



A microscopic view of a dense population of cells, likely bacteria or yeast, showing their individual shapes and interactions. The cells are arranged in a somewhat organized pattern, with some appearing to be in the process of dividing or budding. The overall appearance is that of a complex, multi-layered microbial community.

# **A NEW UNDERSTANDING OF THE ROLE OF GUT MICROBIOTA IN ALLERGY DEVELOPMENT:**

IMPACT OF DYSBIOSIS



# Who we are?

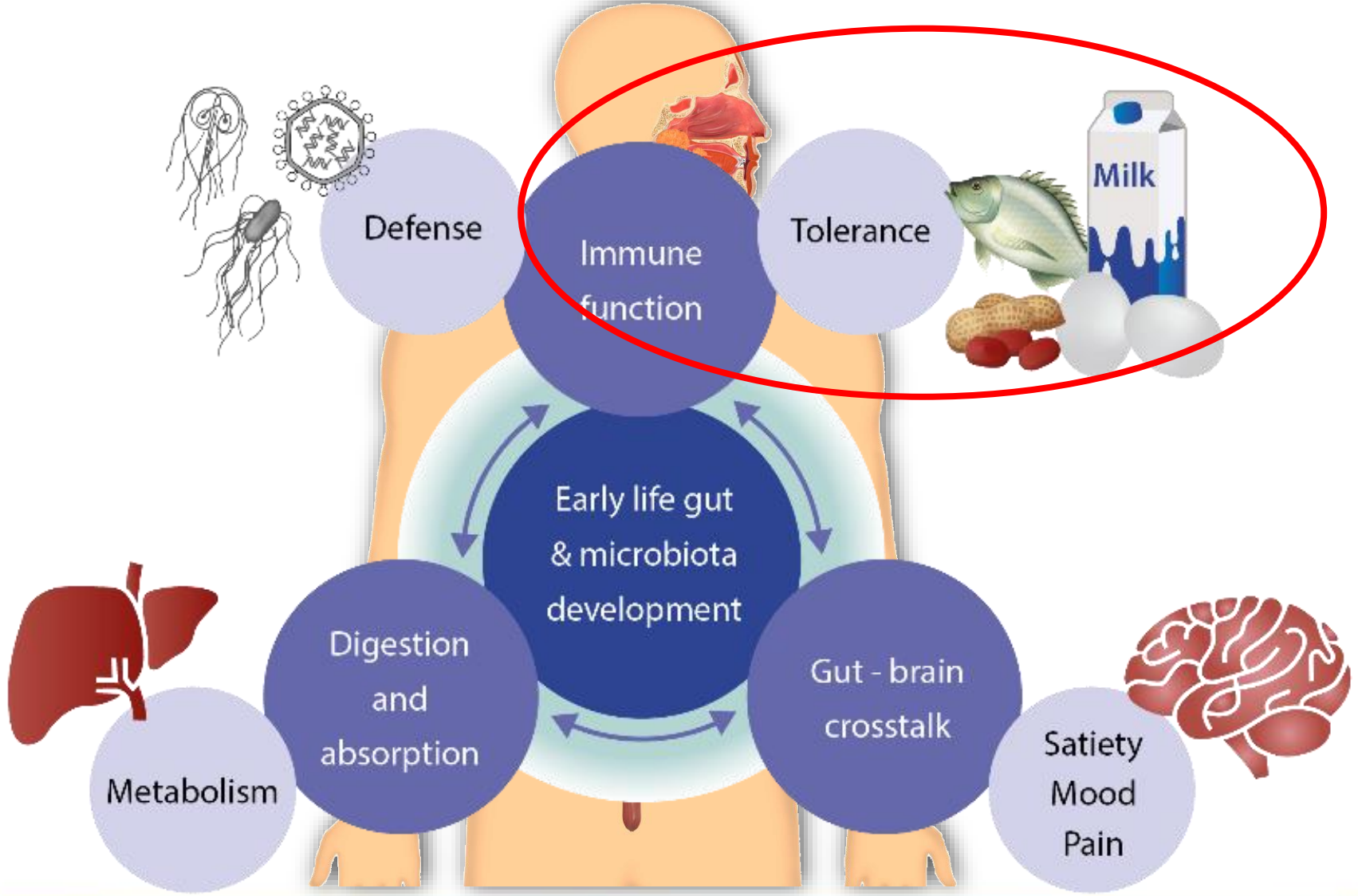
**You are only 10% human**

The microorganisms inside your  
body outnumber your human cells  
10 to 1

