ALLERGY OR TOLERANCE -A QUESTION OF BALANCE

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OUTLINE

- Key players in oral tolerance development
- The role of
  - Exposure to food antigens
  - Commensal microbiota

THE IMMUNE SYSTEM

- A cell and tissue system that protects us against invading pathogens
- Provides tolerance to ”non-threats” such as food components, commensal microbiota and to ”self”

Must learn to

distinguish “harmless” from “dangerous”

- Normally it is protective (=beneficial)
- Both non-specific, innate (natural) responses and specific, acquired responses
- A component of memory
- Involves numerous different cell types including antigen presenting cells (especially dendritic cells), macrophages and T and B lymphocytes

The immune symphony

Norrlandsoperan symphony orchestra

- Like the orchestra that brings different sounds into harmony, the immune system does the same to protect us!
- Immune system and orchestras are fantastic examples of coordination of diverse parts that work together to complement each other

Exposure

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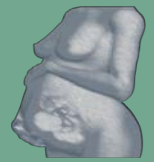
IMMUNE SYSTEM DEVELOPMENT

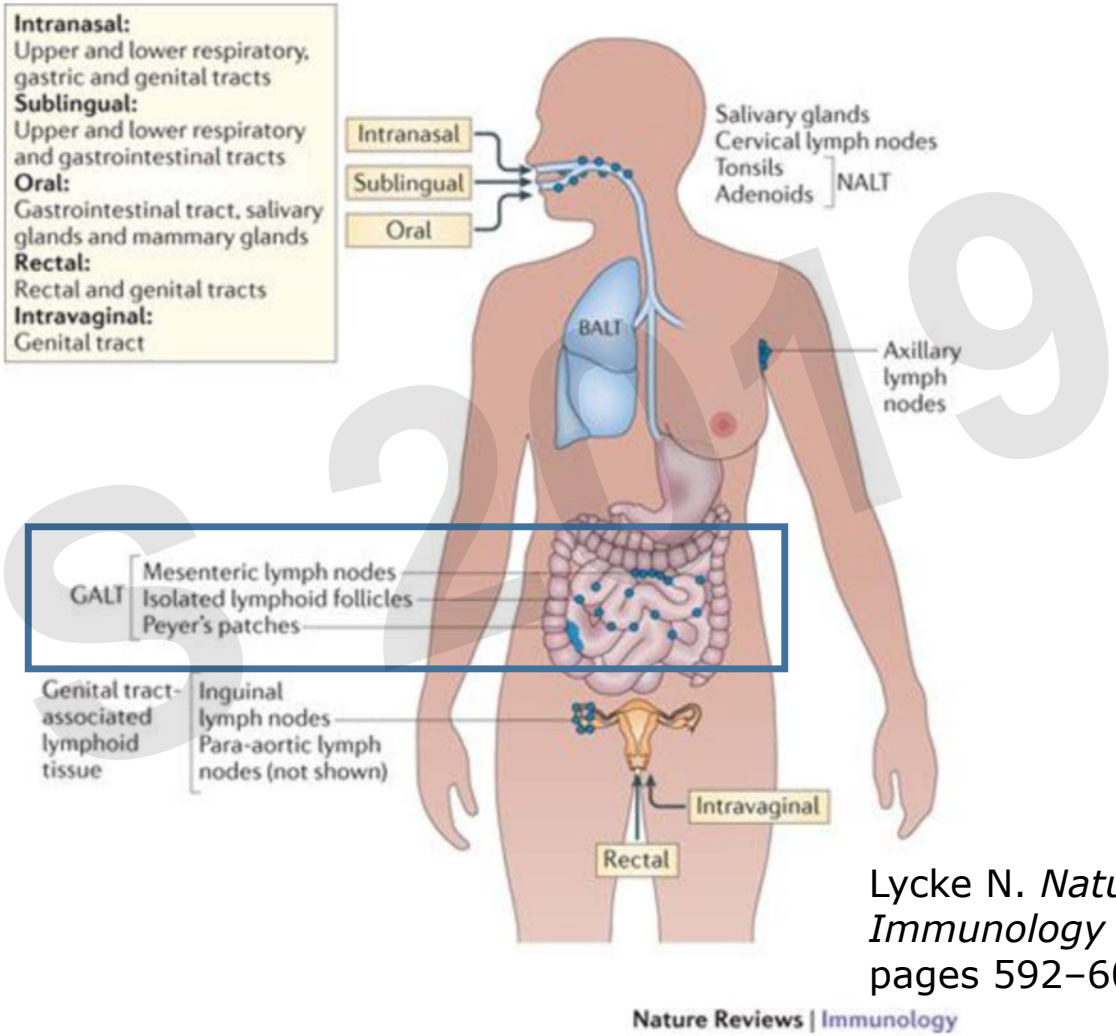
- Immune cells and organs proliferate rapidly in the first trimester



- Development of secondary lymphoid organs largely complete at birth, recent work indicates that these organs, **particularly the GALT*,** are highly responsive to enviromental stimuli (antigens) throughout life

Mold et al, Science 2010
Palmer AC, Advances in Nutrition 2011

*Gut associated Lymphoid Tissue

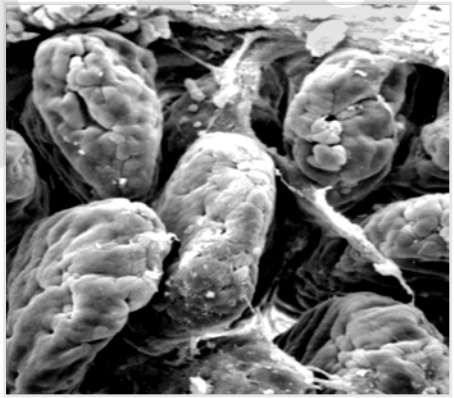


Lycke N. *Nature Reviews Immunology* **volume 12**, pages 592–605 (2012)

THE IMMUNE SYSTEM IN THE GUT MUST LEARN TO <u>NOT REACT TO</u>

- Food components

- Commensal microbiota



Constant and massive antigenic (allergenic) pressure on the IMMUNE SYSTEM IN THE GUT

