

Role Of Gut Microbiota In The Development Of The Immune System

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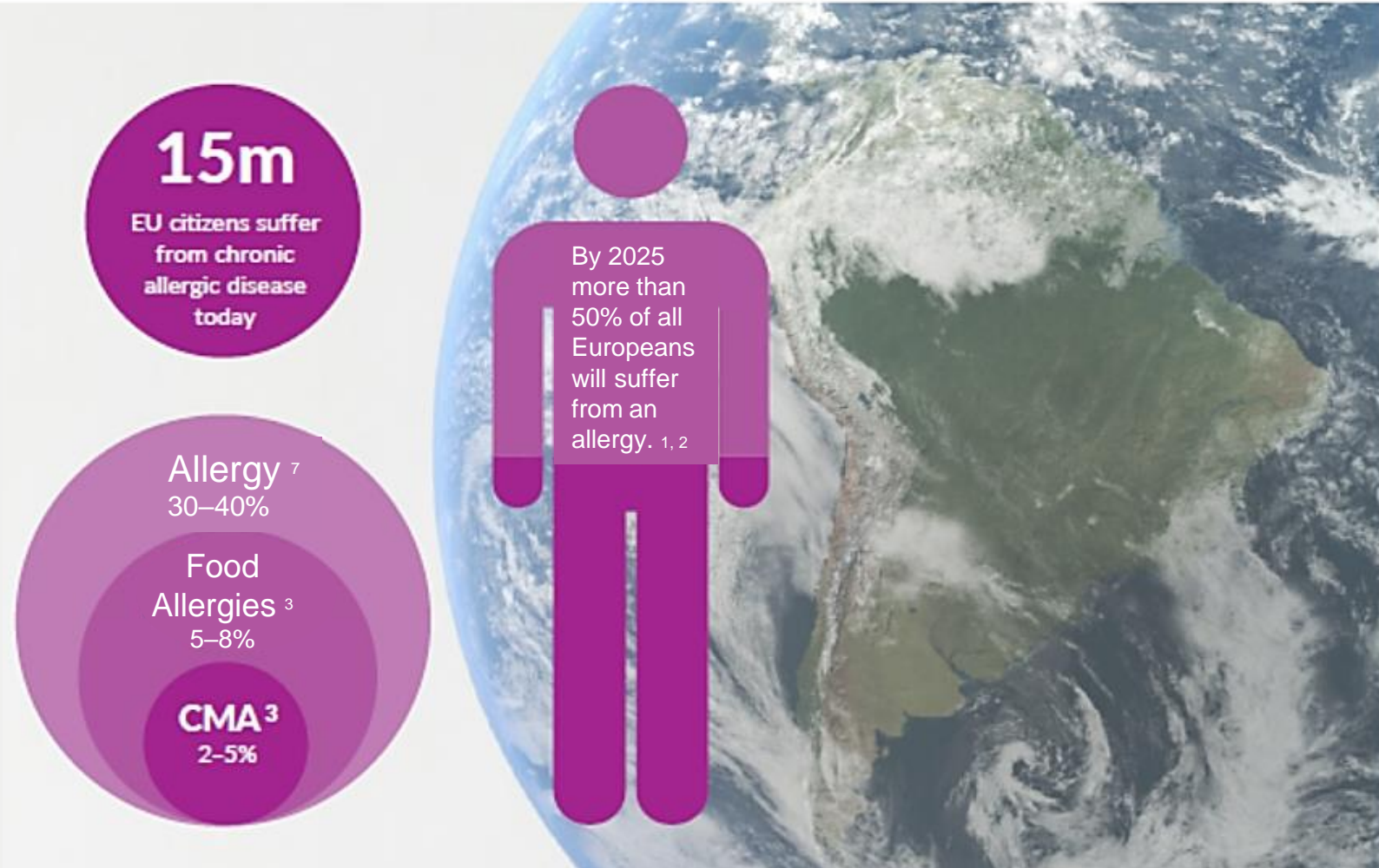
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A young child with curly hair is blowing a dandelion seed head. The child is wearing a light blue shirt with a feather pattern and a dark cardigan. The background is a bright, sunny outdoor area with trees and a path. The image is overlaid with a blue header and a white curved shape containing text.

GLOBAL RISE IN ALLERGY

ALLERGIES ARE ON THE RISE: 30-40% OF THE WORLD POPULATION IS NOW ALLERGIC

- By the 2050s, allergies will affect up to 4 billion people globally^{1,2}
- They are a rapidly increasing burden in developing countries
- Food allergies affect up to 8% of infants and young children globally,³ with cow's milk being the leading cause⁴⁻⁶



THE PATTERN OF COW'S MILK ALLERGY IS BECOMING INCREASINGLY AGGRESSIVE

Prevalence is 2–5 % worldwide¹

There has been a trend towards:

- Increasing **incidence** and **prevalence**²
- Increasing **persistence** into school age and beyond³
- Increasing **severity**⁴
- Increasing rate of hospitalisations⁴



Increasing trend of the number of hospital admissions for FIA among Italian children from 2006 to 2014⁴

ENVIRONMENTAL FACTORS MAY HAVE A ROLE IN INCREASING THE RISK OF DEVELOPING ALLERGIES¹⁻³

GENETIC FACTORS

Family history of allergy



20-40%
higher
allergy risk⁴⁻⁶

ENVIRONMENTAL FACTORS

NEW

C-section



Up to
30%
higher
allergy risk⁷

Antibiotic use



X2
higher
asthma risk⁸

Pollution



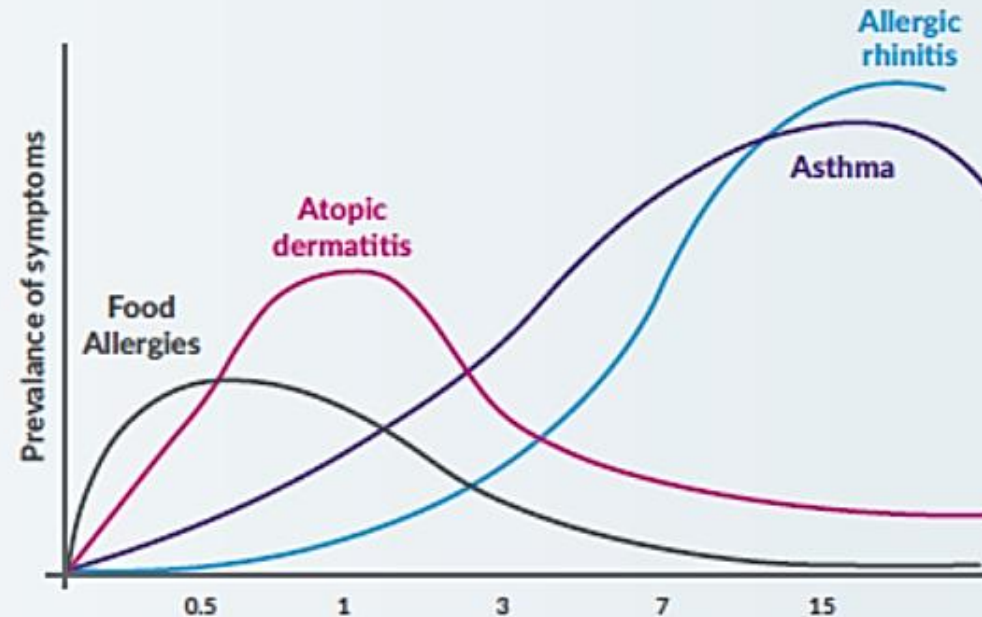
Up to
20%
higher
wheezing risk^{9,10}

GUT MICROBIOTA DYSBIOSIS

associated factor to the increase in allergy incidence^{11,12}

ALLERGY IN EARLY LIFE HAS REPERCUSSIONS FOR FUTURE HEALTH: THE ATOPIC MARCH

Allergies early in life predispose subjects for having other secondary allergies in later life, this is known as the concept of the Atopic March¹⁻³



Prevention of the first allergies matters

The 'Atopic March'. Schematic representation of symptoms according to age. Once a child has developed atopic dermatitis or a food allergy in the first years of life, the child is more likely to develop other allergies, like allergic rhinitis or asthma later in life ¹⁻⁴

THE BURDEN OF ALLERGY GOES BEYOND SYMPTOMS...