These microbes make up about  
1-3% of your body weight

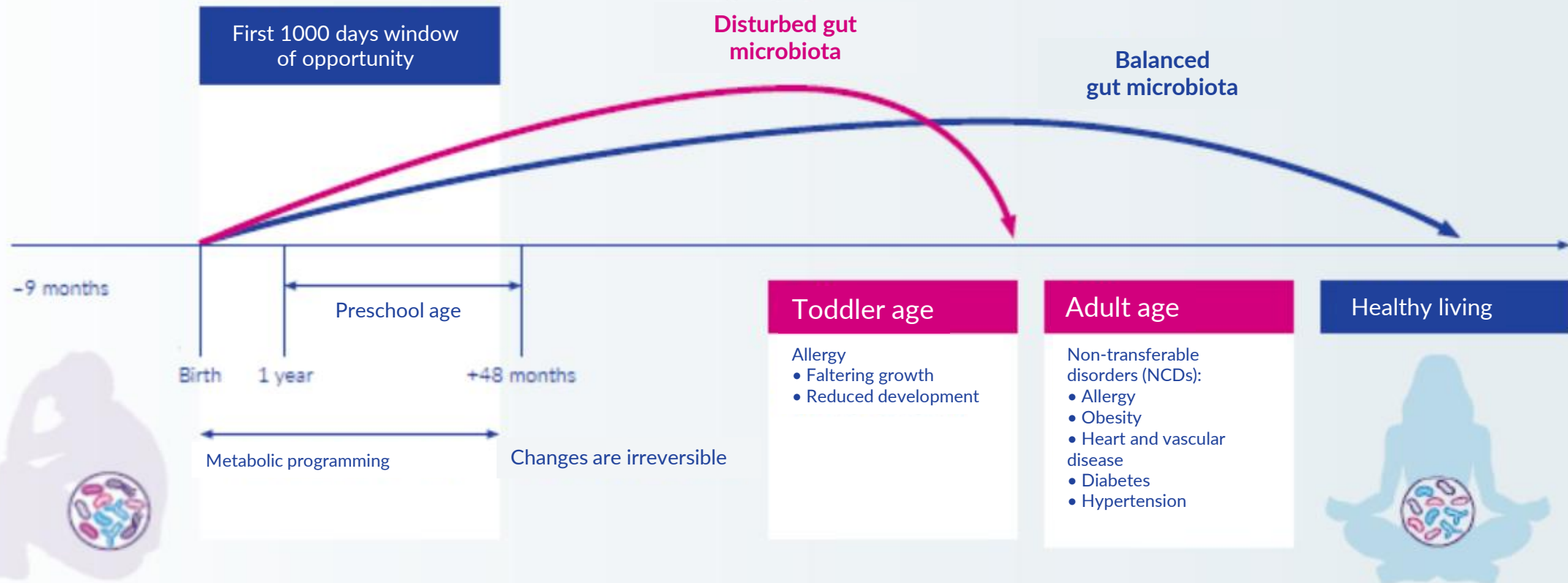
Personal gut microbiota signature

# GUT MICROBIOTA AND IT'S ROLE IN OVERAL HEALTH



# EARLY LIFE IMMUNE MICROBIOME INTERACTION AFFECTS LATER HEALTH

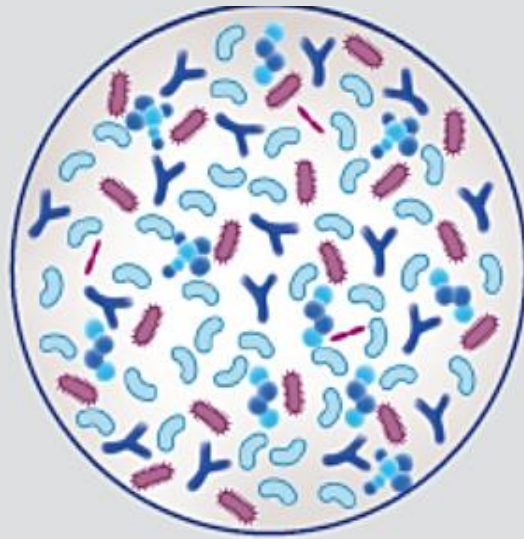
Disruption of the gut microbiome early in life has consequences...



# GUT MICROBIOTA DYSBIOSIS

## HEALTHY

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



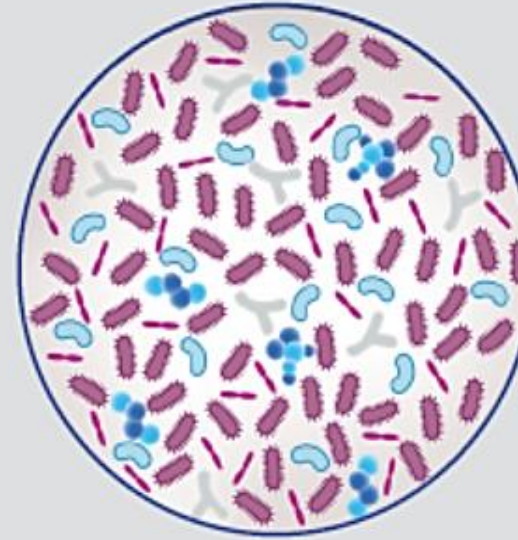
Higher levels of  
beneficial  
bacterial species

*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.