-2/3 of the cellular component situated in the gut

Invasive pathogens

⇒ Strong protective immunity

Food proteins and commensal microbiota

⇒ Immune unresponsiveness

PUTATIVE MECHANISMS IN ORAL TOLERANCE IN HUMANS

- Anergy
  - ”I see but I don’t react”
- Clonal deletion
  - ”I destroy reactive/responsive cells”
- Activation of regulatory cells and/or mediators
  - ”I downregulate overly active immune responses”

Timing

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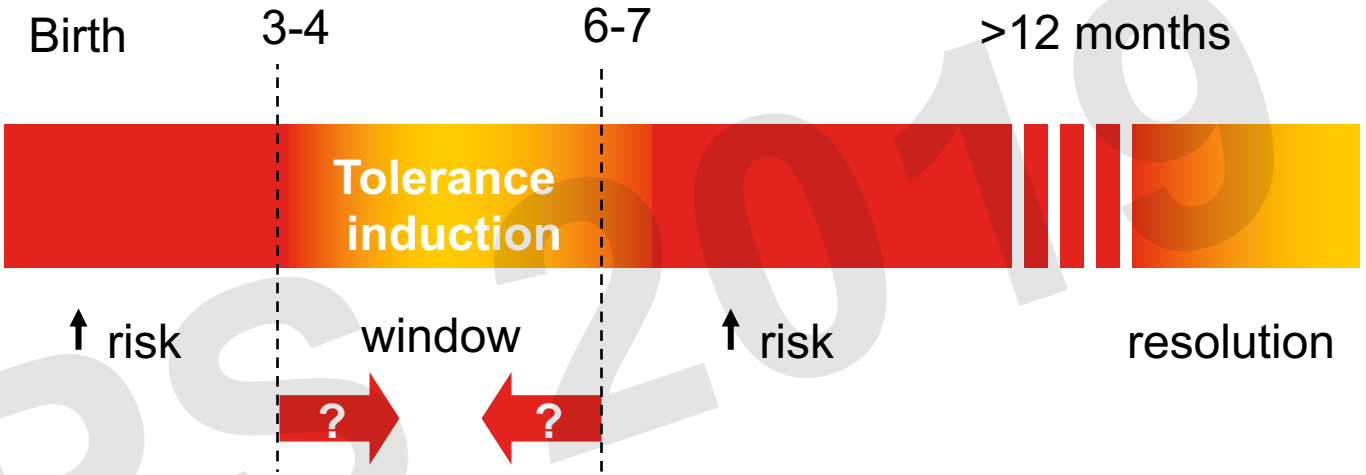
COLONIZATION CRITICAL FOR IMMUNE DEVELOPMENT AND REGULATION

- Clearly shown in murine models that there is an early developmental ”window” during which microbial colonization and exposure to food antigens induce appropriate maturation of type 2 responses and IgE regulation[1]
- If the window of opportunity is missed, **this is no longer possible**

[1]*Sudo K, et al. J Immunol 1997; 159:1739-45.*
[2]*Pecquet C, et al. J immunol 1999;96-278-85.*

“Optimal Window” for induction of tolerance?



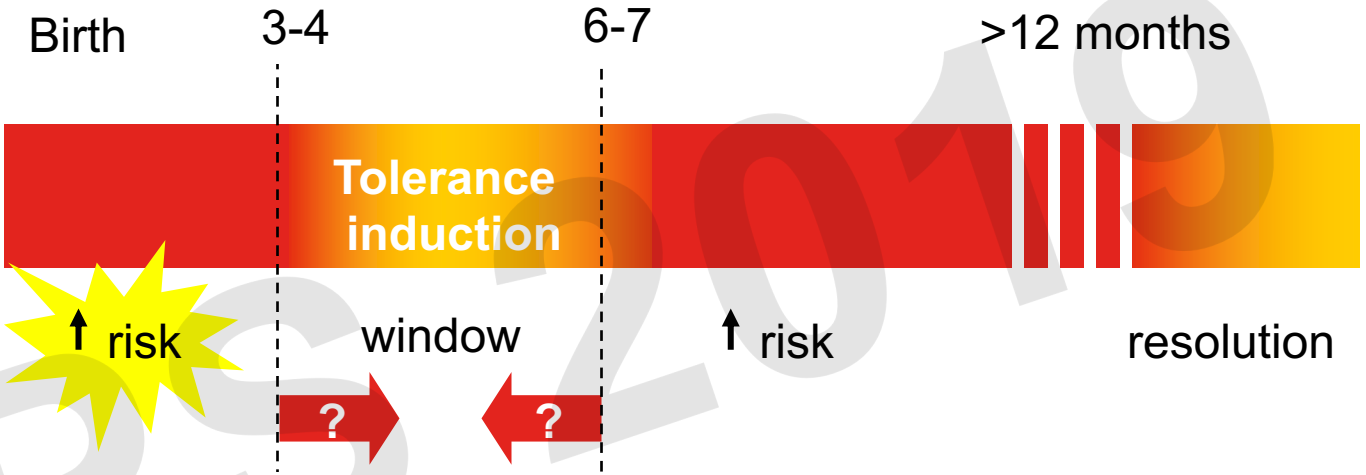
Complementary feeding in 4-6mo window

Reduced risk of:

- Food allergy — *Poole et al. 2006*
- Coeliac autoimmunity — *Norris et al. 2005*
- Islet cell autoimmunity — *Norris et al. 2003*
- Coeliac disease — *Norris et al. 2005*

Courtesy of M Tulic and S Prescott

“Optimal Window” for induction of tolerance?

