Better Foods for Better Health INFANT & CHILDHOOD NUTRITION

Determinants of allergenicity and modulation of allergies. Rational for perinatal intervention. Prebiotics example.

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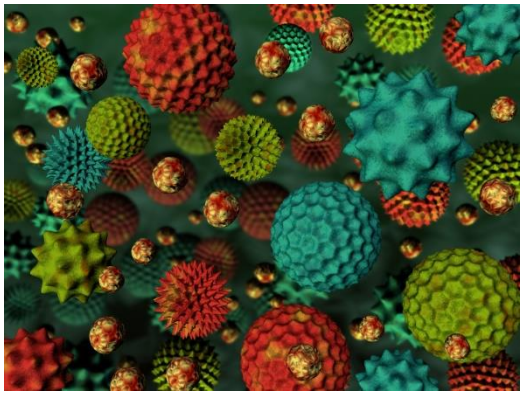
Allergies

- **Public health issue:** 4th World disease according to the WHO.
- The **most common and earliest manifestations** of the vulnerability of the immune system (IS) to the modern environment.
- **30-40% of the world's population** (Prescott, 2011).
- **No cure and no effective preventive strategy established so far.**



The types of Allergies

- **3 different types** of allergies:
  - **Atopic Dermatitis (AD)** :

- chronic disease with worldwide prevalence rates of 1-20%, children: 15-20% and adults: 1 to 3% (Nutten, 2015)
- the most common allergic disease appearing early in life
- pruritic inflammatory skin lesions associated with dry skin.

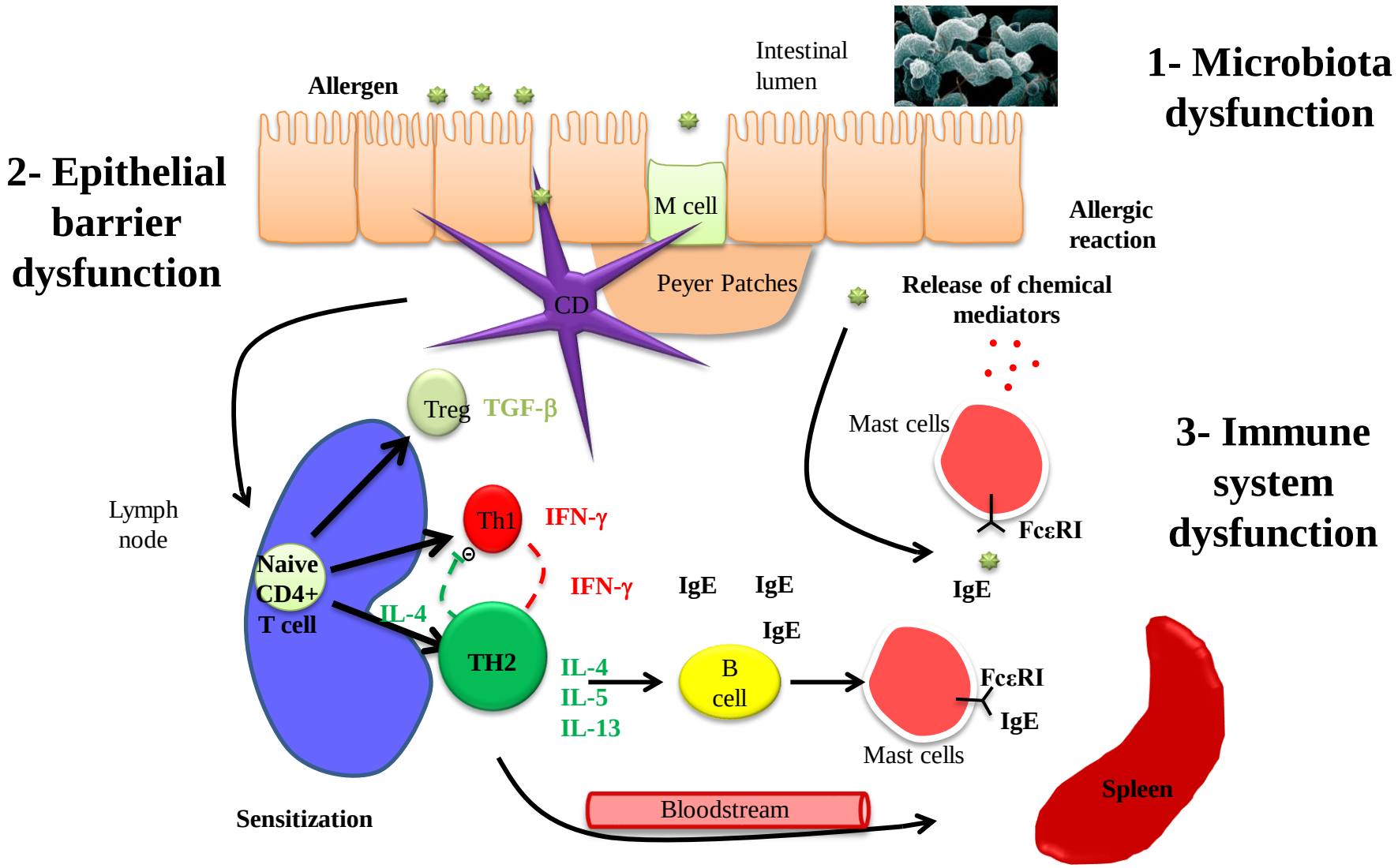
  - **Respiratory Allergy (RA)** :

- the most common allergy observed in western countries (Bjorksten, 2008).
- affects around 20-30% of the European population.
- asthma, rhinitis or rhinosinusitis (Asher, 2006; Pawankar, 2011).