# 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*<sup>1, 2, 3</sup>



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*<sup>4,5</sup>



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

# RISK FACTORS CONTRIBUTING TO ALLERGY PREVALENCE

## GENETIC FACTORS

Family history of allergy



20-40%  
higher  
allergy risk

Global prevalence:  
Up to 20%

## ENVIRONMENTAL FACTORS

↑ C-section



Up to  
30%  
higher  
allergy risk

Global prevalence:  
Europe Urban: up to 35%  
Asia Urban: up to 45%  
South America: up to 45%

↑ Antibiotic use



x2  
higher  
asthma risk

Use in infancy & childhood:  
up to 10 - 20 courses<sup>3</sup>  
up to 40% of newborns<sup>4</sup>  
exposed in perinatal antibiotics  
Use in pregnancy:  
Up to 30%

↑ Pollution



Up to  
20%  
higher wheezing  
risk

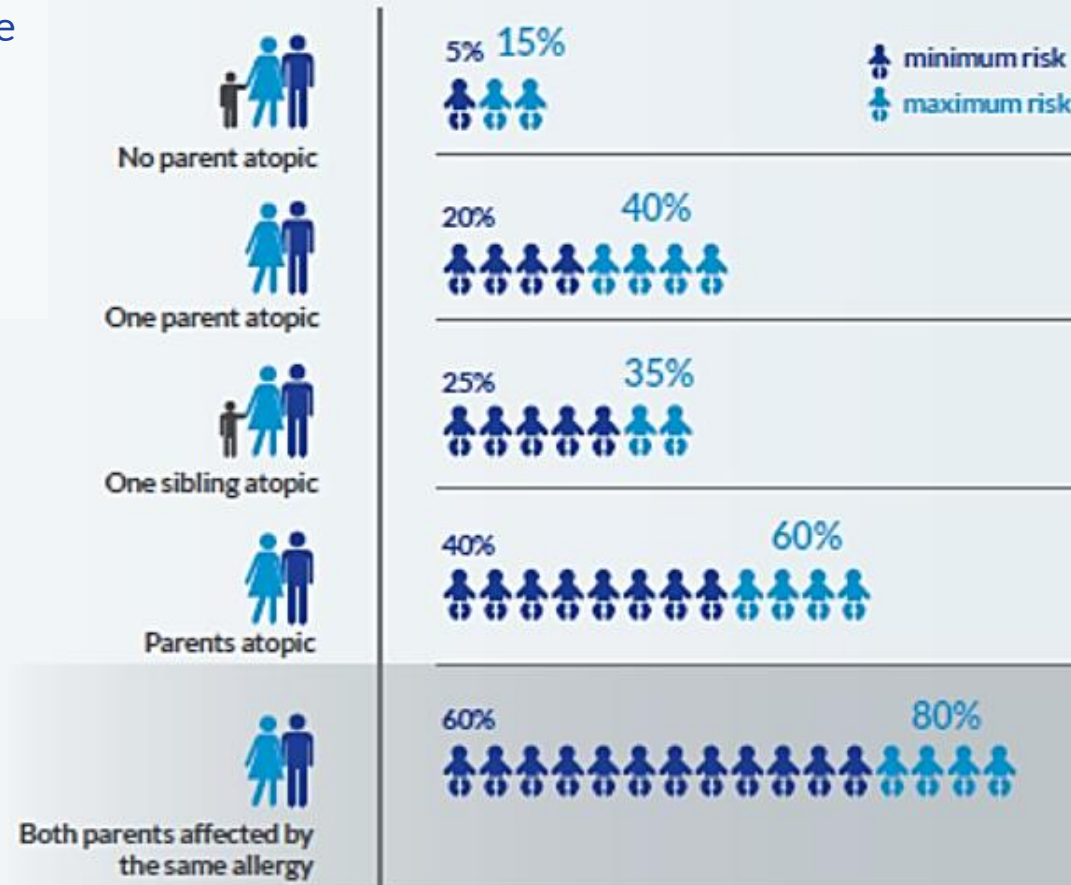
Increase in risk of  
developing allergies:  
up to 20%

GUT MICROBIOTA DYSBIOSIS  
is an associated factor in the increase in allergy incidence<sup>7,8</sup>



# FAMILY HISTORY IS A WELL DEFINED AS A RISK FACTOR FOR DEVELOPING ALLERGIES

In children without any family history of allergies the prevalence of allergies can reach 15-20%. Children who have one or more family members affected by an allergy are carrying significantly higher risk for developing allergies (15-70%)



A close-up photograph of a newborn baby lying on its back, being breastfed by a woman. The woman's hands are visible, gently holding the baby's head and neck. The baby's mouth is open, latched onto the breast. The woman is wearing a white hospital gown with blue stripes. The background is softly blurred, showing a hospital room environment. A white curved graphic element is overlaid on the left side of the image, containing the text.