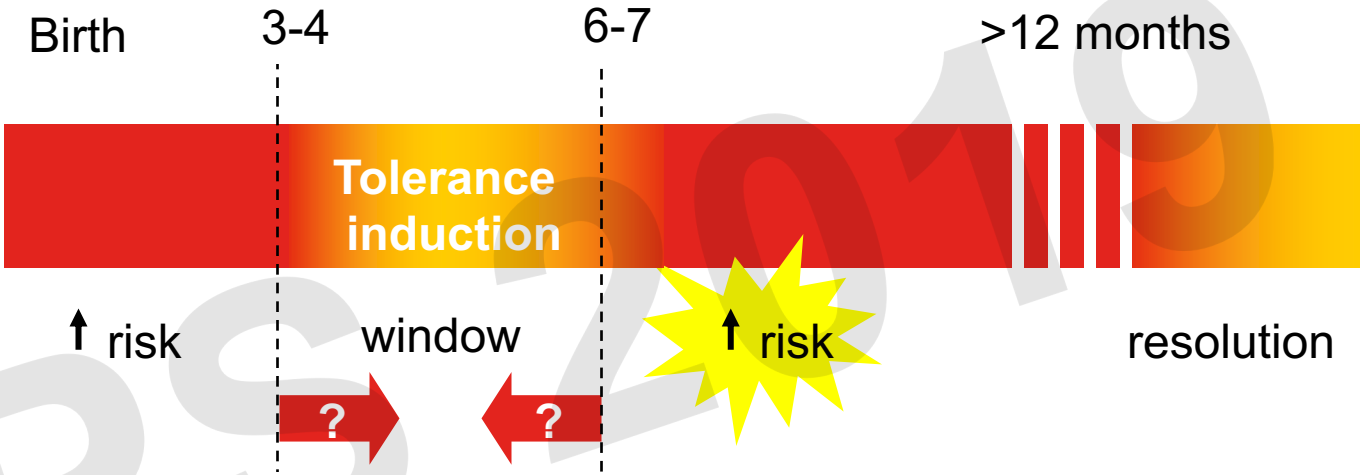


Exposure too early (<3-4 months): increased risk

Of food allergy and autoimmunity *Poole et al. 2006, Norris et al. 2005, Norris et al. 2003*

- colonization not well established
- gut immaturity (increased permeability)

“Optimal Window” for induction of tolerance?



Exposure too late (>6 months): increased risk

Of food allergy and autoimmunity *Poole et al. 2006, Norris et al. 2005, Norris et al. 2003*

- missed optimal “tolerance” window?
- new prevention studies: *earlier* introduction of “allergenic” foods

Conducted RCTs assessing early *vs* late introduction of foods

- 1 RCT peanut
- 5 RCTs egg
- 1 RCT (cow's milk, peanut, hardboiled egg, sesame, cod and wheat)

Table 1. Overview of randomized clinical trials that have assessed early versus late introduction of complementary foods for allergy prevention

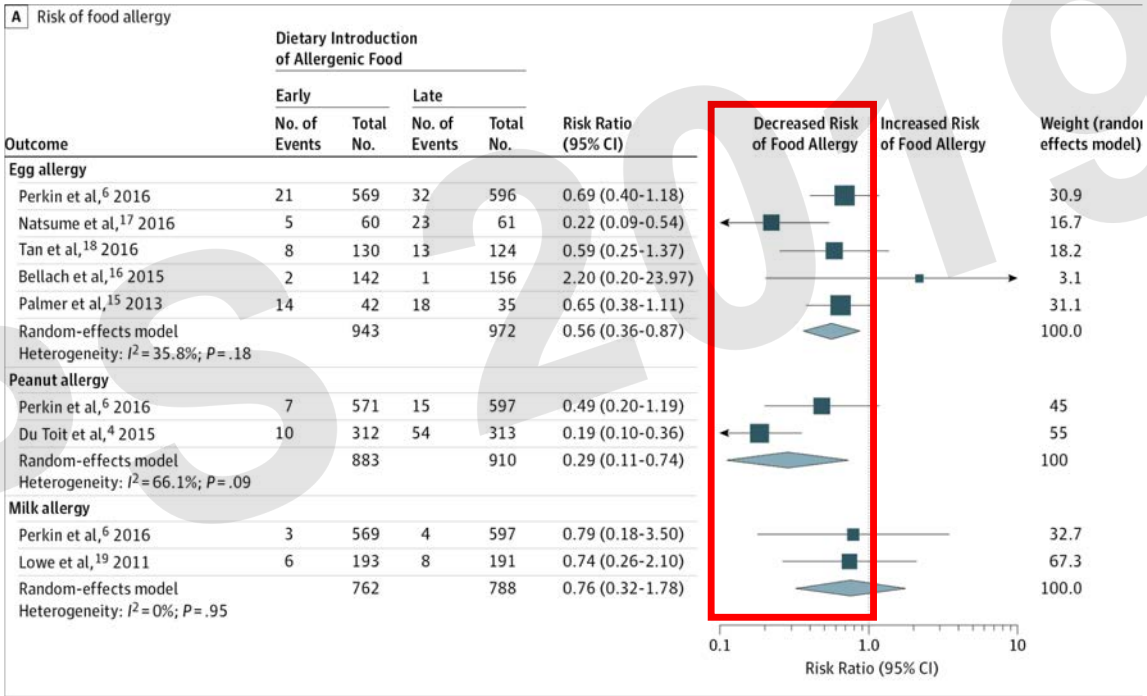
Trial name Country	Study population	Intervention	Primary outcome	Ref.
LEAP (Learning About Peanut Allergy) UK	Infants with severe eczema and/or egg allergy ($n = 640$ randomized, 319 to peanut, 321 to avoidance)	Peanut (snack or peanut butter) from 4 to 11 months to 5 years *or* Peanut avoidance until 5 years	Peanut allergy[1] at 5 years; in the group with negative SPT to peanut ($n = 530$): 1.9% in the active vs. 13.7% in the avoidance group ($p < 0.001$); in the group with SPT to peanut 1–4 mm: 10.6% in the active vs. 35.3% in the avoidance group ($p = 0.004$)	42
STAR (Solids Timing for Allergy Reduction) Australia	Infants with moderate to severe eczema ($n = 86$ randomized, 49 to egg, 37 to placebo)	Pasteurized raw whole egg powder *or* Rice powder (placebo) from 4 to 8 months	Egg allergy[1] at 12 months; 33% in the active vs. 51% in the placebo group (relative risk 0.65, 95% CI 0.38–1.11, $p = 0.11$)	45
STEP (Starting Time of Egg Protein) Australia	Infants of allergic mothers ($n = 820$ randomized, 407 to egg, 413 to placebo)	Pasteurized raw whole egg powder *or* Rice powder (placebo) from 4 to 6 months until 10 months	Egg allergy[1] at 12 months; 7% in the active vs. 10.3% in the placebo group (adjusted relative risk 0.75, 95% CI 0.48–1.17, $p = 0.20$)	46
BEAT (Beating Egg Allergy Trial) Australia	Infants with 1 (or both) parents with a history of allergic disease ($n = 319$ randomized, 165 to egg, 154 to placebo)	Pasteurized raw whole egg powder *or* Rice powder (placebo) from 4 to 8 months	Egg sensitization[2] at 12 months; 11% in the active vs. 20% in the placebo group (odds ratio 0.46, 95% CI 0.22–0.95, $p = 0.03$)	47
PETIT (Prevention of Egg Allergy with Tiny Amount Intake) Japan	Infants with eczema ($n = 147$ randomized, 73 to egg, 74 to placebo)	Heated egg powder (50 mg) *or* Squash powder (placebo) from 6 to 9 months, with a dose increase of egg protein from 9 to 12 months	Egg allergy[1] at 12 months; 9% in the active vs. 38% in the placebo group (risk ratio 0.221, 95% CI 0.09–0.543, $p = 0.0001$)	48
HEAP (Hen's Egg Allergy Prevention Trial) Germany	Infants from the general population ($n = 406$ screened for egg sensitization, 383 nonsensitized randomized, 184 to egg, 199 to placebo)	Pasteurized egg white powder *or* Rice powder (placebo) from 4 to 6 months until 12 months	Egg sensitization[3] at 12 months; 5.6% in the active vs. 2.6% in the placebo group (relative risk 2.20, 95% CI 0.68–7.14, $p = 0.24$)	49
EAT (Enquiring About Tolerance) UK	Exclusively breastfed infants for at least 3 months from the general population ($n = 1,303$ randomized, 652 to early introduction of 6 foods while breastfeeding, 651 to exclusive breastfeeding and no allergenic foods before 6 months)	Continued breastfeeding with introduction of cow's milk, peanut, hard-boiled egg, sesame, cod, and wheat in a sequential order from 3 months (early introduction) *or* Exclusive breastfeeding for 6 months (standard introduction)	Allergy to any of the 6 foods at 3 years: 5.6% in the early-introduction vs. 7.1% in the standard-introduction group (relative risk 0.80, 95% CI 0.51–1.25, $p = 0.32$)	50