PHYSICAL ¹⁻⁴

- Increased risk of future non-communicable diseases (NCDs) e.g. obesity, diabetes, heart disease, hypertension etc.



FINANCIAL ^{1,5,6}

- Increased medication and health costs
- Increased indirect costs (e.g. parental loss of income due to time off work)

€521M*



PSYCHOLOGICAL ^{1,7}

- Distress for child and parents
- Impact on quality of life



SOCIAL ^{1,7}

- Social isolation
- Fear of future health problems



Strong rationale for developing effective strategies for infants at risk and with allergy.

EVOLUTION OF CARE FROM AVOIDANCE TO ACTIVE TOLERANCE DEVELOPMENT

Oral Tolerance development is the ultimate allergy prevention

FROM: AVOIDANCE

- Avoid allergenic foods in hope of prevention
- Educate on management of allergic reactions'
- Wait and watch for the development of tolerance

TO: TOLERANCE DEVELOPMENT

- Early active introduction of potentially allergenic foods to support tolerance development before allergy develops and promoting acquisition of tolerance
- A balancing act between avoiding allergens and promoting acquisition of tolerance

PRESENT: FROM AVOIDANCE TO ACTIVE TOLERANCE DEVELOPMENT

PARADIGM SHIFT

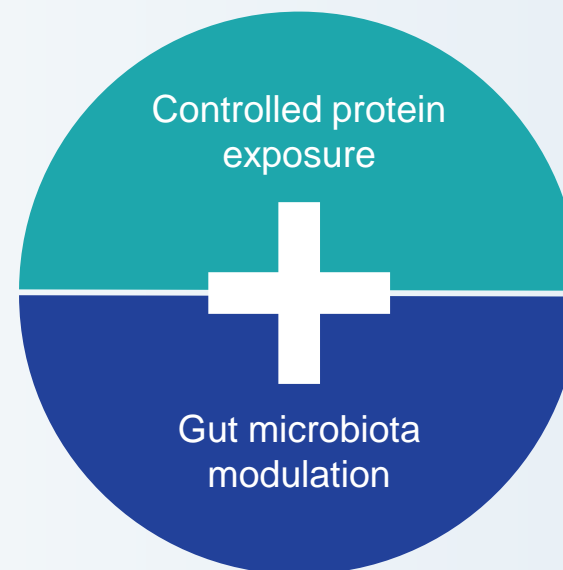
From
Allergen (protein)
AVOIDANCE



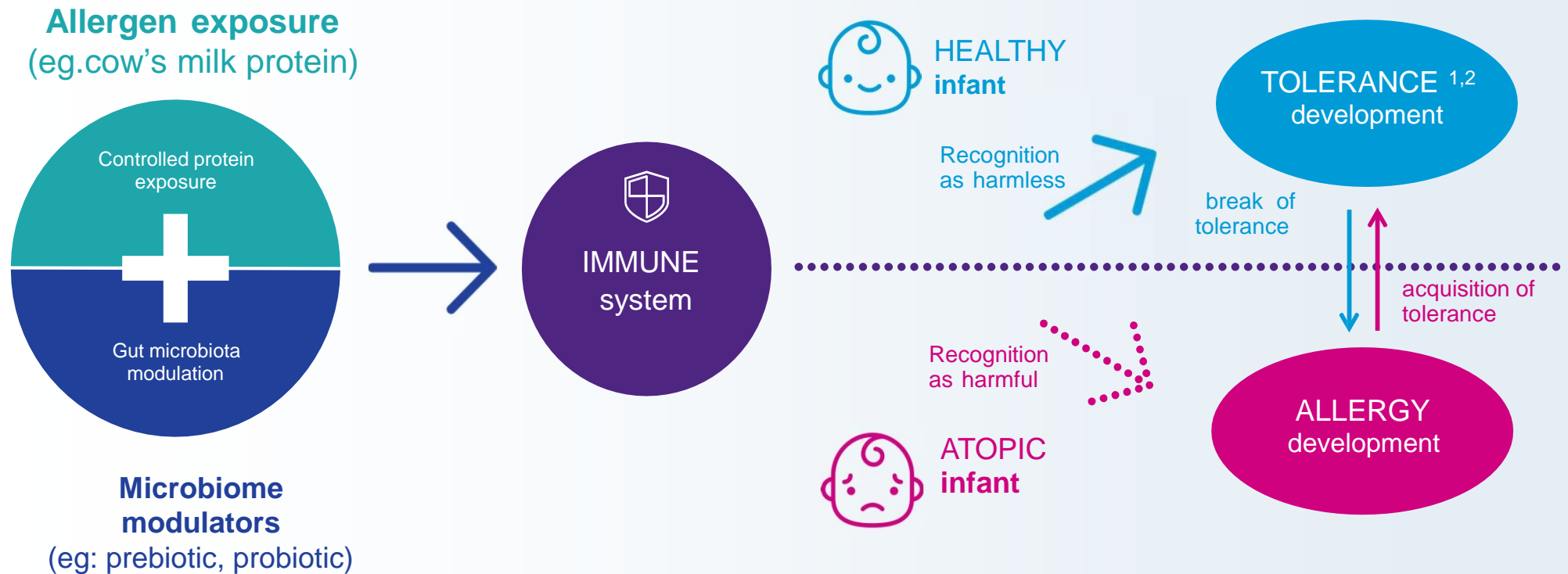
To
Training immune system
to build immune/oral
TOLERANCE to reduce the
risk and manage the
disease (not only the
symptoms)