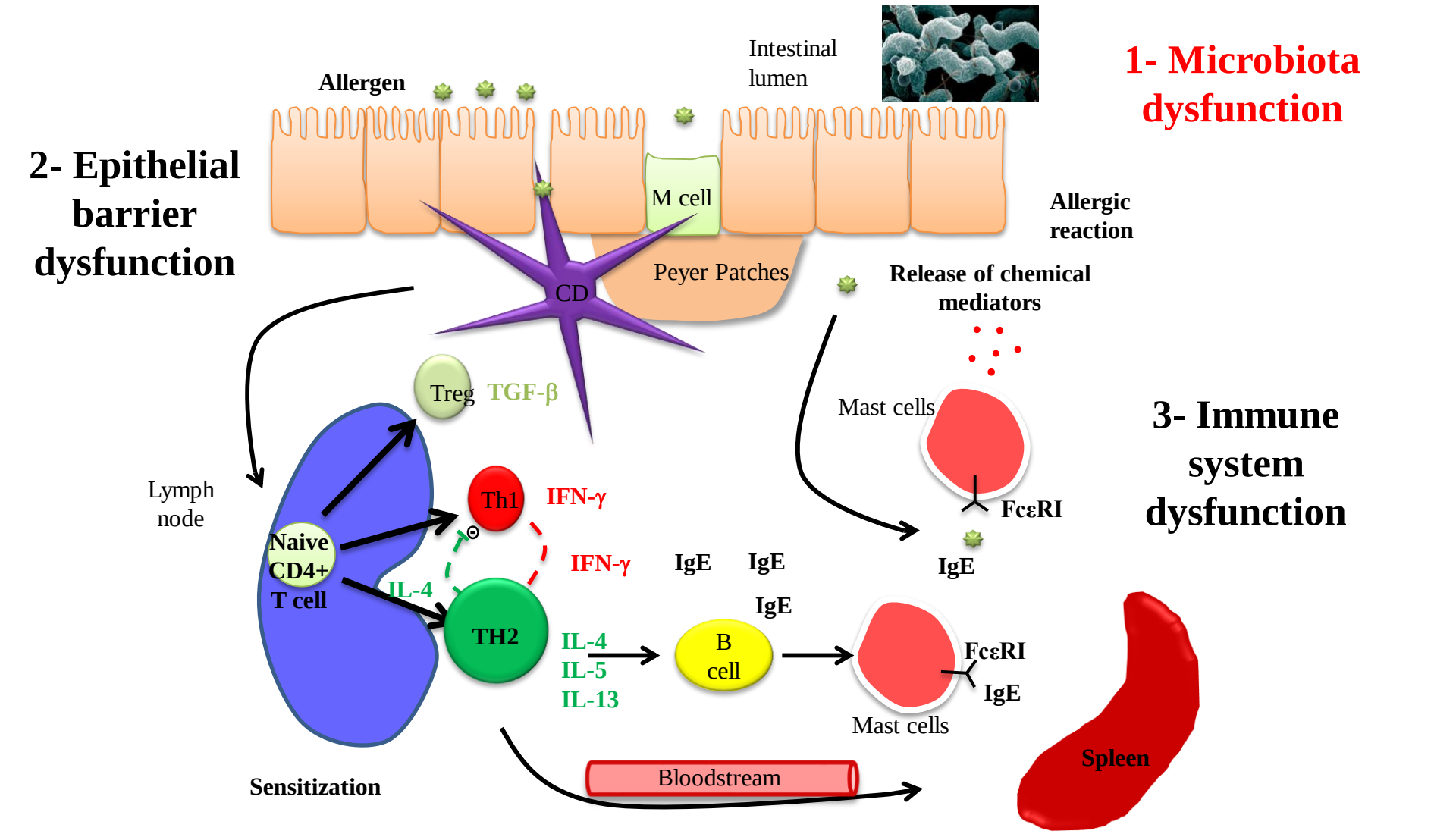
  - **Food Allergy (FA) :**

- prevalence in Europe: 5.9%, children : 4.7%; adults: 3.2% (Nwaru, 2013; Moneret-Vautrin, 2008)
- clinical symptoms: anaphylaxis, skin lesions (urticaria, AD), respiratory tract (asthma, rhinitis) and gut disorders.

Allergy - Mechanisms



Allergy - Mechanisms



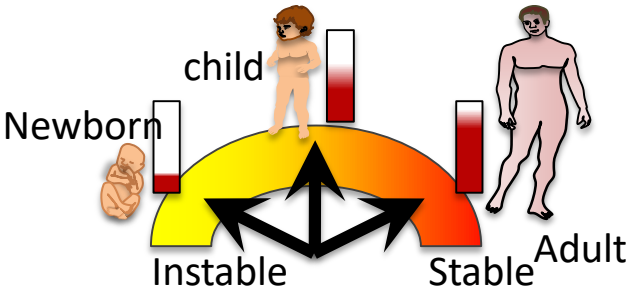
1- Microbiota dysfunction

2- Epithelial barrier dysfunction

3- Immune system dysfunction

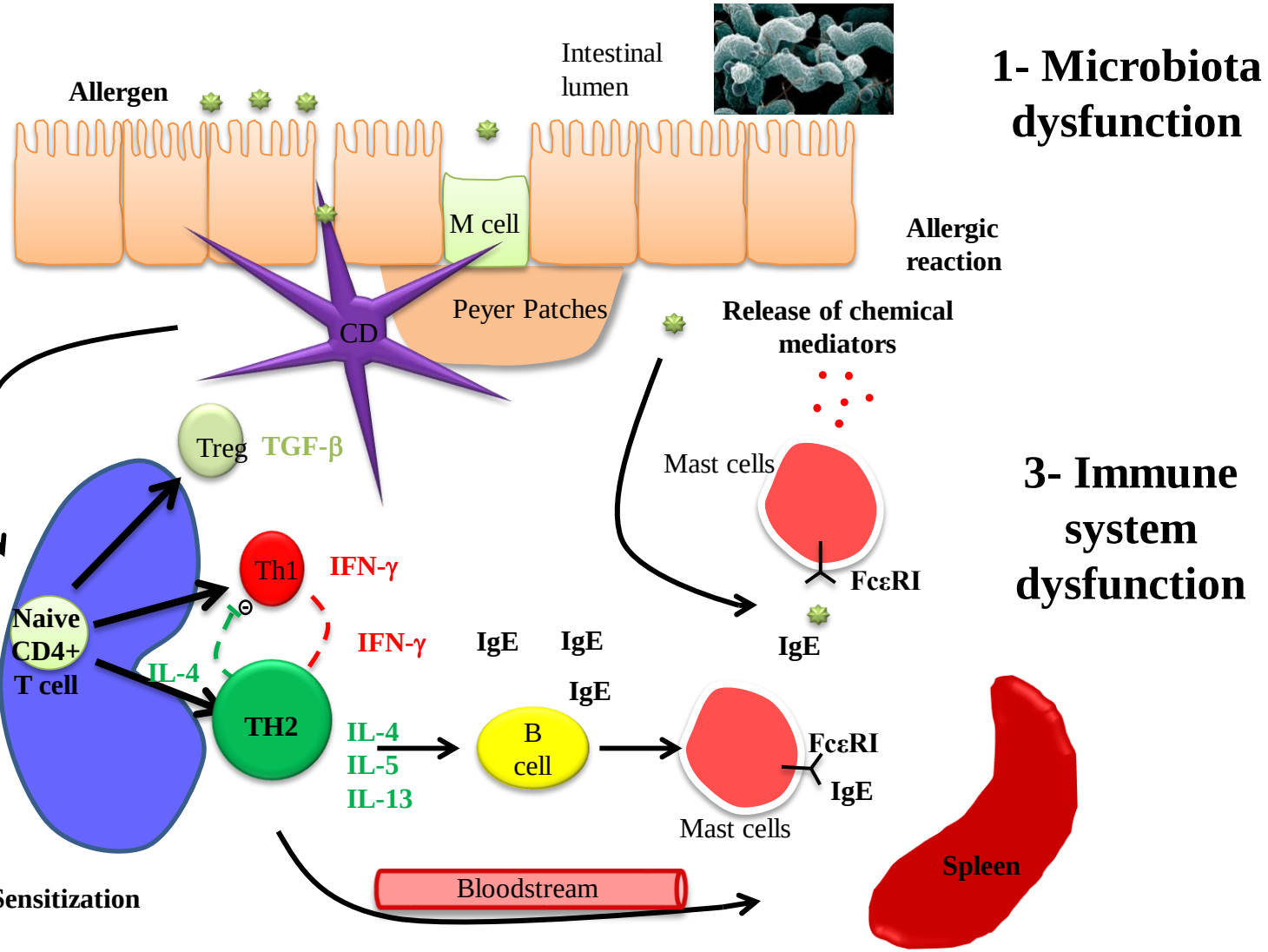
Mechanisms - Microbiota

- **Complex microbial** ecosystem (majority of bacteria: 400 species -1000)
- **10^{14} cells** is more than the total of human cells
- Colonizes nose, eyes, throat, **GI tract (10^{12})**, skin ...