SPT, skin prick test. [1] Confirmed by an oral food challenge. [2] Egg white skin prick test ≥3 mm. [3] Specific IgE to egg ≥0.35 kU/L.

West C. Introduction of complementary foods. Ann Nutr Metab. 2017;70(suppl.2):47-54.

From: **Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease A Systematic Review and Meta-analysis**

JAMA. 2016;316(11):1181-1192. doi:10.1001/jama.2016.12623



A Risk of food allergy

Outcome	Dietary Introduction of Allergenic Food: Early, No. of Events	Early, Total No.	Late, No. of Events	Late, Total No.	Risk Ratio (95% CI)	Weight (random effects model)
Egg allergy						
Perkin et al,[6] 2016	21	569	32	596	0.69 (0.40-1.18)	30.9
Natsume et al,[17] 2016	5	60	23	61	0.22 (0.09-0.54)	16.7
Tan et al,[18] 2016	8	130	13	124	0.59 (0.25-1.37)	18.2
Bellach et al,[16] 2015	2	142	1	156	2.20 (0.20-23.97)	3.1
Palmer et al,[15] 2013	14	42	18	35	0.65 (0.38-1.11)	31.1
Random-effects model Heterogeneity: $I^2 = 35.8\%$; $P = .18$		943		972	0.56 (0.36-0.87)	100.0
Peanut allergy						
Perkin et al,[6] 2016	7	571	15	597	0.49 (0.20-1.19)	45
Du Toit et al,[4] 2015	10	312	54	313	0.19 (0.10-0.36)	55
Random-effects model Heterogeneity: $I^2 = 66.1\%$; $P = .09$		883		910	0.29 (0.11-0.74)	100
Milk allergy						
Perkin et al,[6] 2016	3	569	4	597	0.79 (0.18-3.50)	32.7
Lowe et al,[19] 2011	6	193	8	191	0.74 (0.26-2.10)	67.3
Random-effects model Heterogeneity: $I^2 = 0\%$; $P = .95$		762		788	0.76 (0.32-1.78)	100.0

”…early egg or peanut introduction to the infant diet was associated with lower risk of developing egg or peanut allergy. These findings must be considered in the context of limitations in the primary studies.”