Via

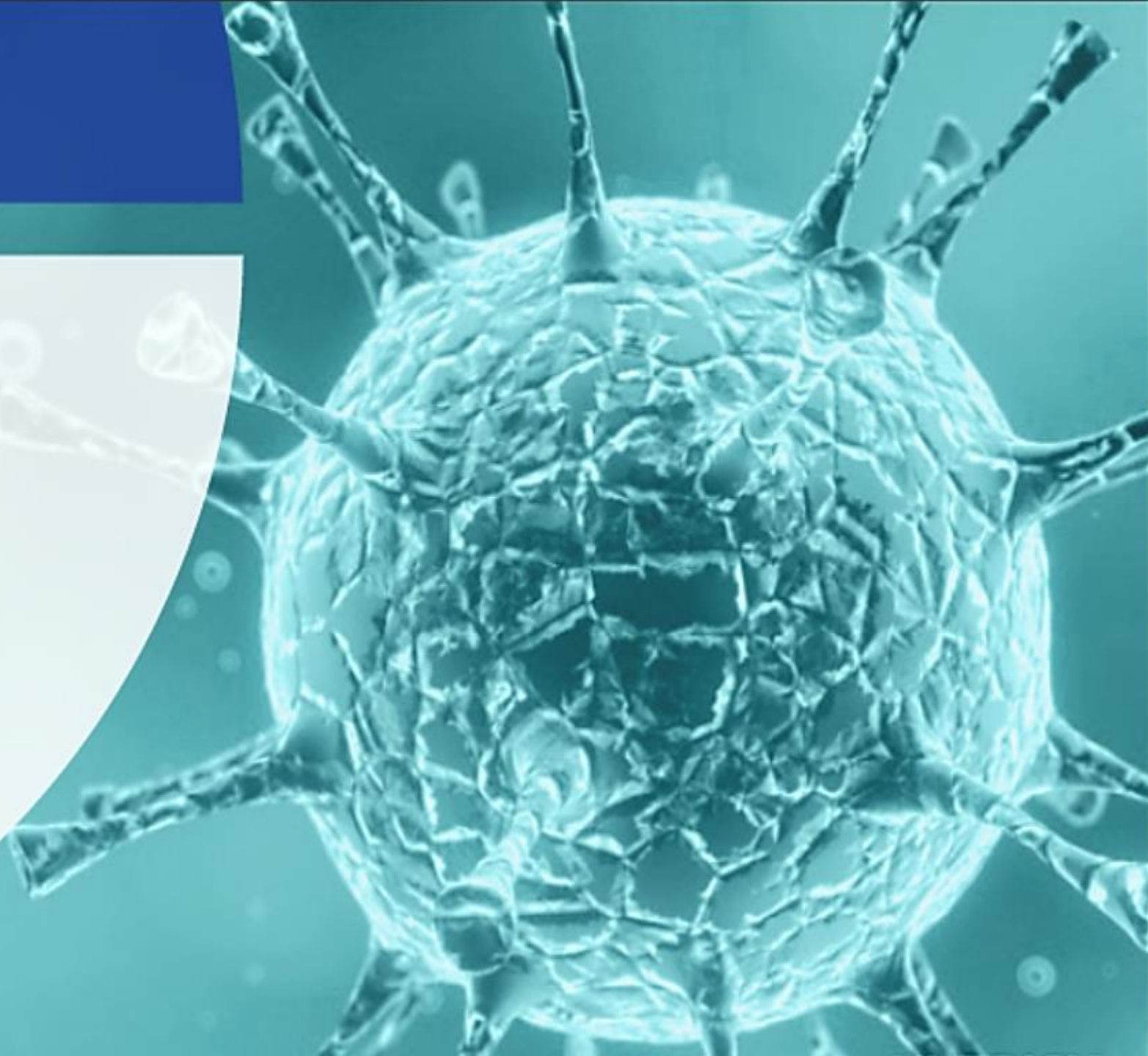


PRESENT: FROM AVOIDANCE TO ACTIVE TOLERANCE DEVELOPMENT - EXPOSURE NEEDED TO TRAIN THE IMMUNE SYSTEM



TRAINING THE IMMUNE SYSTEM:

INTERPLAY WITH
THE GUT MICROBIOTA



HEALTHY IMMUNE SYSTEM IS KEY FOR HEALTH IN LIFE

The immune system is one of the most important organ systems in the body.

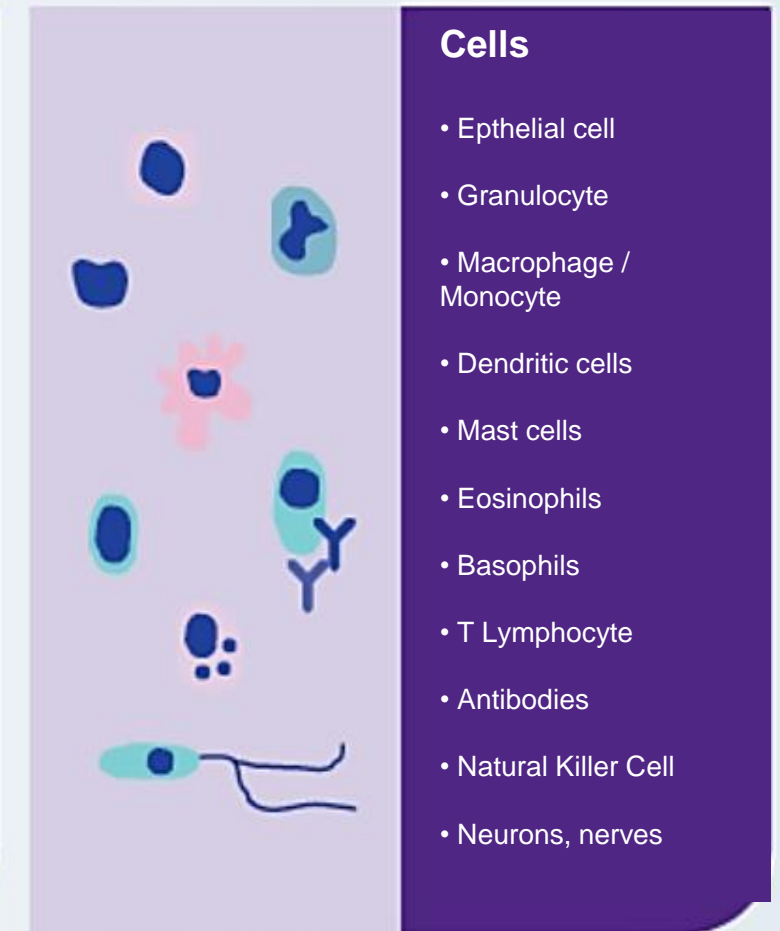
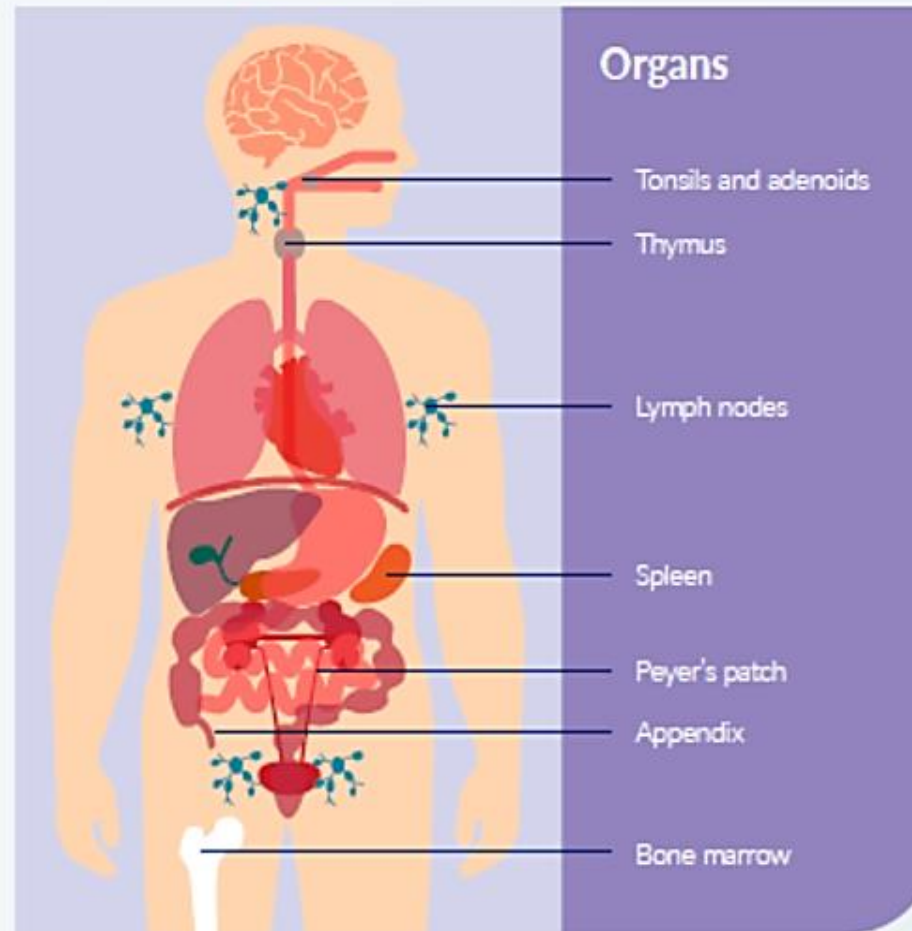
- Its a complex system involving multiple organs and cells to ensure:

