
Mouse allergic sensitisation

- The same experiment as before was performed in MHC II-deficient mice, to test whether the production of high-titre IgA is T-cell dependent.
- No difference in total IgA levels (A) but clear difference in peanut-specific IgA (B) and cholera toxin IgA (C).
- Peanut IgA sustained weeks after immunisation (D).



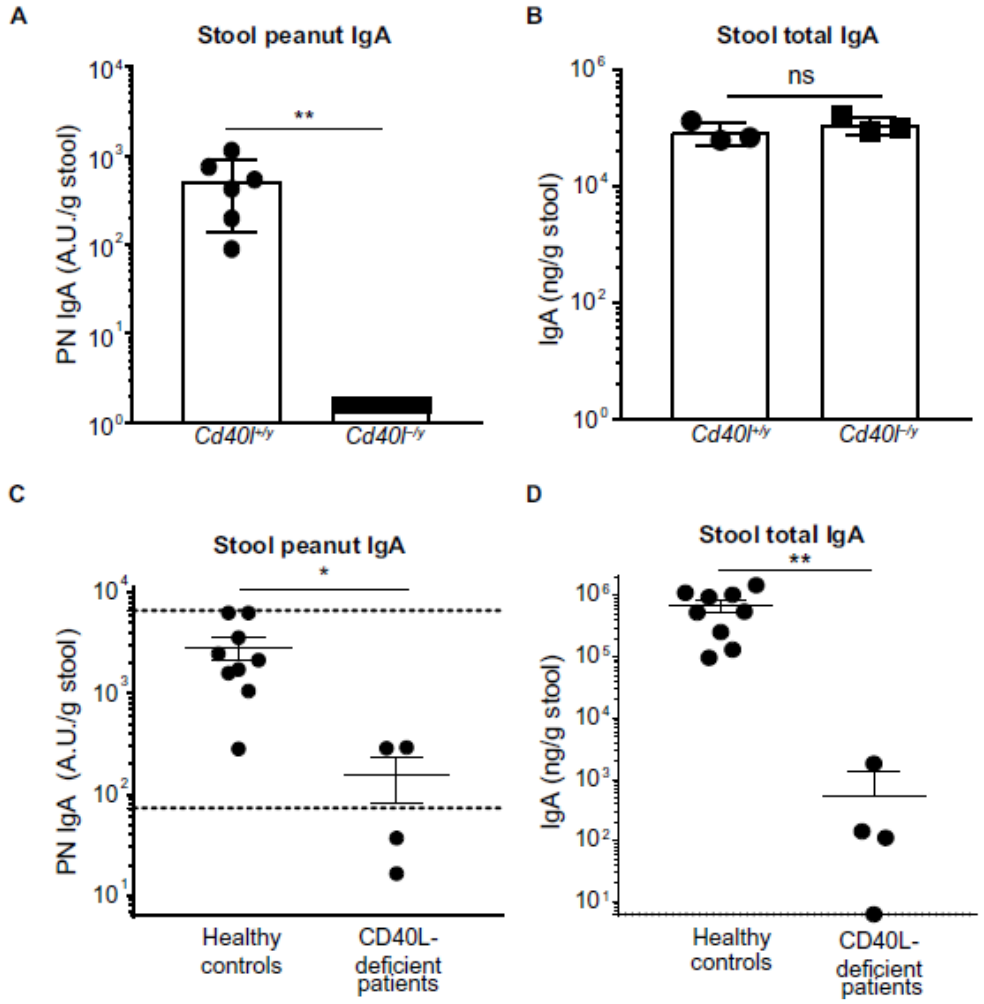
Mouse allergic sensitisation

- TFR cells are thymus-derived regulatory T cells that control GC B cell responses and can be distinguished from TFH cells via FOXP3 expression.
- TFR cells are important in modulating antibody responses.
- Treg Bcl6-/-: significant reduction in TFR but not TFH cells.
- Comparable total IgA and peanut-specific IgA titers in stool (E and F), indicting that TFR cells are dispensable for the production of gut IgA to peanut.



Mouse allergic sensitisation

- Induction of peanut-specific gut IgA requires CD40L in both mice and humans



Mouse allergic sensitisation - summary

- Using peanut as a model food antigen, they show that there is only modest production of IgA to food antigens during daily exposure to food.
- However, in the presence of a mucosal adjuvant, a strong, highly specific, and long-lived IgA response is induced to peanut.
- Using mice with specific deletion of T cell subsets, they found that the induction of highly specific IgA to peanut requires CD4+ T cells, but unexpectedly, not TFH or TFR cells.
- *Not shown here*: Data also revealed a dichotomy between peanut-specific IgA (PN IgA) as compared with IgG1 and IgE induction, whereby the latter two isotypes require TFH cells.

Conclusions

- The role of the immune system is to protect from pathogens.
- Breakage of self-tolerance: Autoimmunity.
- Misdirected immune response against innocuous proteins can lead to allergy.
- Allergies can have a fatal outcome.
- Studying how an immune response is directed against food components can increase the understanding of the physiological process underlying immunity.
- Studies can be extremely promising, or the opposite, depending on variables chosen to evaluate the outcome.
- Model systems are important in dissecting more detailed mechanisms.

Literature

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THANK YOU

And have a good afternoon!