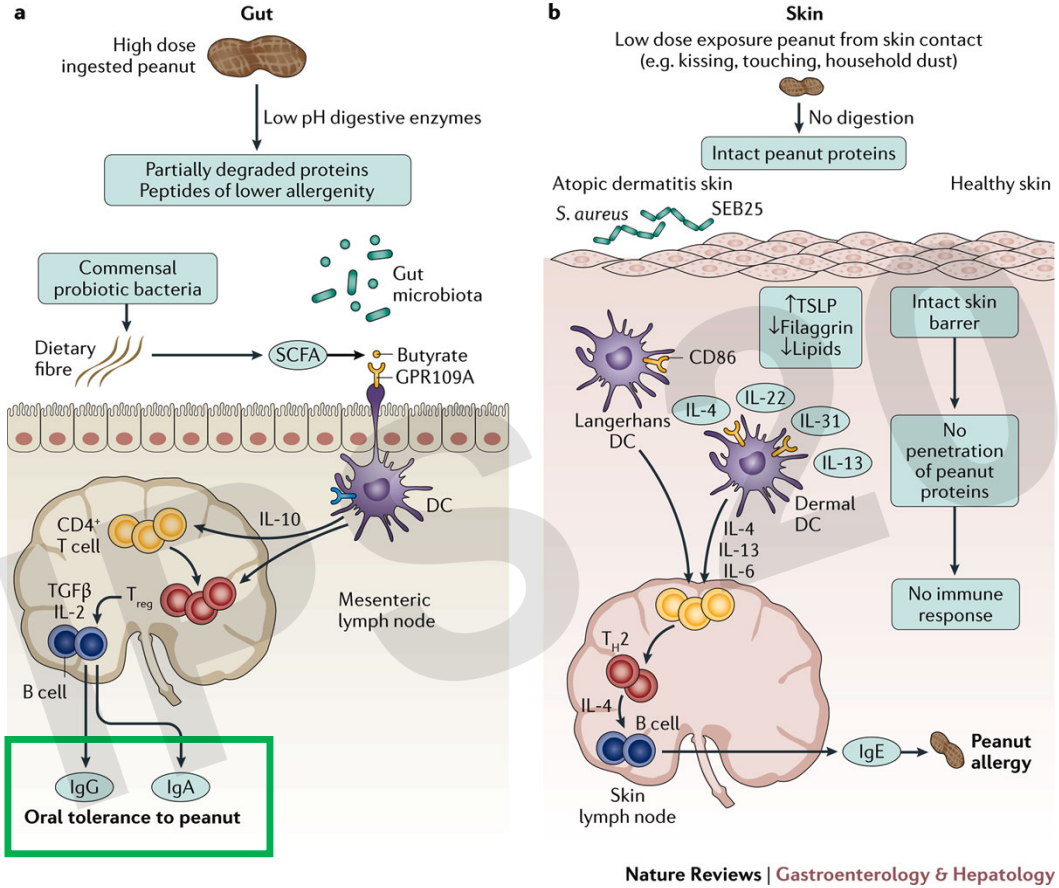
Ierodiakonou D, et al. Jama. 2016;316:1181-92.

Few studies, (mostly) high risk cohorts, different interventions, implementation?

- Infant feeding guidelines recommend complementary foods, including allergenic foods, to be introduced from 4 to 6 months of age irrespective of family history risk (EAACI, ESPGHAN)

- Interim guidelines from 10 International Pediatric Allergy Associations state that healthcare providers should recommend the introduction of peanut-containing products into the diets of infants at high risk of allergic disease in countries where peanut allergy is prevalent, **for allergy prevention**

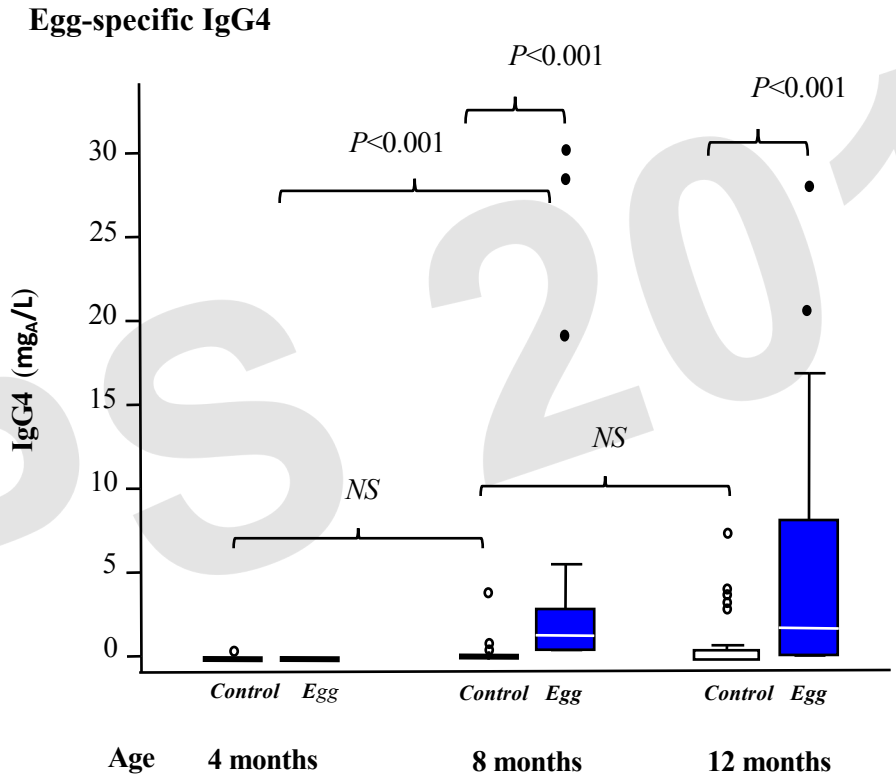
Fleischer DM, et al. J Allergy Clin Immunol. 2015;136:258-6.



Differential immune responses in the gut (oral tolerance) and skin (IgE sensitization and food allergy)

Nowak-Wegrzyn, A. *et al.* (2016) Food allergy and the gut. *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2016.187