**HUMAN MILK:  
THE GOLD STANDARD  
FOR INFANT FEEDING**

# HUMAN MILK IS BEST FOR INFANT HEALTH

## IMPROVES AND SUPPORTS

Optimal growth and maturation



Brain and eye development



Cognitive development



## REDUCES RISK OF

Childhood obesity



Cardiovascular and metabolic diseases



## REDUCES RISK OF

Infections



Sudden death syndrome



Allergies and asthma



Pediatric Cancer



Diarrhea



# 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

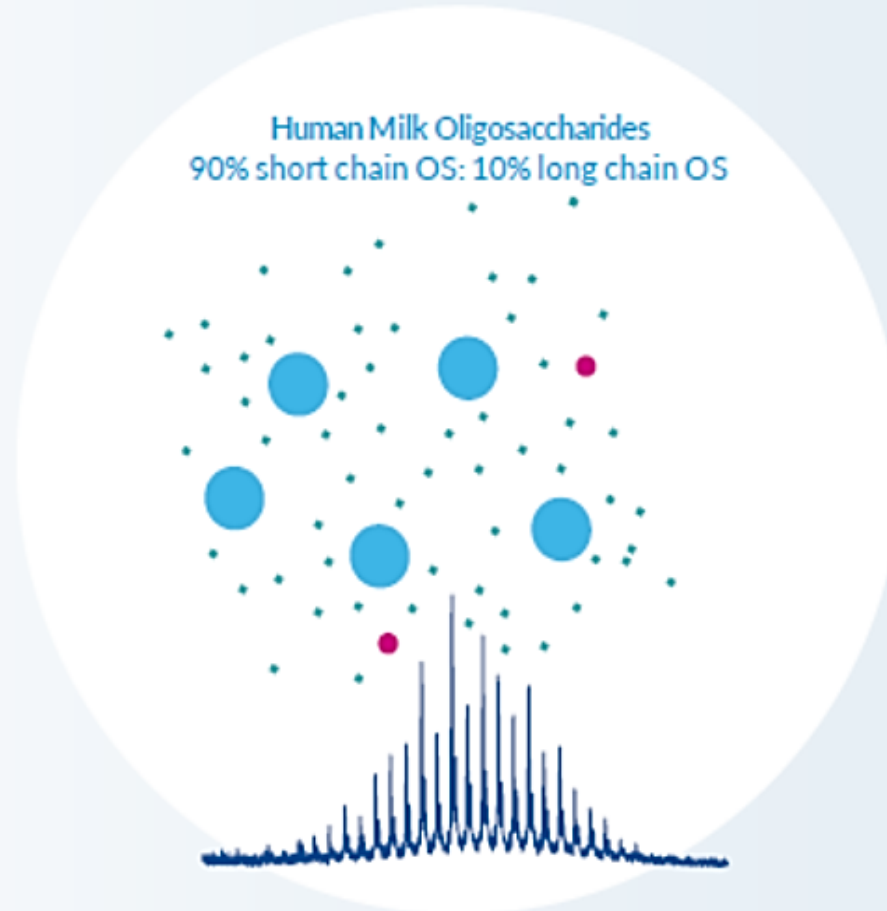


**HUMAN MILK  
OLIGOSACCHARIDES**

# DIVERSITY OF HUMAN MILK OLIGOSACCHARIDES (HMOS)

- High diversity of structures (HMOs): >100 can be found in one human milk sample
- Relative stability of profile (size distribution) HMOs in human milk have a size distribution of 90% short chain OS to 10% long chain OS

Mothers of infants with CMA have a different HMO profile in breast milk compared to mothers of non-allergic infants





**BENEFICIAL  
BACTERIA IN  
HUMAN MILK**

# 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 <sup>1,2</sup>

### CONTROLLED PROTEIN EXPOSURE

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



### GUT MICROBIOTA MODULATION

DELIVERY OF OLIGOSACCHARIDES (prebiotic) to feed beneficial bacteria

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





# BREASTFEEDING IS RECOMMENDED FOR PREVENTION OF FOOD ALLERGY



Breast milk is the gold standard to train the immune system

- 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.