- Defence against pathogens: bacteria, viruses, parasites, fungi

- **Tolerance induction**

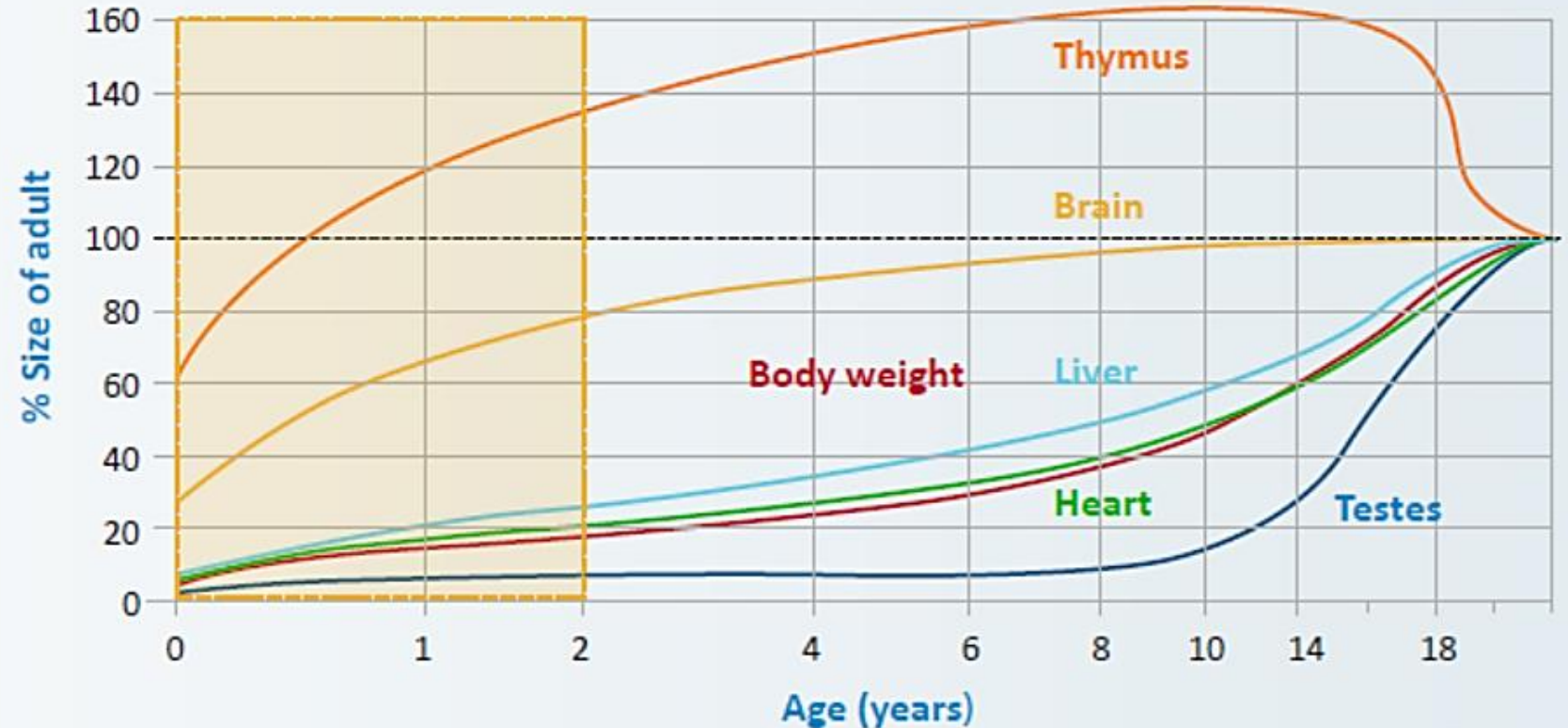
- Assistance in anti-cancer responses

- Removal of foreign / non-self compounds



KEY DEVELOPMENT STAGES OF THE IMMUNE SYSTEM OCCURS IN THE FIRST 1000 DAYS ⁽¹⁾

- The immune system is not fully developed at birth, but matures over the first few years of life.
- Newborns have a limited capacity to initiate immune responses. Different components of the immune system develop at different times.¹