Early egg introduction induces egg-specific IgG4



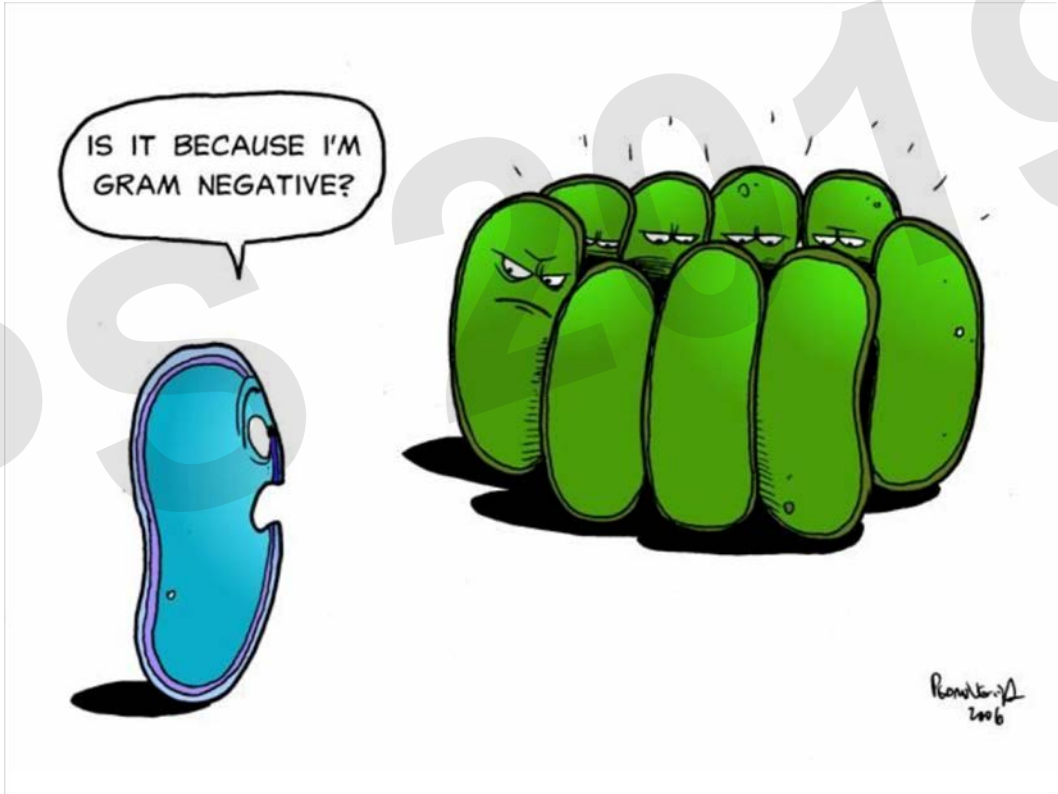
STAR study
HR cohort
Egg from 4-6 mo
vs 8 mo

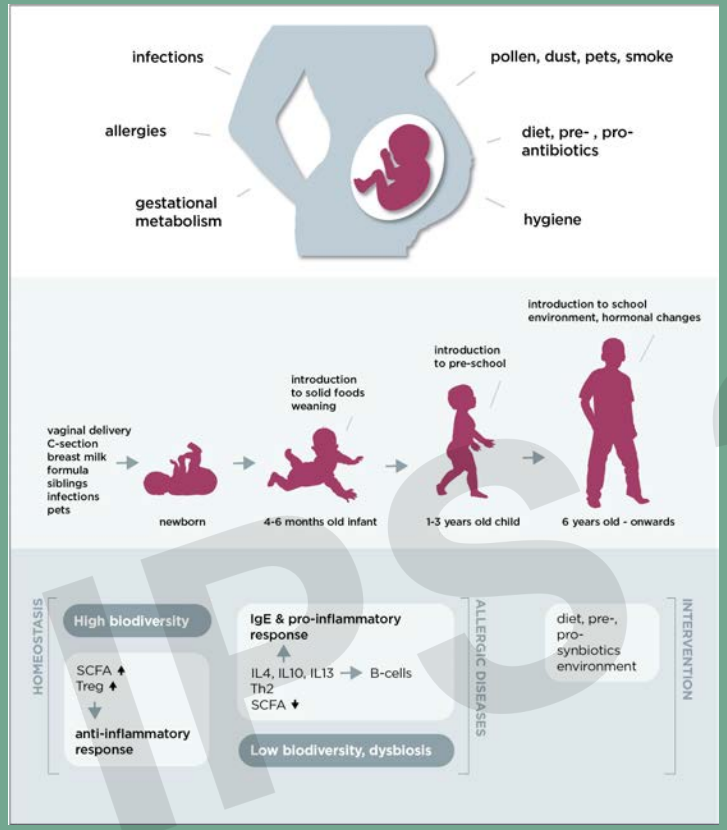
Infants on normal diet
(egg from 8 months)

Infants on early egg
(egg from 4 months)

Metcalfe JR, D'Vaz N, Makrides M, Gold MS, Quinn P, West CE, Loh R, Prescott SL, Palmer DJ.
Clin Exp Allergy 2016.

The role of our commensal gut microbiota





- **Microbiota establishment**

Driven by host factors and enviromental exposures

- **Reduced microbial stimulation**

Will delay immune maturation and regulation

- **High biodiversity**

Short-chain fatty acid (SCFA) production and induction of T regulatory cells

- **Low biodiversity/dysbiosis**

IgE production and pro-inflammatory responses

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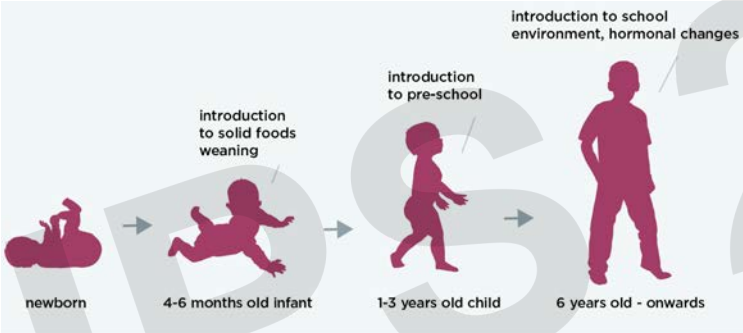
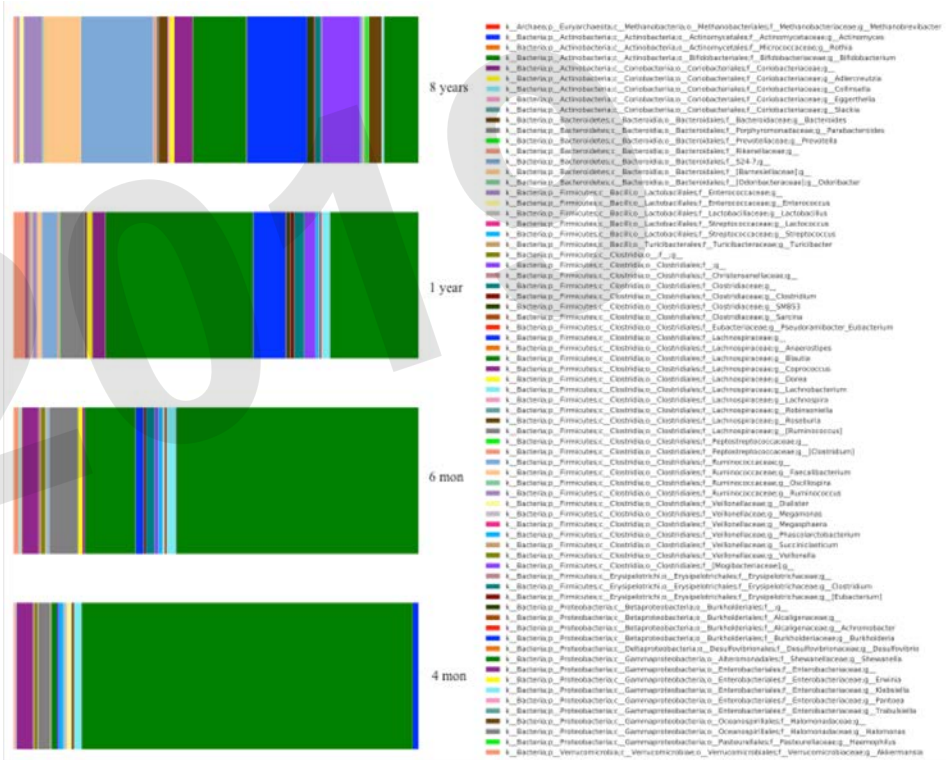
Sjödin KS, Vidman L, Rydén P, West CE. Emerging evidence of the role of gut microbiota in the development of allergic diseases.
Curr Opin Allergy Immunol. 2016;16:390-5.