- **Composition evolves all over the life:**
  - implantation at birth through contact with the mother's perineal and vaginal microbiota (Lehmann, 2011).
  - modified by environment : diet, antiobiotic, …
- **Unique** to each individual and **tolerated by IS**
- Major role in immune response modulation : **oral tolerance** and gut barrier maturation (Chehade, 2005; Mazmanian, 2005)
- Balanced microbiota = eubiosis : **positive effect on health**
- Deviant microbiota = dysbiosis : **induction of inflammatory** phenomena related to IS such as **allergies**

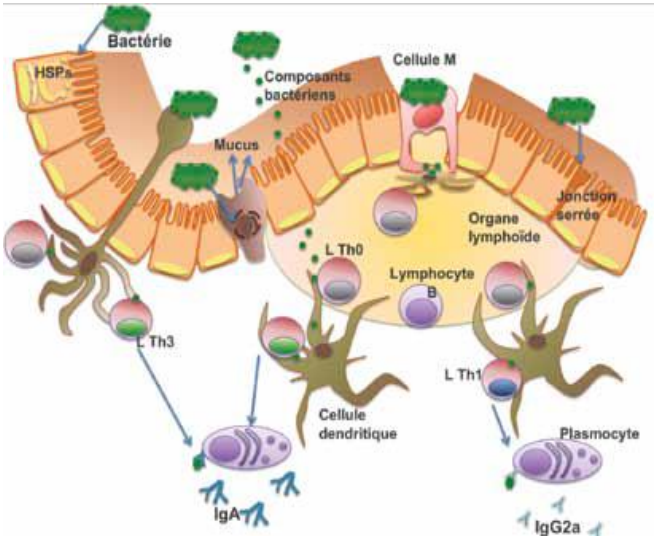
Allergy - Mechanisms



Mechanisms - Mucosa

Mucosa (nasal, respiratory, intestinal and cutaneous) : defensive barrier

- It's composed of polarized cells connected by tight junction to ensure sealing
- It secretes defense molecules: mucins, antimicrobial peptides and enzymes
- It's associated to a diversified immune system (gut) to ensure **defense** and **tolerance**

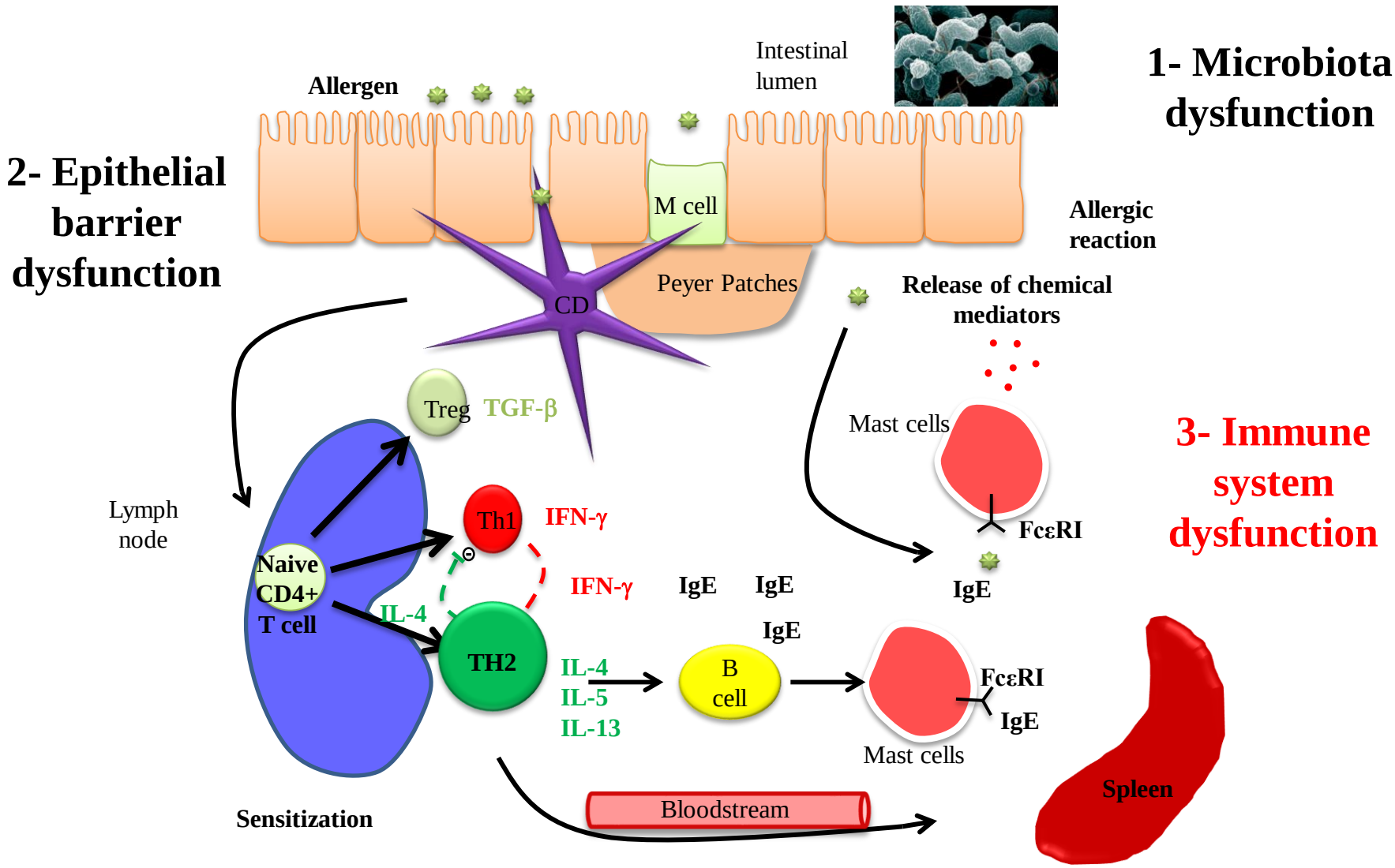


- Mucosa Associated Lymphoid Tissue (MALT) : T cells (CD4 +), B, DC, innate cells (NKT, ILC…)
- IgA secretion: protection against pathogens, immune tolerance (microbiota, food ...)
- IgA-related to optimal microbiota