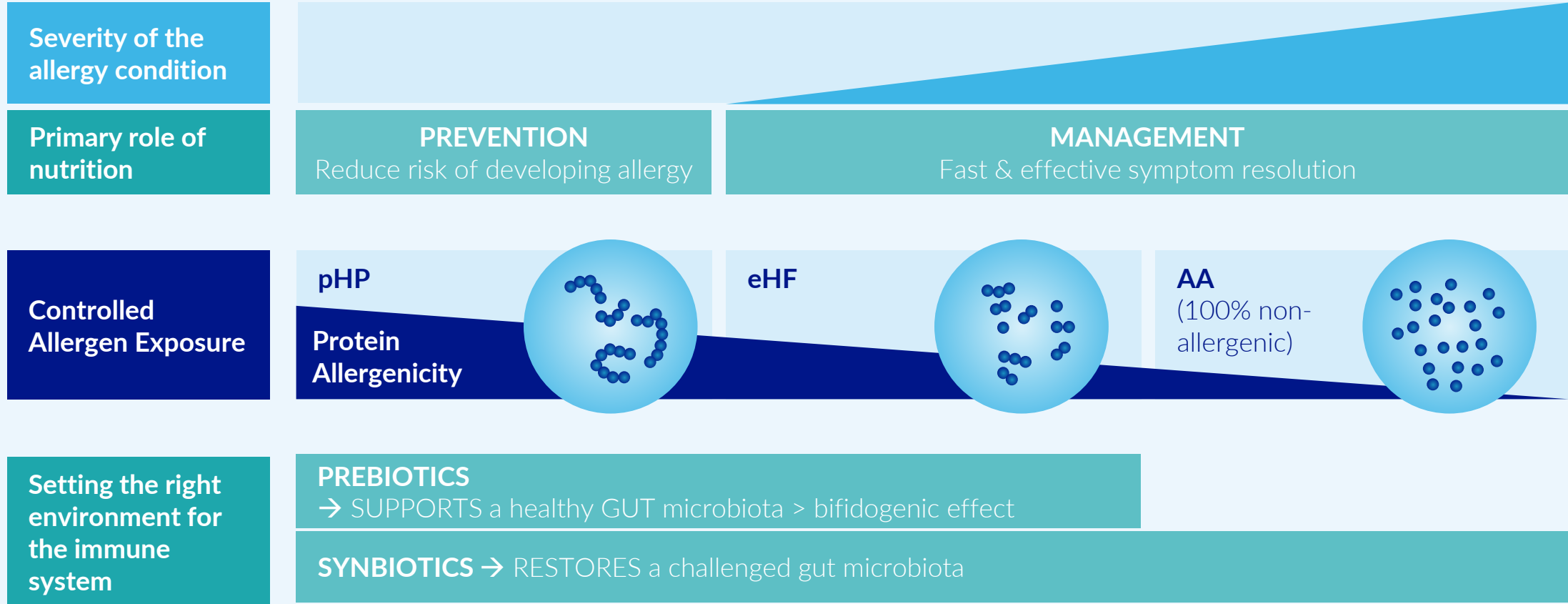


The World Health Organization recommends exclusive breast-feeding for the first six months of life

- 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.

- **International guidelines also recommend the use of ‘prebiotic supplementation in not-exclusively breastfed infants’ for the prevention of allergy, and the additional positive recommendation on the use of probiotics in not-exclusively breastfed infants at high risk of developing allergies.**

# APPROACH TO ALLERGY MANAGEMENT IN NON BREASTFED INFANTS



# PARADIGM SHIFT

## A PARADIGM SHIFT IN THE MANAGEMENT OF CMA



From allergen avoidance alone

To stimulation of the immune system





## Biotics

- Another area of interest in FA management involves the potential role of biotics in modulating the allergic response.
- Resolution of CMA is associated with higher gut microbiota diversity.
- There has been a **paradigm shift** towards active management of CMA, targeting of the gut microbiota with **biotics**

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

# BIOTICS

## Prebiotic:

are substrates that are selectively utilised by host microorganisms conferring a health benefit (ISAPP, 2017)



## Biotics:

Specific nutritional components that support a healthy gut microbiome



## Probiotics:

are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (ISAPP, 2014)



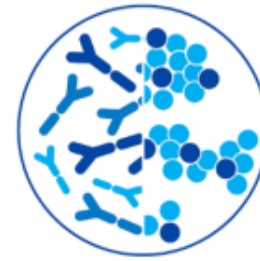
## Postbiotics:

are preparations of inanimate microorganisms and/or their components that confer a health benefit on the host (ISAPP, 2021)



## Synbiotics:

Are the combination of Pre- and Probiotics - A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host (ISAPP, 2020)



# PROBIOTICS

Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (ISAPP, 2014)

- The two most frequently studied bacterial probiotic genera in infant formula are:
    - *Bifidobacterium* spp.
    - Lactic acid bacteria such as *Lactobacillus* spp.
- Regarded as SAFE for food use in the EU (based on QPS-list) and USA (included in GRAS notice inventory)



## BENEFICIAL BACTERIA PROBIOTIC STRAIN - BIFIDOBACTERIUM BREVE M16-V

- Increases the balance of beneficial bacteria
- *B. breve* is a natural species that can be found in the infant gut<sup>4</sup>
- From the family of bifidobacterial species **commonly isolated in breast milk**<sup>5-8</sup>
- Selected among 400 strains<sup>7</sup>
- Clinically shown to have **immune- modulating effect**<sup>9</sup>
- Has been shown to have a **synergistic effect**<sup>10</sup>
- **Safely administered** in extremely premature infants and free from allergens<sup>11-14</sup>

The effects of probiotics are considered to be strain specific, although there are some potential common benefits such as:

- ✓ Benefits to the immune system.
- ✓ Modulation of intestinal microbiota composition and activity
- ✓ Protection against pathogen colonization and infection

# PREBIOTICS

Substrates that are selectively utilized by host microorganisms conferring a health benefit (ISAPP, 2017)

- Prebiotics are naturally present in many fiber-rich foods, these dietary fibers have various direct and indirect health effects. • Prebiotics pass undigested to the colon, where they: ✓ Provide nourishment to support the developing gut microbiota.
- The most common prebiotics are carbohydrate compounds such as cellulose, pectin, fructan and the polysaccharides; • Galactooligosaccharides (GOS) • Fructooligosaccharides (FOS) ✓ IcFOS (inulin) ✓ scFOS (oligofructose)

Breast milk contains great amounts of natural prebiotics, i.e., **HMOs**.  
HMOs can be considered as short- and long-chain and human milk contains a specific short-chain and long-chain **HMOs ratio of 9:1**

**Short-chain (sc) =**

Active in the proximal (=upper) part of the gut, ensuring potential substrates are available for the gut microbiota along the full GI tract.