Succesive establishment of the gut microbiota in childhood



4 mo **6 mo** **1 yr** **8 yrs**



Sjödin KS, Vidman L, Rydén P, West CE. Emerging evidence of the role of gut microbiota in the development of allergic diseases.
Curr Opin Allergy Immunol. 2016;16:390-5.

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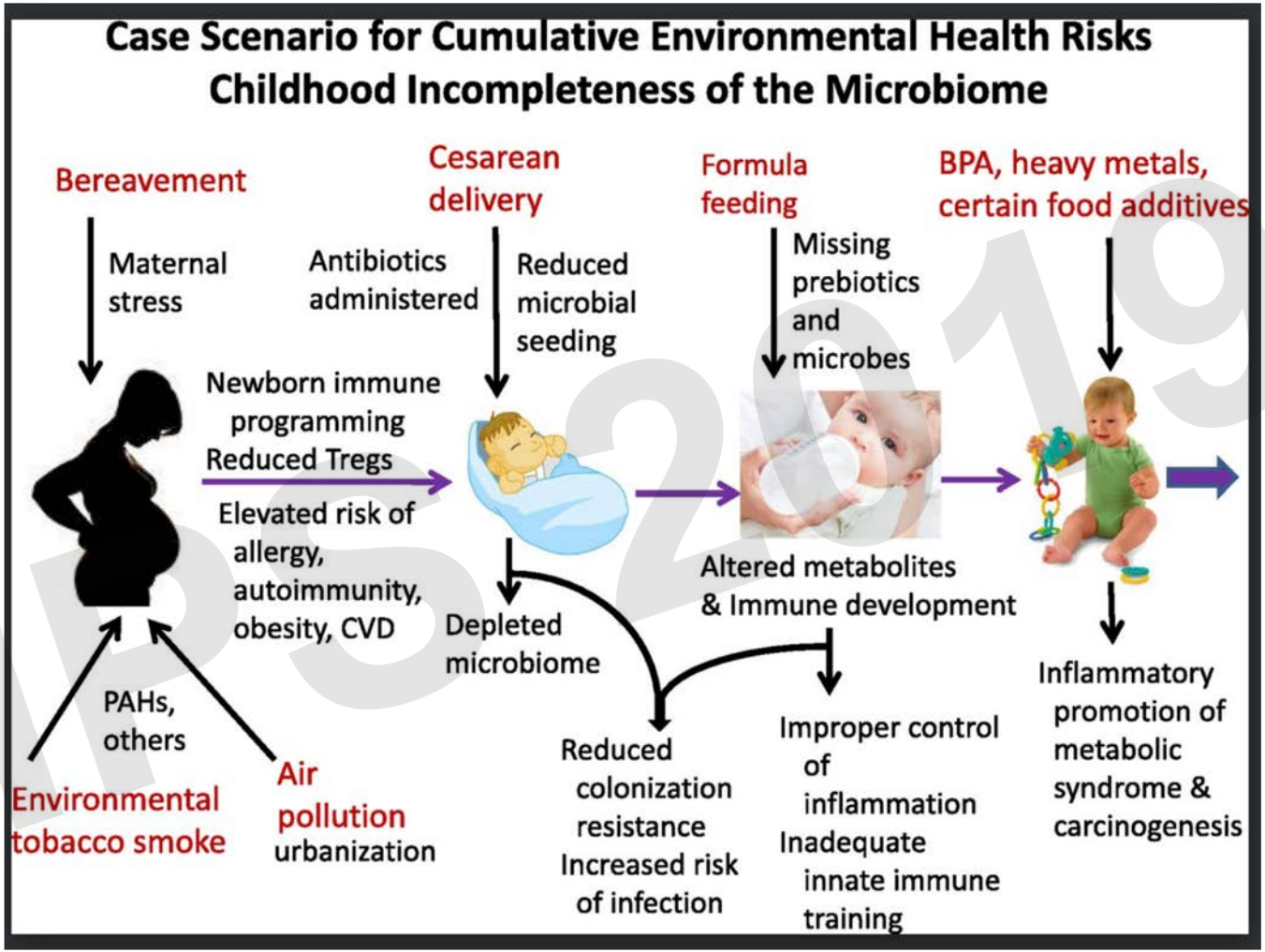
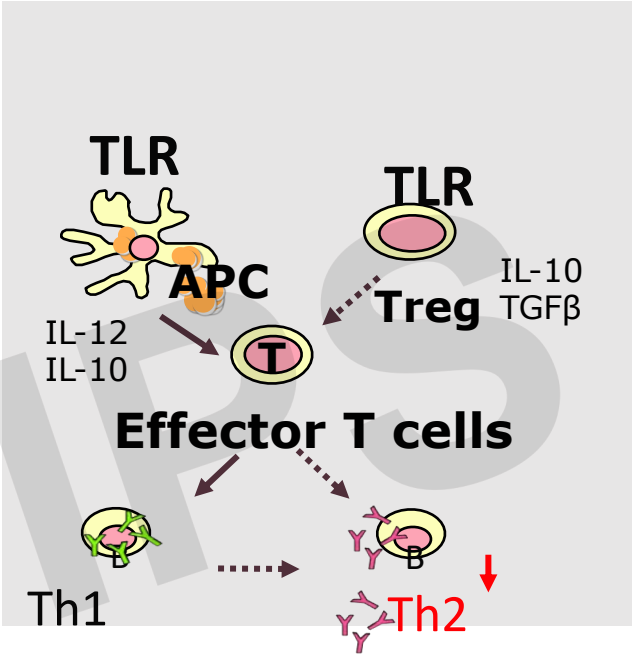