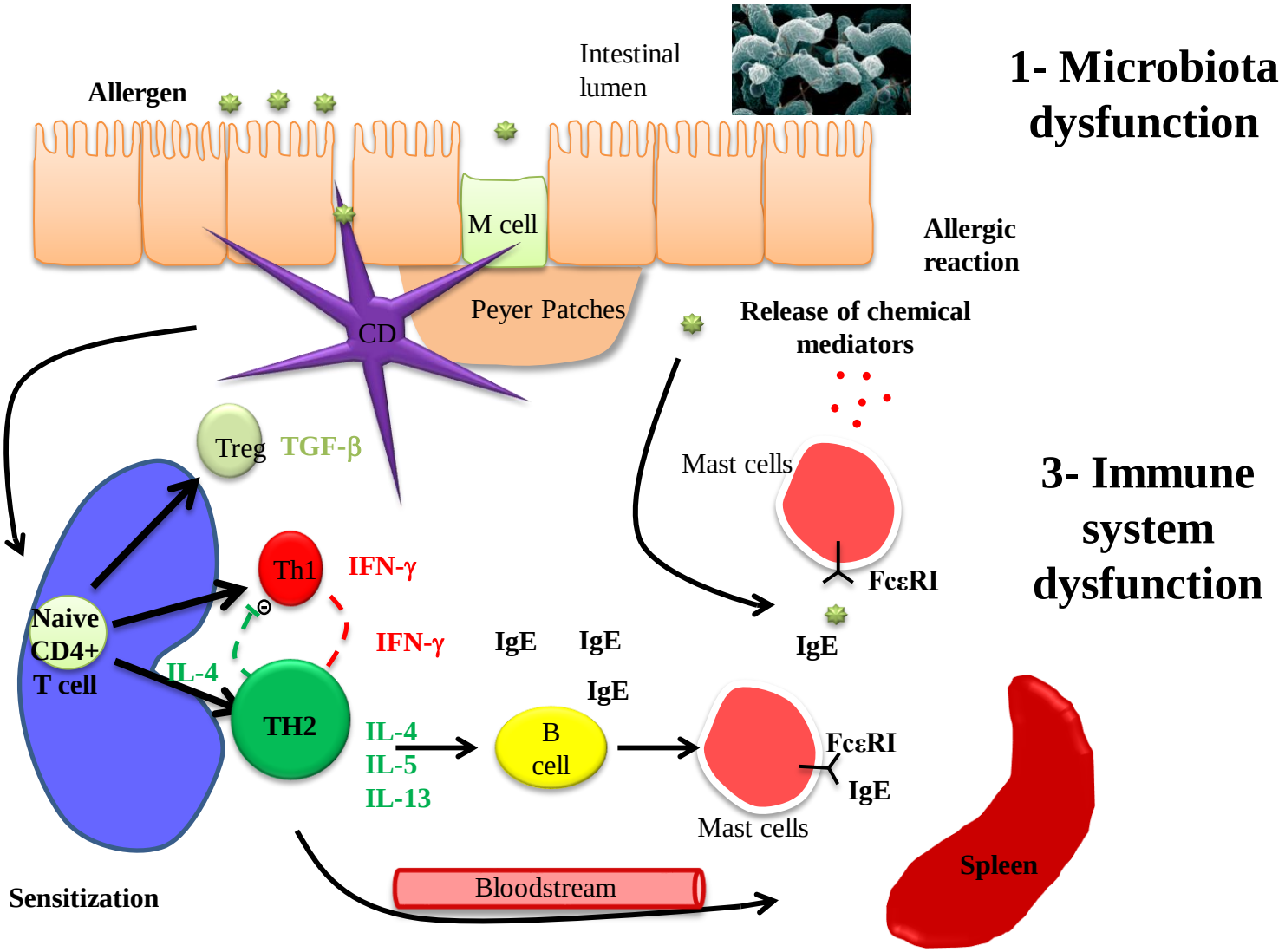
- Dysfunctions/ alterations of mucosa : - They increase permeability
  - They induce defects in immune tolerance

→ **pathologies such as allergies ….**(Hammad, 2015)

Mechanisms - Immune system



Allergy - Mechanisms



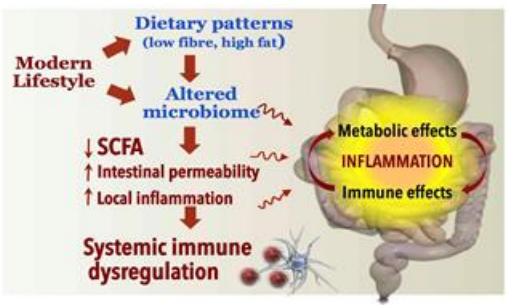
- **The most frequent and earliest manifestation of the vulnerability of immune, microbial and mucosal systems related to our modern environment.**

Environnemental causes of allergy

- **Modern lifestyle:**
  - ✓ **Dietary pattern:** low fibres and high fat (Nauta, 2013)
  - ✓ **Hygiene** (Strachan, 1989)
  - ✓ **Stress**
  - ✓ **Environmental pollutants**
  - ✓ **Mode of delivery**
  - ✓ **Antibiotics**

⇒ Declining microbial diversity (Abrahamsson, 2012)

⇒ Causing disruptions of mucosa and immune system maturation (Macia, 2013; Maslowski, 2011)



Prescott, 2013

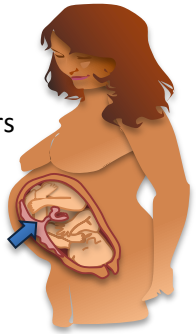
Inflammatory diseases : allergies

- detectable immune dysregulation at birth
- clinical expression of allergy within the first months of life (Prescott, Paediatr Allergy Immunol 2011)

Perinatal period: a critical time of risk/opportunity

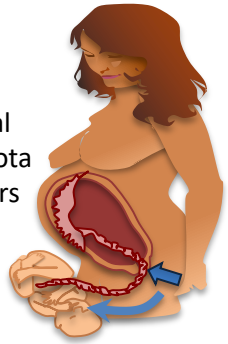
- Exchanges of immune and bacterial factors between the fetus/infant and the mother

(Jimenez, 2008; Pfefferle, 2010; Verhasselt, 2010)



Immune factors and bacteria transfers *via* cord blood

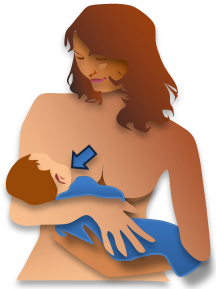
Pregnancy



Vaginal microbiota transfers

Delivery

Fetus: Th2 profile



Immune factors (TGFβ , IgA) and bacteria transfers *via* breastmilk

Breastfeeding

Fetus: induction of Th1/Treg

- Environment in both pregnancy and early childhood can determine physiologic, immune, metabolic, and bacterial development which will influence future disease susceptibility (Hanson 2011)