Reference 2

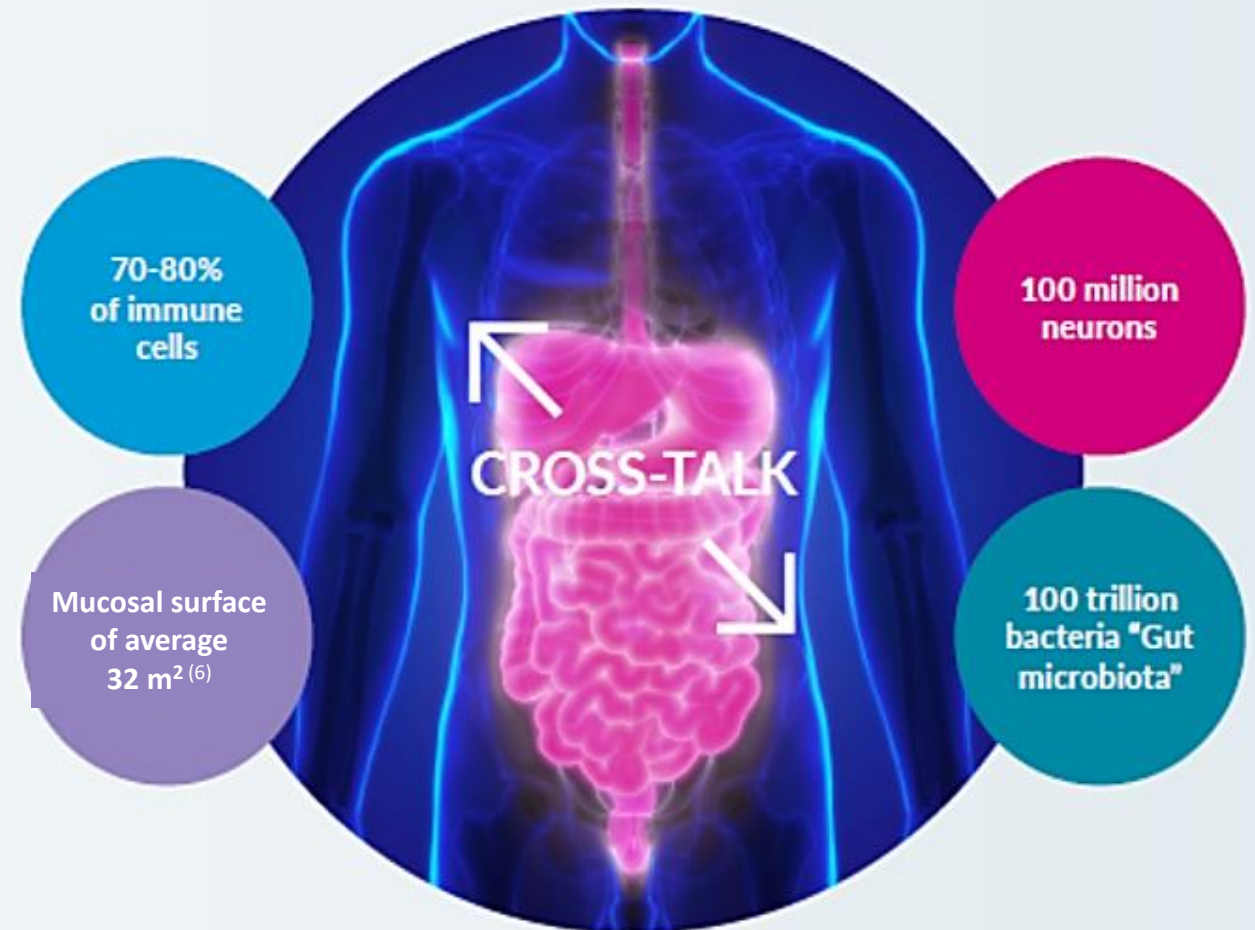
KEY DEVELOPMENT STAGES OF THE IMMUNE SYSTEM OCCURS IN THE FIRST 1000 DAYS ⁽¹⁾

	Birth	6 months	1 year	2 years	3 years	4 years	5 years	5-15 years	Adult
Acidic mucins	developing	developing	Adult level	Adult level	Adult level	Adult level	Adult level	Adult level	Adult level
Microbiota composition	developing	developing	developing	developing	Adult level	Adult level	Adult level	Adult level	Change again while aging
NK cells	developing	>adult level	>adult level	>adult level	>adult level	>adult level	Adult level	Adult level	Adult level
IgG	immature	immature	developing	developing	developing	developing	developing	Adult level	Adult level
IgM	immature	developing	Adult level	Adult level	Adult level	Adult level	Adult level	Adult level	Adult level
IgA	immature	developing	developing	developing	developing	developing	developing	developing	Adult level
Th1 mediated immunity	immature	developing	developing	developing	Adult level	Adult level	Adult level	Adult level	Decreases again while aging
T cell independent antibody response	immature	immature	immature	developing	developing	developing	developing	Adult level	Adult level

immature
 developing
 Adult level

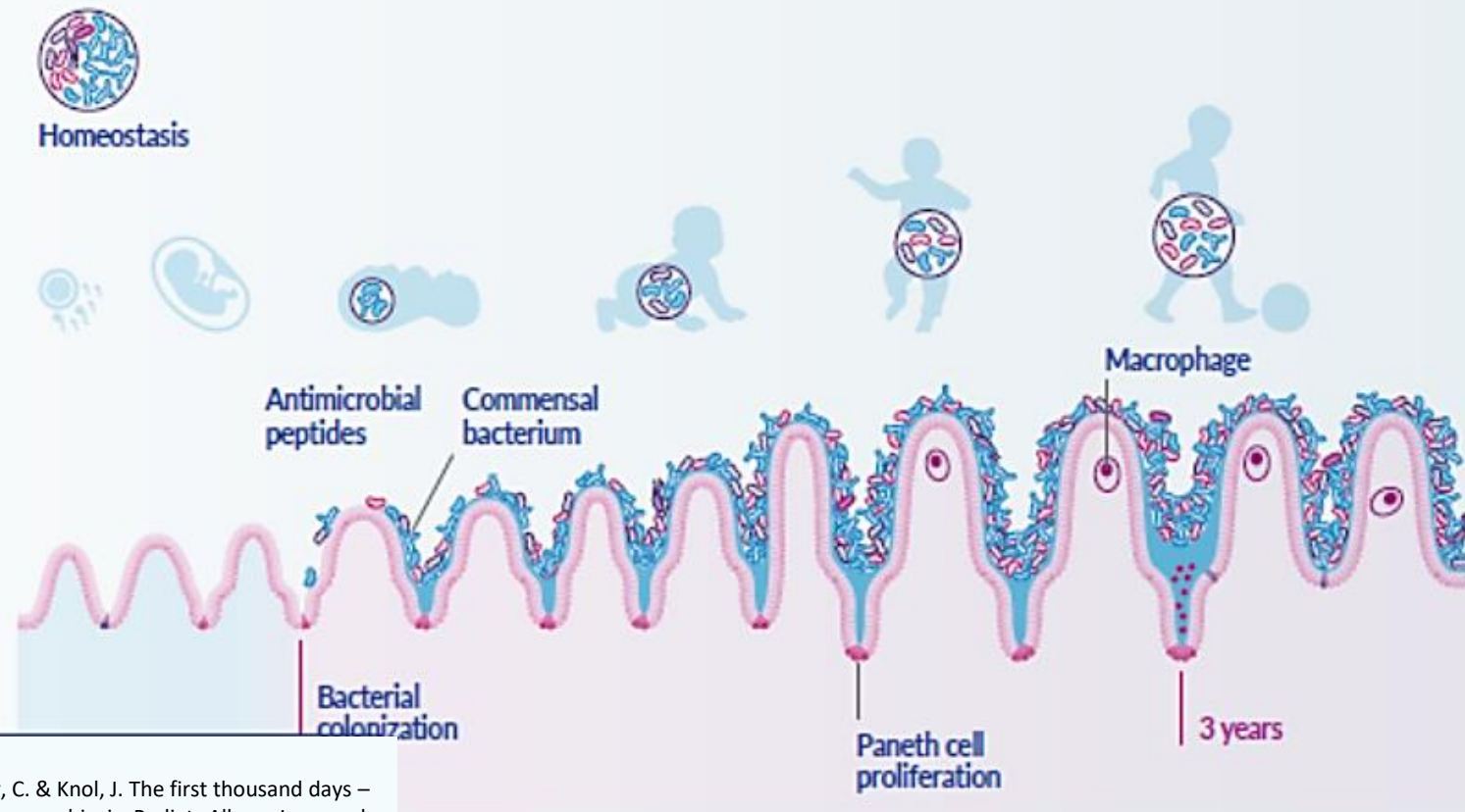
BEYOND DIGESTIVE FUNCTION THE GUT IS OUR LARGEST IMMUNE ORGAN

- Early life is a critical period, as the infant's immune system is still maturing and is influenced by the gut microbiota.
- There is high potential for crosstalk between the gut microbiota¹ and the immune system as 70-80% of immune cells reside in the gut microbiota.²
- Consists of several types of lymphoid tissue, e.g. Peyer's patches, known as the gut-associated lymphoid tissue (GALT).^{3,4}
- The GALT is important both for defense and **tolerance**.^{3,4}
- The gut plays a critical role in developing and sustaining immune balance.^{2,5}
- Microbial interactions are important drivers in the maturation of the immune system.⁵