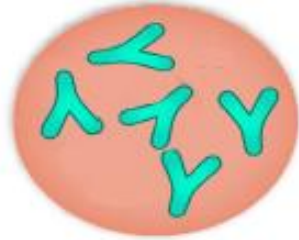


**Long-chain (lc) =**

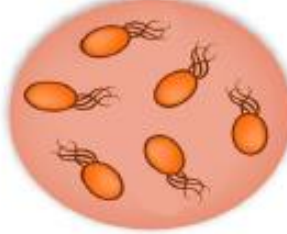
Less easily fermented by the gut microbiota, more active in the lower part of the gut

# Gut microbiota is unbalanced by non-absorbed iron (75-95%)

Beneficial host bacteria have little or no need for iron<sup>1,2</sup>



Iron is an essential nutrient for the growth and proliferation of pathogenic bacteria<sup>1,2</sup>



Unabsorbed iron alters the **balance** of the gut microbiota: increase in digestive disorders such as **diarrhoea**<sup>2</sup>

1. Moustarah F, Mohiuddin S. Dietary Iron. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK540969/>. Accessed 26 Nov 2020; 2. Jaeggi T et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut 2015; 64: 731-42.





# The goals: to increase iron absorption and protect the gut microbiota

ScGOS/lcFOS\* prebiotics (9:1): promote good digestive health



**+ 30**

clinical studies

Stimulates the growth of beneficial bacteria in the breast milk model<sup>1,2</sup>

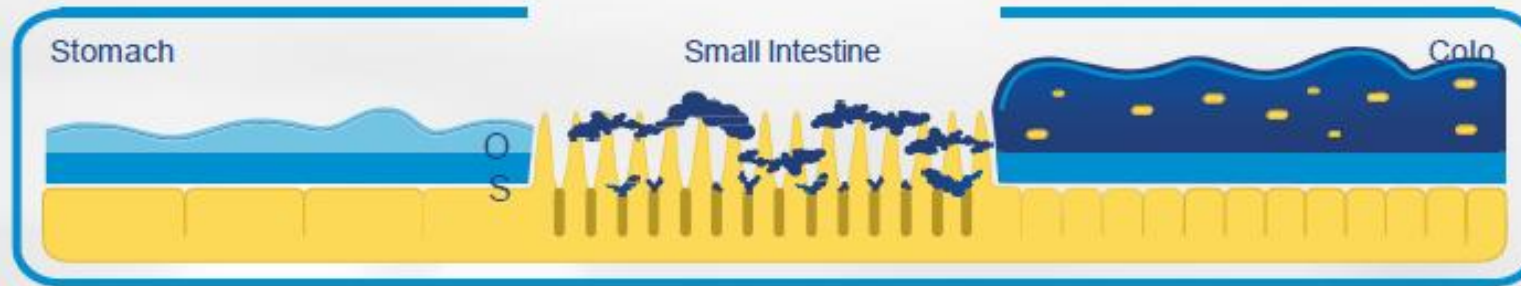
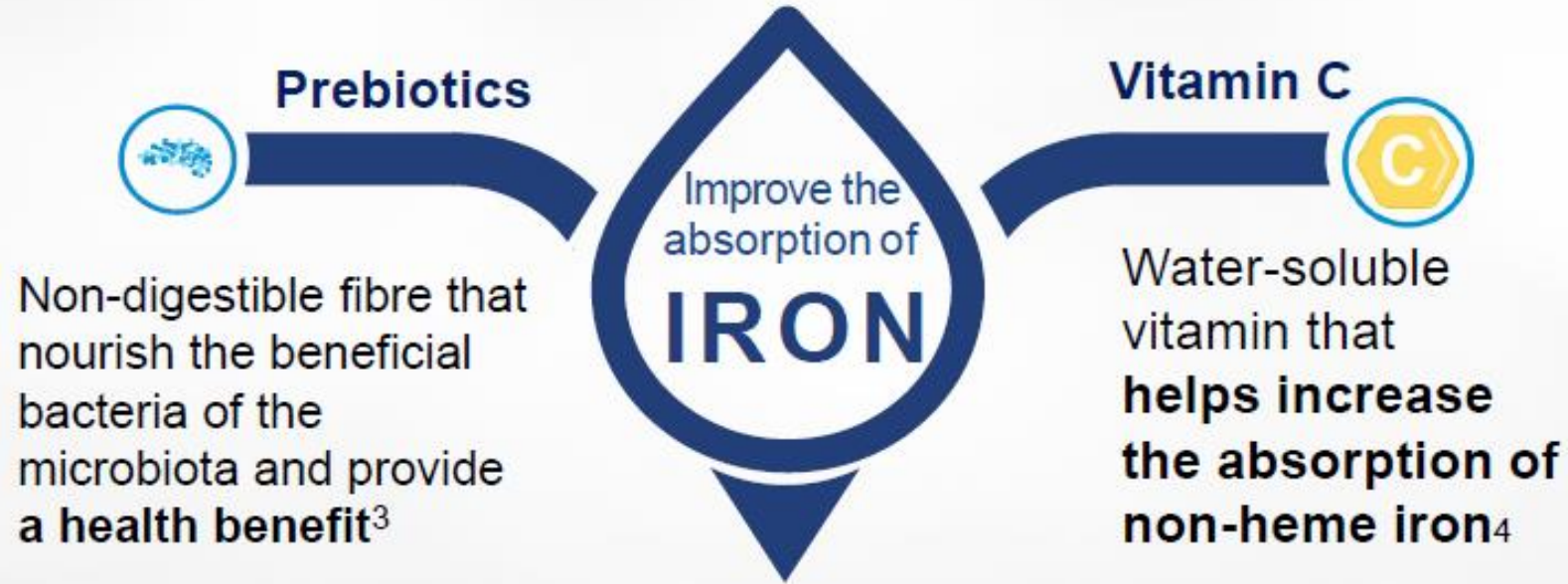
Stool frequency and consistency close to that of breastfed babies<sup>1,2</sup>