Interest to study the **early effects of lifestyle interventions** on immune function and **allergic disease** (Prescott, 2013)

Especially nutritional interventions

Nutritional strategies for allergy prevention

Nutrients : able to modulate microbiota and immune system

Allergy : induced by immune and bacterial disorders

Nutrients attractive for allergy prevention

- **Human Milk Oligosaccharides (HMO)** (Castillo-Courtade et al, 2015)
- **Probiotics** (West et al, 2017)
- **Omega-3** (Miles and Calder, 2017)
- **Vitamin D** (Yepes-Nuñez et al, 2018)
- **Food introduction** **(Turcanu et al, 2017)**
- **Prebiotics**

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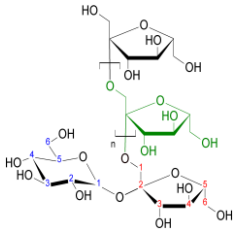
Prebiotics

- **Definition:** Non-digestible food ingredient which stimulates selectively the growth of bacteria in the microbiota supposed beneficial for the host health (Schrezenmeir, 2001)

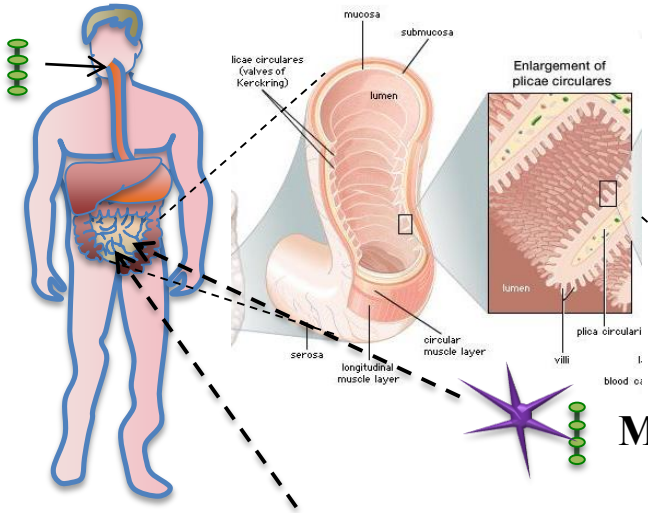
- **Main prebiotics :** GOS, FOS, inulin (Roberfroid, 2007): found in chicory, artichokes, grains … (Barrett and Gibson, 2012)

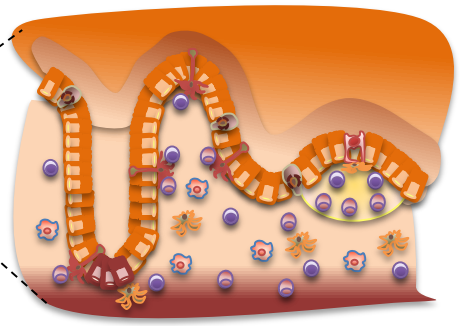
- **Breast milk:** HMOS (5-8 g/L) → gut maturation and immune system development

inulin



Effects of prebiotics



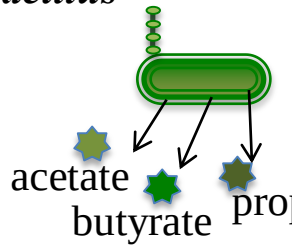


On IS and gut barrier

MAMP receptors and lectins on immune and mucosal cells. → Direct effect

Promote growth of certain types:
Bifidobacterium, *Lactobacillus*

Impact on microbiota metabolism: SCFA (Baldwin, 1970)



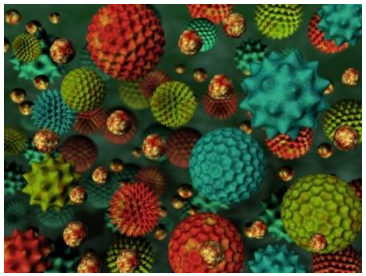
Microbiota → SCFA
Epigenetic properties and GPR receptor activation → Indirect effect

- **Suggested effect of prebiotics:**
  - ✓Strengthen intestinal barrier and immune system (Vinolo, 2009; Peng, 2009)
  - ✓Reduce infection risks (Gibson, 2005; Kaila, 1995)
  - ✓Act on allergies?

Prebiotics in allergy

Prebiotics : able to modulate microbiota and immune system

Allergy : induced by immune and bacterial disorders



Prebiotics: attractive for allergy prevention

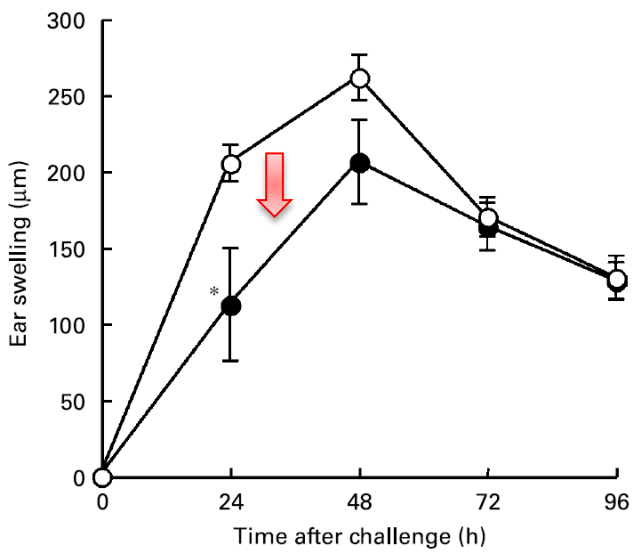
- **POSTNATAL:**
  - ✓ 10 animal studies
  - ✓ 2 positive human studies and 1 meta-analysis

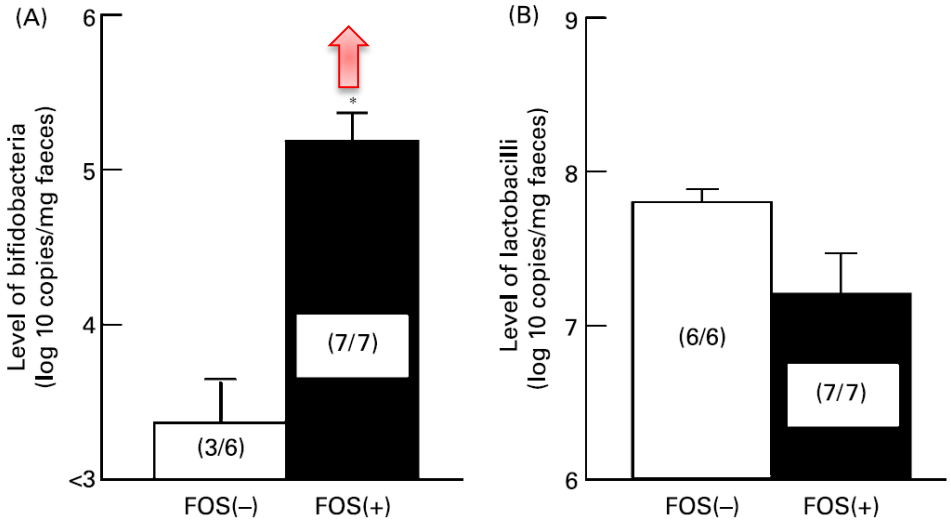
- **PERINATAL (on mother: gestation and/or lactation):**
  - ✓ 4 animal studies
  - ✓ 2 ongoing human studies