DEVELOPMENT OF THE GUT MICROBIOTA AND IMMUNE SYSTEM TAKES PLACE OVER TIME

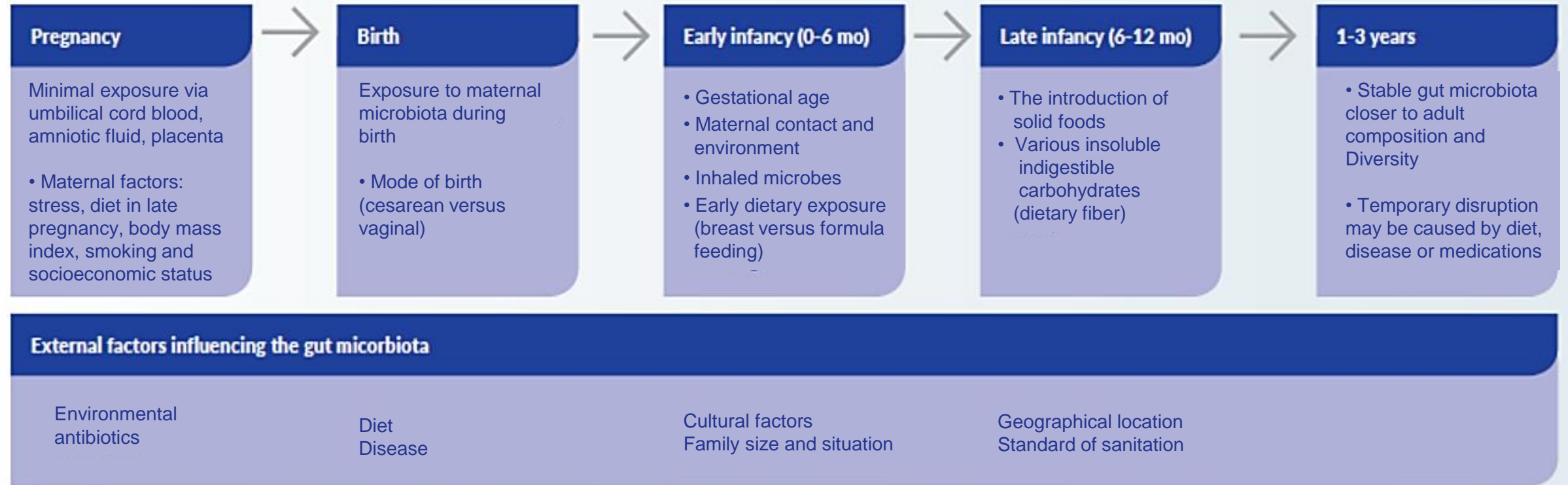
Development of the gut microbiome takes place in early life¹.



References

1. Wopereis, H., Oozeer, R., Knipping, K., Belzer, C. & Knol, J. The first thousand days – intestinal microbiology of early life: establishing a symbiosis. *Pediatr Allergy Immunol* 25, 428-438, doi:10.1111/pai.12232 (2014).

GUT MICROBIOTA COLONIZATION IS A PROCESS OVER TIME AND IS AFFECTED BY MANY FACTORS



BIOACTIVE COMPOUNDS BEYOND MACRONUTRIENTS IN HUMAN MILK

Milk Constituent	Bioactive Component	Immunological Effect
Cells	Lymphocytes, Macrophages, Granulocytes	Active protection against infections
Proteins	Antibodies, Growth Factors, Cytokines	Protection against infections Maturation of the immune system
▶ Live Bacteria	Bifidobacteria, Lactobacilli, and others	Colonization, immune system
▶ Oligosaccharides	(HMOs) >100 "from one human milk sample"	Colonization, immune system, gut barrier function
Fatty Acids	Saturated (45%), MUFA (40%), PUFA (15%): 0.35% DHA 0.60% ARA	Membrane structure Maturation of the Immune system Precursor for Immunological Mediators
Protein, carbohydrates; others, macromolecules	Allergens, Lactose, Nucleotides	Immune system, colonization, precursor for DNA/RNA synthesis
Minerals, Vitamins	Mg, Zn, Fe, Se, Vit A, C, E	-Enzyme, Anti-oxidant

- Intestinal flora composition plays an important role in the development of allergic diseases and airway inflammation because of its potential effects on TH1-type immunity, generation of TGF, and IgA production.



- There has been speculation that exposure to these microbial agents in early life, when immune maturation is critical, could play an important role in maturation of type 1 T helper cell (TH1) immune responses and could inhibit the development of allergic type 2 T helper cell (TH2) responses and IgE antibody production .



- Probiotics are a class of active microorganisms that are beneficial to the host by colonization in the human body and altering the composition of the flora at a certain part of the host.
- Prebiotics are non digestible food ingredients that have a beneficial effect on the host by selectively stimulating the growth and activity of probiotics to improve host health.
- Symbiotic are a combination of probiotics and prebiotics .



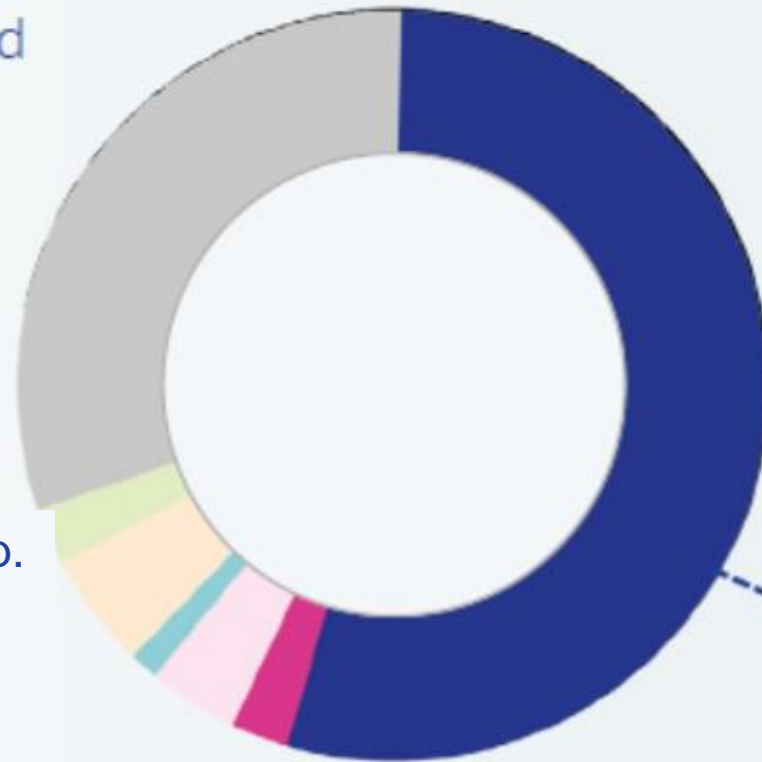
- Probiotics, prebiotics, and symbiotic can ameliorate the host immune system via gut ecosystem and may be beneficial for the treatment of allergic diseases such as asthma.
- Some animal experiments have shown that probiotics can effectively inhibit IgE production and the accumulation of eosinophils.
- Probiotics also show effects in the prevention and treatment of allergic diseases.