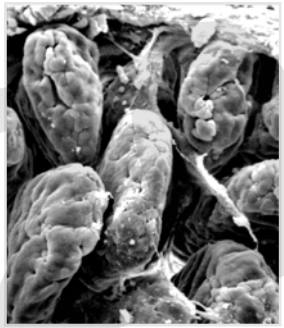
Dietert RR. NeoReviews February 2018, VOLUME 19 / ISSUE 2 pp. e78-e88.

Gut microbiota

1) Keep the **regulatory tone** of the immune system



West et al, Clin Exp Allergy 2015; 45:43-53
Ho et al, Curr Allergy Asthma Rep 2018;18:27



2) Modulate **Th2** responses

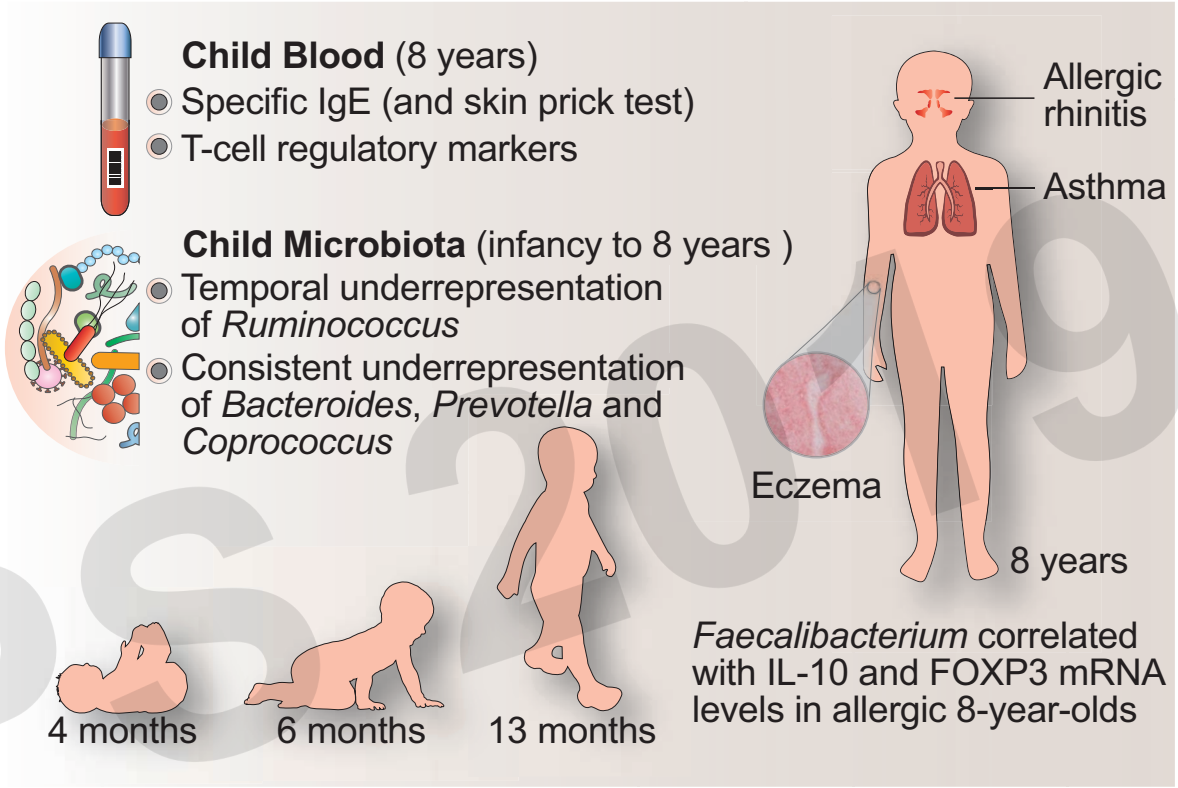
3) Enhance **gut barrier integrity** and **functions**

Mucin production

Gut-lung-axis

Ligands (LPS, peptidoglycan)
Metabolites (SCFA)
Immune cells

4) **Cross-talk** between the gut microbiota and distant organs



Sjödin Simonyté K, Hammarström ML, Rydén P, Sjödin A, Hernell O, Engstrand L, West CE. Temporal and long-term gut microbiota variation in allergic disease: A prospective study from infancy to school age. Allergy, 2019;74:176-185.

Oral tolerance

Postnatal phenomenon

Timing and exposure to food antigens and commensal microbes IgA, IgG4

Antigen presentation

T regulatory cells FOXP3, IL-10, TGF-b


Umeå University
Pediatric study nurses
Pediatric laboratory analysts
Dr Kotryna Simonyté Sjödin
A/Prof Patrik Rydén
Dr Andreas Sjödin
Prof Olle Hernell
Prof Marie-Louise Hammarström
Univ. of Western Australia
Prof Susan Prescott
Prof Meri Tulic
Dr Debbie Palmer
SciLife Lab/Karolinska Institute
Prof Lars Engstrand
Dr Daniel Lundin
Dr Maike Seifert
Dr Hugo Wefer
Participating families
Funding Bodies