Animal studies: allergy prevention by prebiotics in POSTNATAL

Studies on pup supplementation (3 to 8 weeks old) with various prebiotics:
2 to 3 weeks of prebiotics exposure before sensitization to allergen
Supplementation during all the protocol

➢ **Skin allergy (CHS 2,4DNB)** *Watanabe et al, 2008*

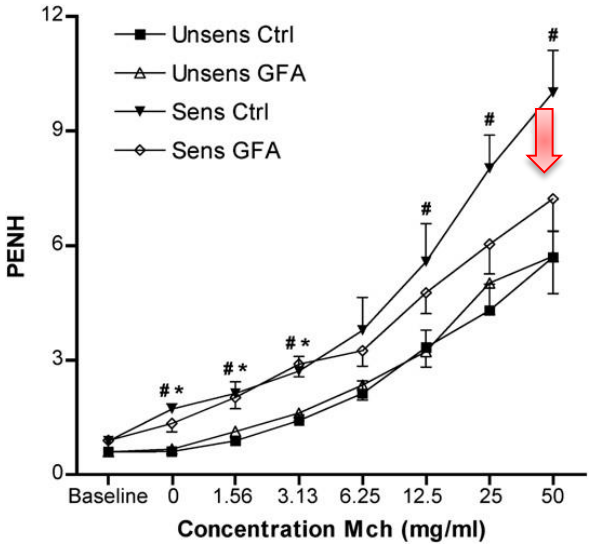


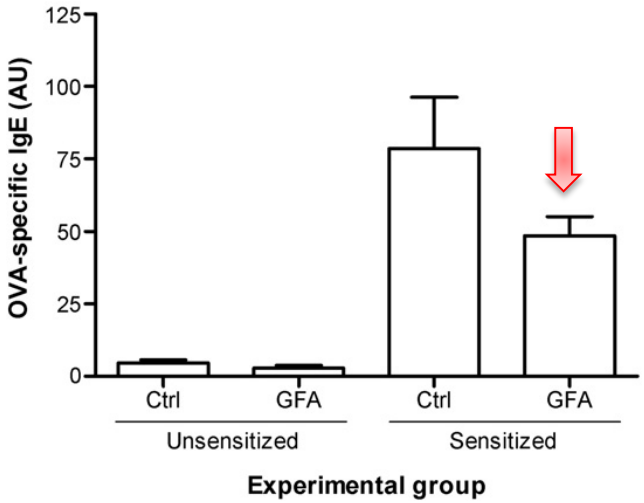


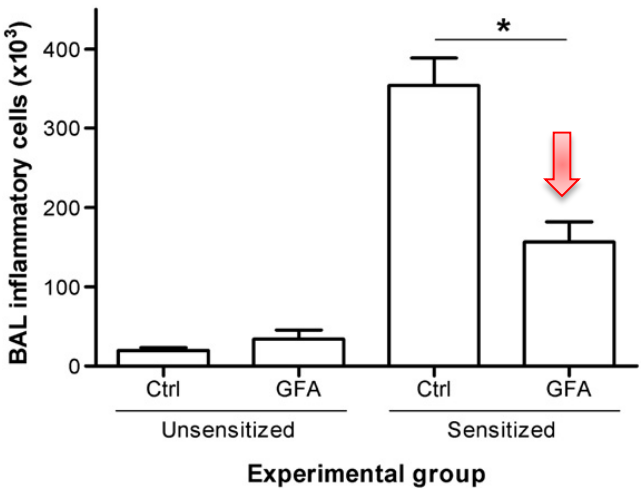
FOS prebiotic decreases the skin inflammation via microbiota modulation (increase of bifidobacteria)

Animal studies: allergy prevention by prebiotics in POSTNATAL

➢ **Respiratory allergy (OVA)** *Vos et al, 2007*





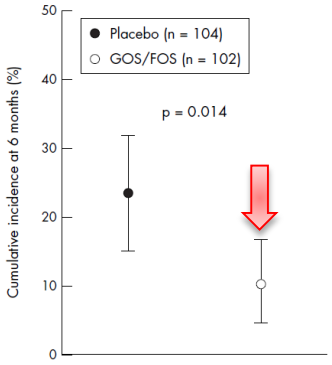


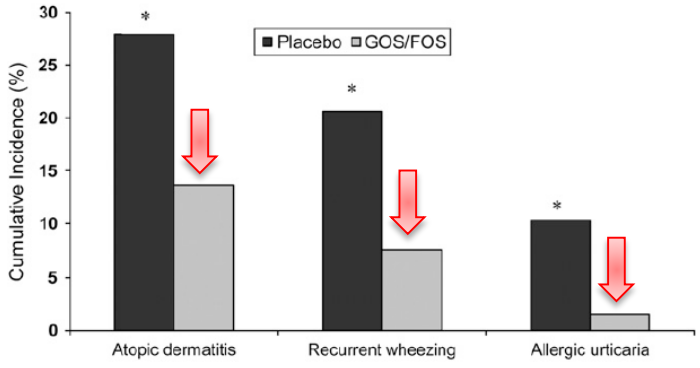
Balb/c mice supplemented with GOS / FOS / PAOS (9/1): reduction of airway hyper-responsiveness, specific IgE and pulmonary inflammation.

Human studies: allergy prevention by prebiotics in POSTNATAL

Only 2 favorable studies:

- **Moro's studies** (Arslanoglu , 2008; Moro, 2006) **using mixture of GOS/inulin ratio 9/1 in a hydrolyzed milk formula**
  - Italian cohort of infants at high atopic risk (206)
  - Formulas given during a 6-month lactation
  - Decrease of allergic disease incidence at 6 and 24 months old





- **Gruber's study** (Gruber, 2010) **using mixture of GOS/inulin/pectin**
  - Multicenter study in 5 European countries
  - Children at low atopic risk (414) supplemented during 6-month lactation
  - Prevention of atopic dermatitis
  - Peventive effect on AD obtained in one year does not last 5 years (Gruber 2015).

Human studies: allergy prevention by prebiotics in POSTNATAL

A meta-analysis of four studies (1428 infants at high or no risk of allergy)
(Osborn & Sinn 2013):

- Meta-analysis of 2 studies (226 infants) showed no significant difference in infant asthma.
- Meta-analysis of 4 studies demonstrated a significant reduction in eczema (1218 infants).
- One study reported no significant difference in urticaria.