scGOS/lcFOS \* = short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides

1. Moro G et al. Dosage-related bifidogenic effects of galacto- and fructo-oligosaccharides in formula-fed term infants. *J Pediatr Gastroenterol Nutr* 2002; 34:291-6.
2. Moro G et al. Effects of a new mixture of prebiotics on faecal flora and stools in term infants. *Acta Paediatr Suppl*. 2003 Sep;91(441):77-9.



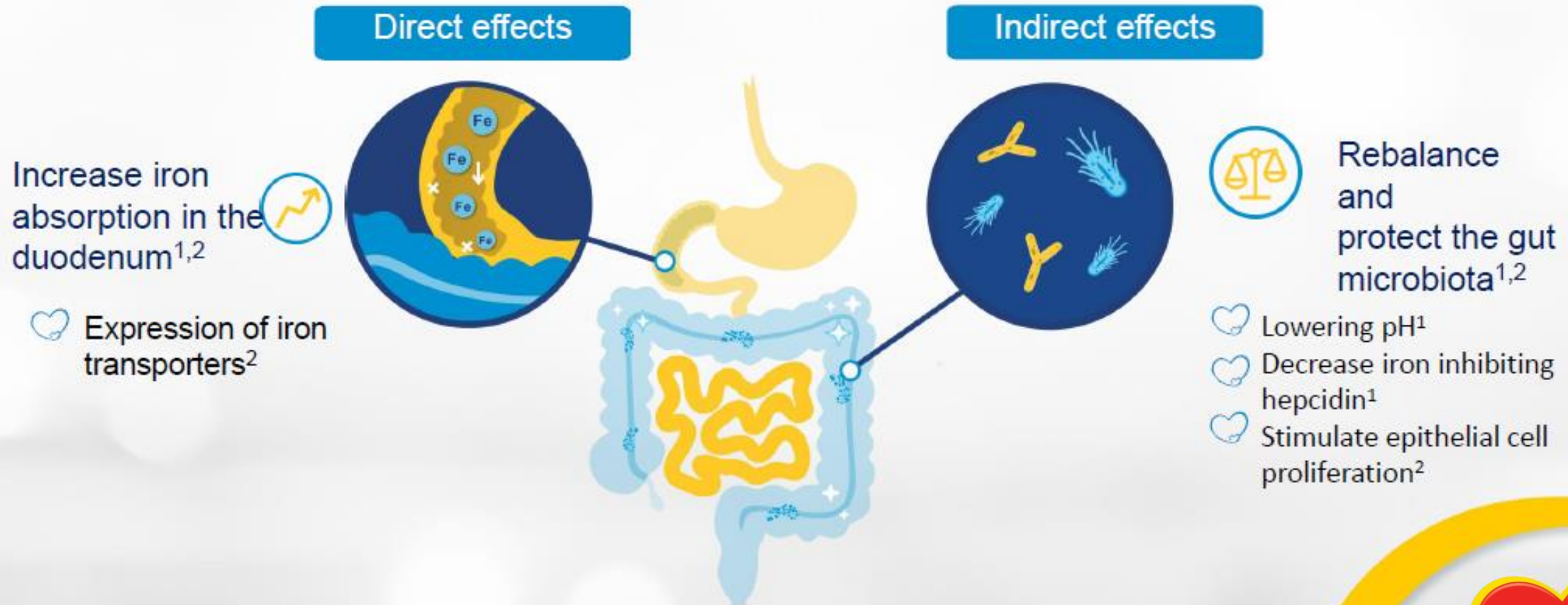
# Prebiotics and vitamin C promote dietary iron absorption<sup>1,2</sup>



1. Moustarah F., Mohiuddin S. Dietary Iron. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK540969/>. Accessed 26 Nov 2020; 2. Rusu I, Suharoschi R, et al. Iron Supplementation Influence on the Gut Microbiota and Probiotic Intake Effect in Iron Deficiency—A Literature-Based Review. Nutrients 2020;12:1993; 3. Holscher H. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes. 2017; 8(2): 172–184.; 4. Yilmaz B, Li H. Gut Microbiota and Iron: The Crucial Actors in Health and Disease. Pharmaceuticals (Basel). 2018; 11(4): 98.



# Prebiotics favor iron absorption and re-balance the intestinal microbiota<sup>1,2</sup>



1. Rusu I, Suharoschi R et al. Iron Supplementation Influence on the Gut Microbiota and Probiotic Intake Effect in Iron Deficiency—A Literature-Based Review. *Nutrients* 2020;12:1993;2. Yeung CK et al. Prebiotics and Iron Bioavailability—Is There a Connection? *J Food Sci* 2005; 70: 88-92.