HUMAN MILK INFLUENCES THE DEVELOPMENT OF THE GUT MICROBIOTA

Healthy vaginally born breastfed infants have *Bifidobacteria* dominated gut bacteria¹

- *Bifidobacterium* spp.
- *Clostridium* &
- *Eubacterium* spp.
- *Bacteroides* spp.
- *Escherichia coli*.
- *Atopobium* spp.
- *Lactobcillus* spp.
- Other genera

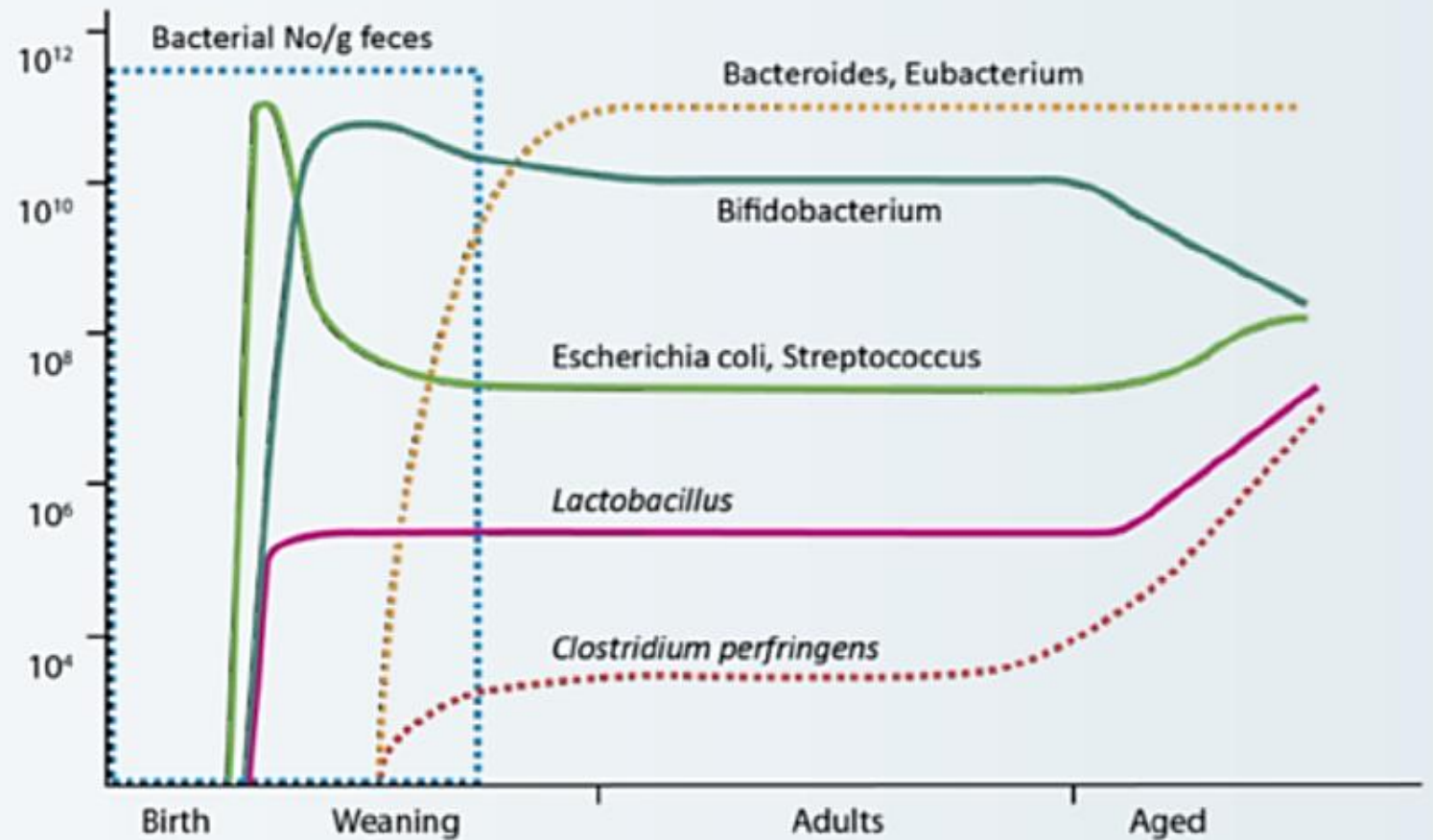


Gut microbiota of healthy, breast-fed infants



BIFIDOBACTERIA IS ONE OF THE MOST DOMINANT SPECIES IN EARLY LIFE

The gut of a healthy breast-fed infant is typically dominated by bacteria of the *Bifidobacterium* species. These species are first transmitted from the mother during birth and via the breast milk



FACTORS CAN IMPACT GUT MICROBIOTA

- **Developmental origins or maternal microbiota**
- **Mode of delivery**
(vaginal vs. caesarean section)
- **Duration of gestation**
(term vs. preterm)
- **Early dietary feeding**
(breast vs. formula complementary feeding)
- **Use of antibiotics, and/or probiotics**
- **External environmental factors**
(geographical environment, family size, exposure to pets)



Healthy status

- Immune tolerance
- Gastrointestinal homoeostasis
- Healthy metabolism

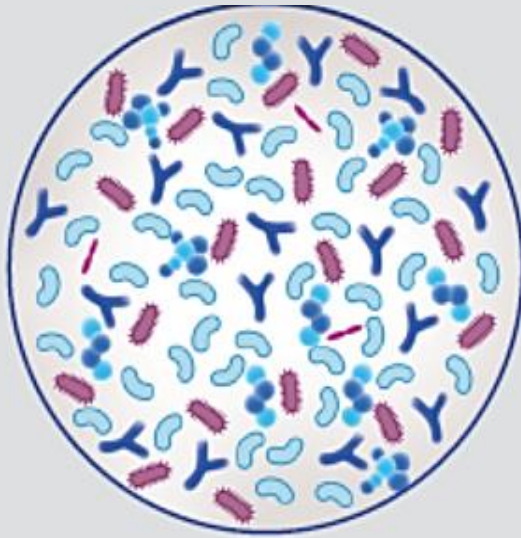
Dysbiosis

- Immune disease
(allergy, asthma)
- Gastrointestinal disease
(IBD)
- Metabolic disease
(obesity, diabetes)

GUT MICROBIOTA DYSBIOSIS

HEALTHY

Gut microbiota composition of healthy, vaginally delivered breast-fed infants



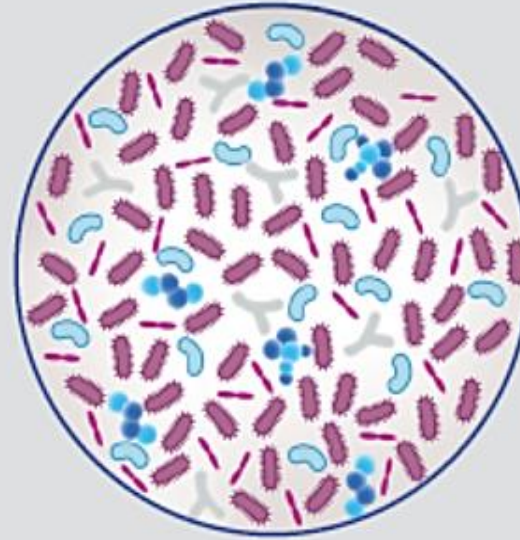
Higher levels of
beneficial
bacterial species

Bacteroides fragilis
Bifidobacterium
Lactobacillus

Bacteroides
Enterococcus

DYSBIOSIS

Gut microbiota composition of C-section delivered infants



- Higher levels of potentially harmful bacteria
- Reduced levels of beneficial bacterial species

Clostridium difficile
Staphylococcus aureus

Escherichia coli
Enterobacteriaceae

Figure 1. Hypothetical image to illustrate the concept of dysbiosis.