Heterogeneity of the studies (type of prebiotics, period, dose…)

Further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula-fed infants

Perinatal period interest

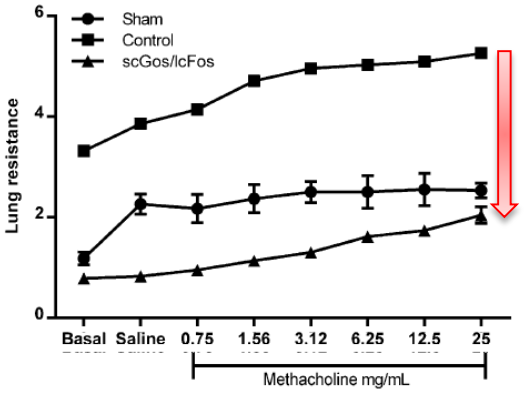
Animal studies: allergy prevention by prebiotics in PERINATAL

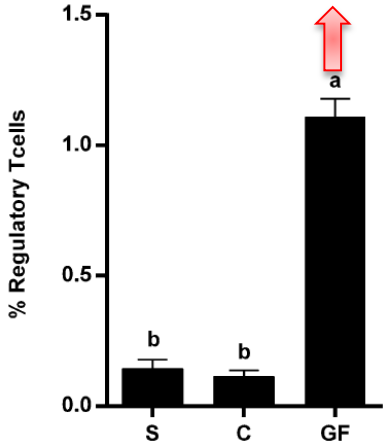
Only 4 studies on mother supplementation:

- **Respiratory alllergy** *Hogenkamp et al, 2015*

  Diet enriched in FOS/GOS during gestation

  OVA model of allergy in pups





A diet enriched in prebiotics (FOS / GOS) during gestation decreases airway hyper-responsiveness in offsprings through the induction of regulatory T cells at systemic level

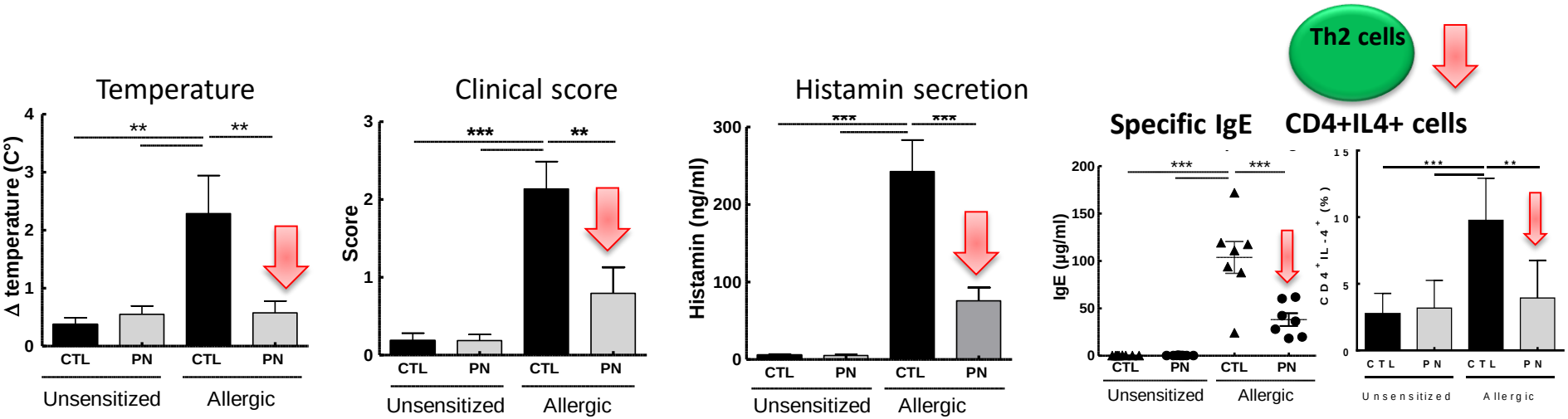
Animal studies: allergy prevention by prebiotics in PERINATAL

Only 4 studies on mother supplementation:

- **Food alllergy** *Bouchaud and Bodinier, 2016*

  Diet enriched in GOS/inulin during gestation and lactation

  Wheat gliadins model of food allergy in pups



- ✓ Reduction of food allergy symptoms and allergy markers in pups.

A diet enriched in GOS/inulin prebiotics during gestation/lactation protects againts food allergy in mice.

Clinical studies: allergy prevention by prebiotics in PERINATAL

9 g/day: GOS/inulin prebiotics

Modification of immune system

Modification of microbiota

Immune factors transfered *via* cord blood

Vaginal microbiota transfered

Immune factors and bacteria transfered *via* breastmilk

PREGRALL clinical trial

SYMBA clinical trial

PREGNANCY

DELIVERY

BREASTFEEDING

FIRST DEGREE ATOPIC RISK CHILDREN

Tolerance induction

Specific microbiota implantation

Allergy prevention

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

CRNH

INRA SCIENCE & IMPACT

Australian Government National Health and Medical Research Council NHMRC

TELETHON KIDS INSTITUTE

Childhood Allergy and Immunology Research

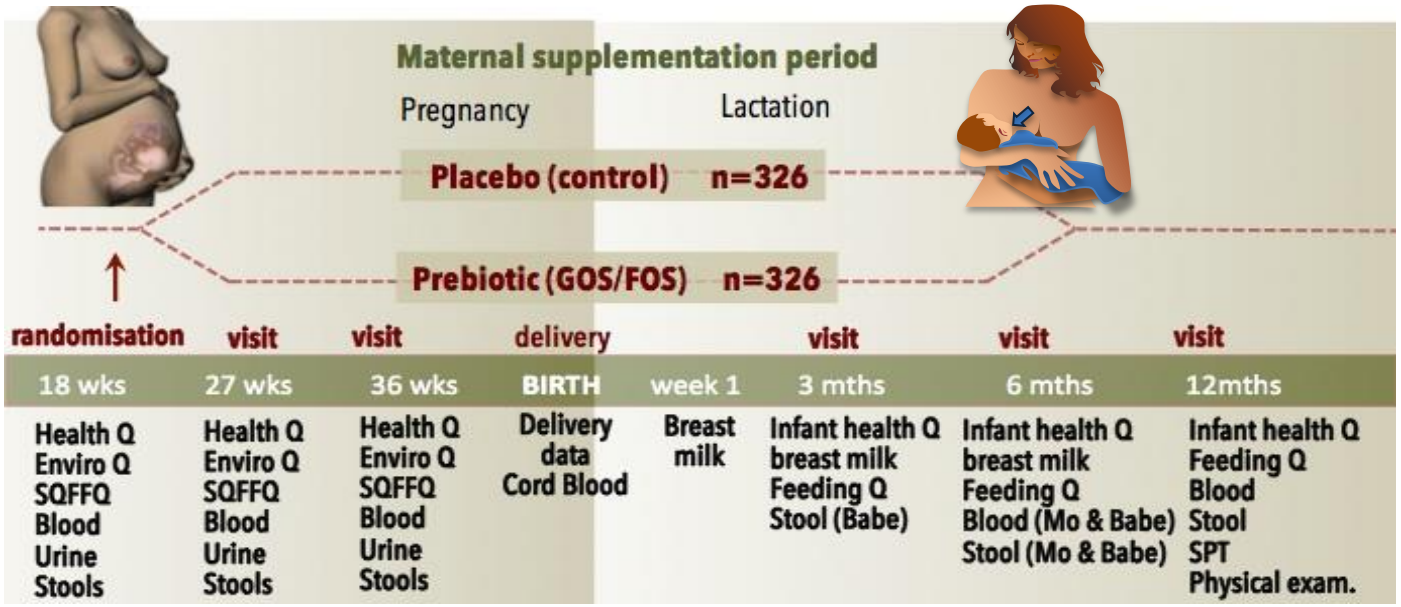
JOONDALUP HEALTH CAMPUS

THE ORIGINS PROJECT

SYMBA clinical trial

Double-blinded RCT design : monocentric trial

Inclusion Criteria: 652 pregnant women whose infants have a first-degree relative with a history of medically-diagnosed allergic disease