GUT MICROBIOTA IN INFANCY

Gut microbiota dysbiosis in early life may delay oral tolerance, which can play an important role in the development of immunerelated diseases such as food allergy and atopic dermatitis



Gut microbiota dysbiosis in allergic infants in early life



Acquisition of oral tolerance may be Delayed¹⁻³

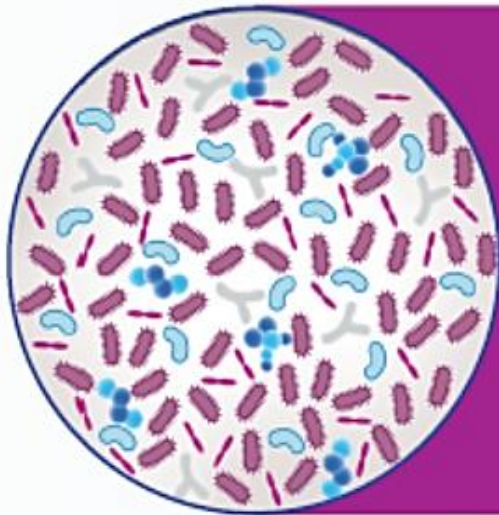


Immune related diseases may develop¹⁻³

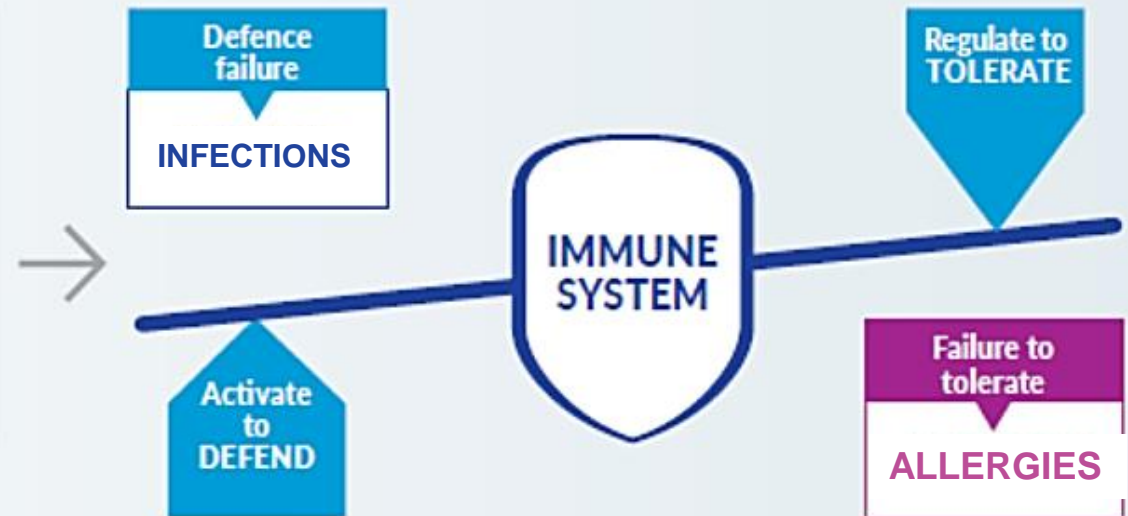
Addressing the underlying dysbiosis is critical and nutrition can play a role in modulating the gut microbiota⁴

GUT MICROBIOTA DYSBIOSIS

GUT MICROBIOTA DYSBIOSIS



Lower levels of beneficial bacteria (ie *Bifidobacterium*) may impair development of appropriate immune response, which can affect the ability to recognise substances as harmful or harmless.^{1,2}



DIFFERENCES IN GUT MICROBIOME HAVE BEEN OBSERVED BETWEEN ALLERGIC AND HEALTHY BREASTFED

Infants with food allergies such as CMA have been shown to have low levels of *bifidobacteria* and *lactobacilli* in their gut microbiota compared with healthy, breast-fed infants

Gut microbiota of healthy, breastfed babies
dominated by healthy *Bifidobacteria* ^{1, 2, 3}



Bifidobacterium



Clostridium & Eubacterium spp.



Other genera. (not analysed)

Gut microbiota of CMA babies

with lower levels of healthy *Bifidobacteria* and higher levels of potentially harmful *Clostridia* and *Eubacteria* ^{4,5}



Strong rationale for the need of gut microbiota modification in the dietary prevention and management of allergy.

BREAST MILK IS ONE OF THE KEY INFLUENCERS OF GUT MICROBIOTA TO SUPPORT DEVELOPMENT OF HEALTHY IMMUNE RESPONSE

BREASTMILK NATURALLY TRAINS
THE IMMUNE SYSTEM VIA ^{1,2}

CONTROLLED PROTEIN EXPOSURE

INTRODUCTION OF
HARMLESS PROTEINS
(ie food proteins) in a controlled
manner³



GUT MICROBIOTA MODULATION

DELIVERY OF
OLIGOSACCHARIDES
(prebiotic) to feed beneficial
bacteria ^{4,5}



DELIVERY OF
BENEFICIAL BACTERIA
(probiotic) to interact with
immune cells ⁶



HUMAN MILK: THE BEST IMMUNO-NUTRITION



Human milk contributes to immune health via direct interaction with the developing immune system¹



Human milk supports a bifidobacteria dominant gut microbiota, ² being also beneficial for optimal development for immune health (i. e. oral tolerance)³



Human milk contains small amounts of food proteins and thus may support oral tolerance ⁴



Human milk is our reference for nutritional solutions that drive healthy immune development for dietary prevention and management of allergies.



BREASTFEEDING IS RECOMMENDED FOR PREVENTION OF FOOD ALLERGY



Breast milk is the gold standard to train the immune system¹



The World Health Organization recommends exclusive breast-feeding for the first six months of life²

- International guidelines for allergy prevention universally recommend **breastfeeding for at least 4-6 months with parallel introduction of complementary feeding from 4-6 months including potentially allergenic foods.**
- If breastfeeding is insufficient or not possible, infants at high-risk based on atopic heredity can be recommended a **hypoallergenic formula** to reduce the risk of allergy development.^{2, 3}
- International guidelines also recommend the use of '**prebiotic supplementation** in not-exclusively breastfed infants' for the prevention of allergy ⁴, and the additional positive recommendation on the use of probiotics in not-exclusively breastfed infants at high risk of developing allergies.⁵

PROSYNEO CONCEPT

SUPPORT THE TRAINING OF THE IMMUNE SYSTEM WITH
APTAMIL PROSYNEO HA, BY TARGETING GUT MICROBIOTA

CONTROLLED PROTEIN EXPOSURE

Unique peptide profile



- = allergenic epitope
- = tolerogenic epitope

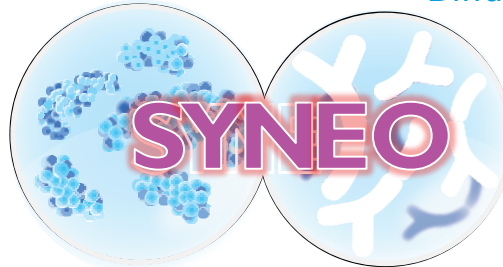
- **Reduced allergenicity**¹⁻³
- Promotion of natural development of **immune tolerance**^{1,4,5}
- **Easy to digest**⁶⁻⁸



GUT MICROBIOTA MODULATION

Unique oligosaccharides scGOS/lcFOS

Beneficial bacteria Bifidobacterium breve



- **Modulation of the gut microbiota balance** closer to that of healthy breastfed infants^{9,10}
- Setting the right gut environment for **immune tolerance development**⁹⁻¹²
- **Softer stool closer to that of breastfed infants**¹³



OUTLOOK

- The pattern of CMPA are becoming increasingly aggressive
- Prevention of first allergies matter to stop the Allergic March
- Active management of Allergy : from Avoidance to Tolerance Induction
- Gut microbiota plays a critical role in infant's "Immune Development and Allergy"
- Healthy breastfed infant's gut is dominated by Bifidobacterium species.
- Gut DYSBIOSIS may delay oral tolerance which contribute to the development of immune related diseases as Allergy.
- Human milk naturally trains the immune system and prevents and manage CMPA via :
 - Controlled protein exposure,
 - HMOS(prebiotic effect))to feed healthy bacteria,
 - Beneficial bacteria like Bifidobacterium Breve (probiotic effect)



Thank You