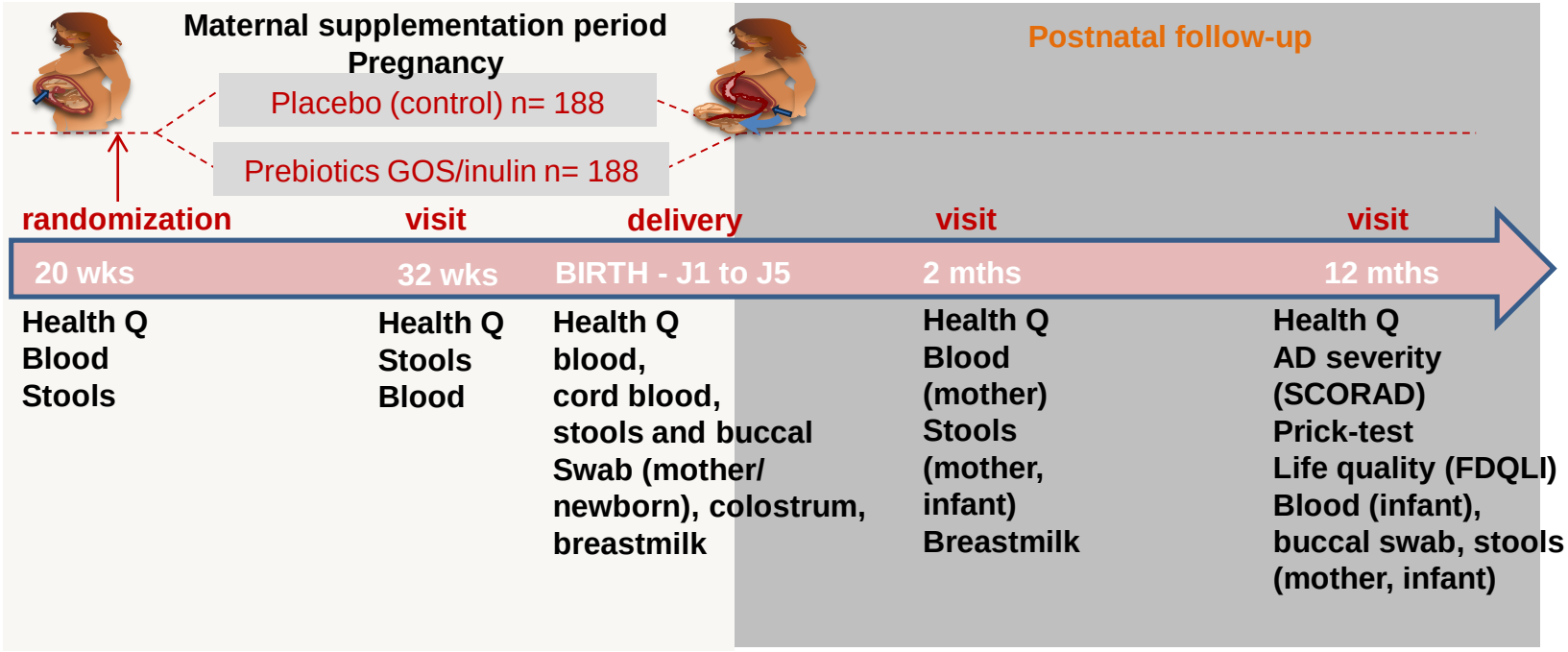
Study Sites

- Joondalup Health Campus, Joondalup, Western Australia : the main site for recruitment, randomization and follow-up.
- Telethon KIDS Institute: the main academic coordinating centre.
- Principal chief investigators: Susan Prescott, Debra Palmer, Desiree Silva

PREGRALL clinical trial

Double-blinded RCT design: multicenter trial

Inclusion Criteria: 376 allergic pregnant women



Study Sites

- Nantes, Angers, Tours hospitals: the main sites for recruitment and follow-up.
- Centre of clinical investigation for women, children and teens: the main coordinating centre.
- Principal chief investigators: Hélène Aubert, Sébastien Barbarot
- Scientific coordinator: Marie Bodinier

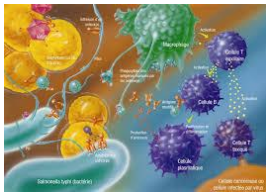
SYMBA and PREGRALL aims

AIM 1. The effects of the intervention on allergic disease outcomes in the offspring at 1 year of age:

- SYMBA: **eczema**.
- PREGRALL: **AD**.

AIM 2. The effects on colonization patterns and SCFA microbial metabolites:

- on both maternal and infant gut microbiota.



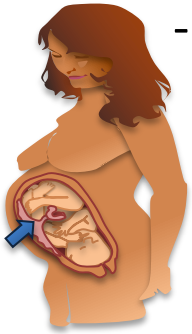
AIM 3. Assessment of the immunomodulatory effects during the intervention:

- Immune functions in blood of mother and offspring, both at birth (antenatal effects) and during infancy, to examine the trajectory of immune development.

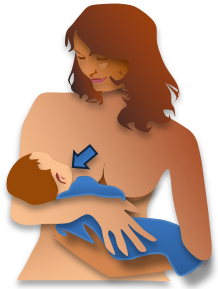
AIM 4. Analyse of the breast milk composition (PREGRALL).

Translation of future results obtained by SYMBA and PREGRALL RCTs

- **Demonstrating the interest of prebiotics to prevent allergies via 2 clinical trials run in different countries.**



- **Defining the most effective timing and duration of maternal prebiotics supplementation: gestational period alone or combined with lactation ?**



- **Demonstrating the importance of microbiota and IS balance early in life in correlation with the emergence of allergic disease.**

Conclusion

- **Allergy: linked to microbial, mucosal and immune disorders.**

- **Perinatal period: window of modulation for allergy prevention.**

- **Nutritional strategy in early life: very encouraging.**

Thanks for your attention

My Allergy team

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FRANCE

My French collaborators

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Debbie Palmer and Susan Prescott