# SYNBIOTICS

The combination of Pre- and Probiotics - A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host (ISAPP, 2020)

- The aim of combining probiotics with prebiotics is to achieve a synergistic effect meaning  $1+1>2$ , thus a stronger positive effect than with either component alone.

- **Synbiotics in allergy management**

Infants with allergies have been found to have an imbalanced gut microbiota, and since the gut microbiota plays a critical role in immune system development, The addition of a synbiotic blend to infant formula is a compelling nutritional strategy in CMA management.

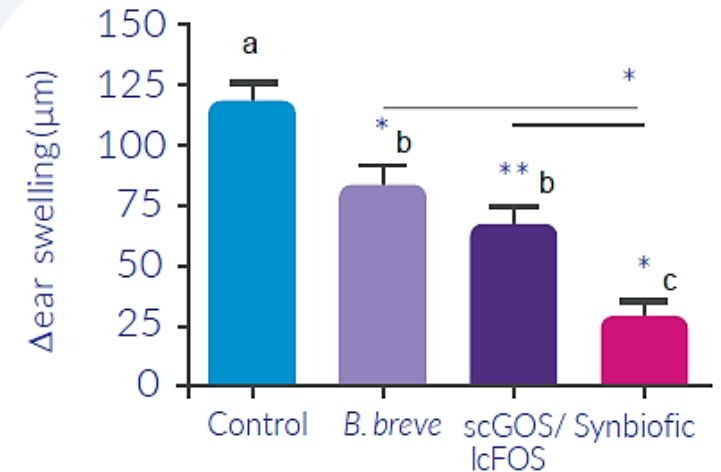


**There is a recent (2023) review that summarizes the expected benefits and effects for infants of pre-, pro-, syn-, and postbiotics added to infant formula regarding the microbiota, immunity, and allergies.**

# PRECLINICAL EVIDENCE: SYNEO MOST EFFECTIVE IN PREVENTING ACUTE ALLERGIC SKIN REACTION

## Syneo reduces the allergic response to food allergens (pre-clinical data)

- The synergistic effect of SYNEO, compared to the individual ingredients scGOS/lcFOS or *B. breve* M-16V, has been investigated in a murine model of CMA.<sup>1</sup>
- Mice fed a diet with SYNEO demonstrated strongest effect in reducing allergic skin response (scGOS/lcFOS or *B. breve* M-16V responses alone were significantly less effective).
- This model shows the potential for dietary intervention with SYNEO in reducing the allergic response to food allergens.

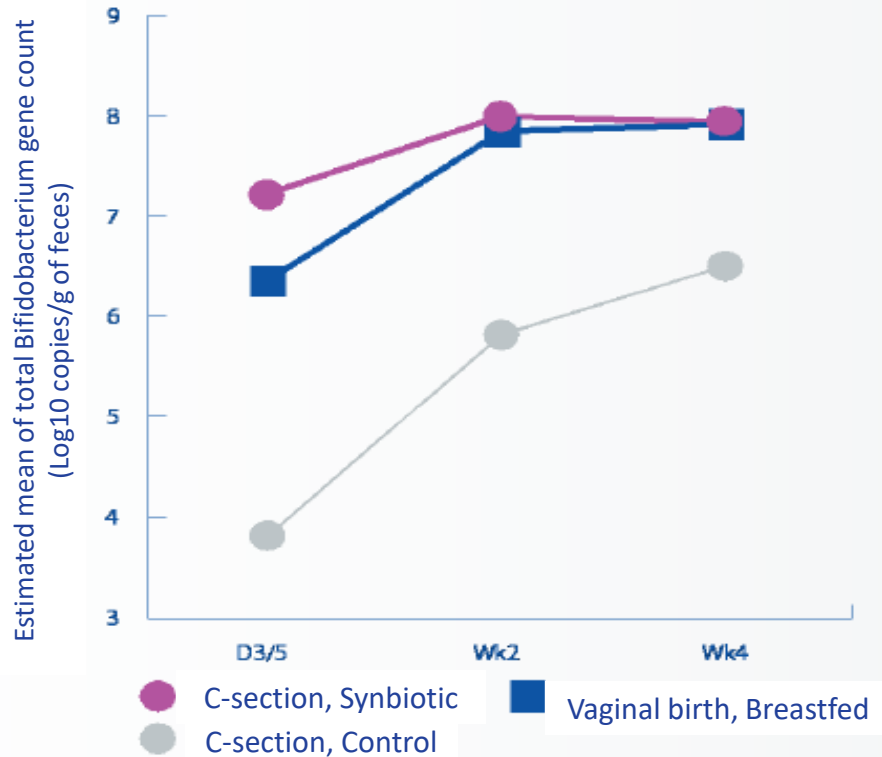


Acute ear swelling response of whey-sensitized mice fed a control, *B. breve* M-16V, scGOS/lcFOS or synbiotic diet; means without a common letter differ,  $p < 0.05$ .<sup>1</sup>

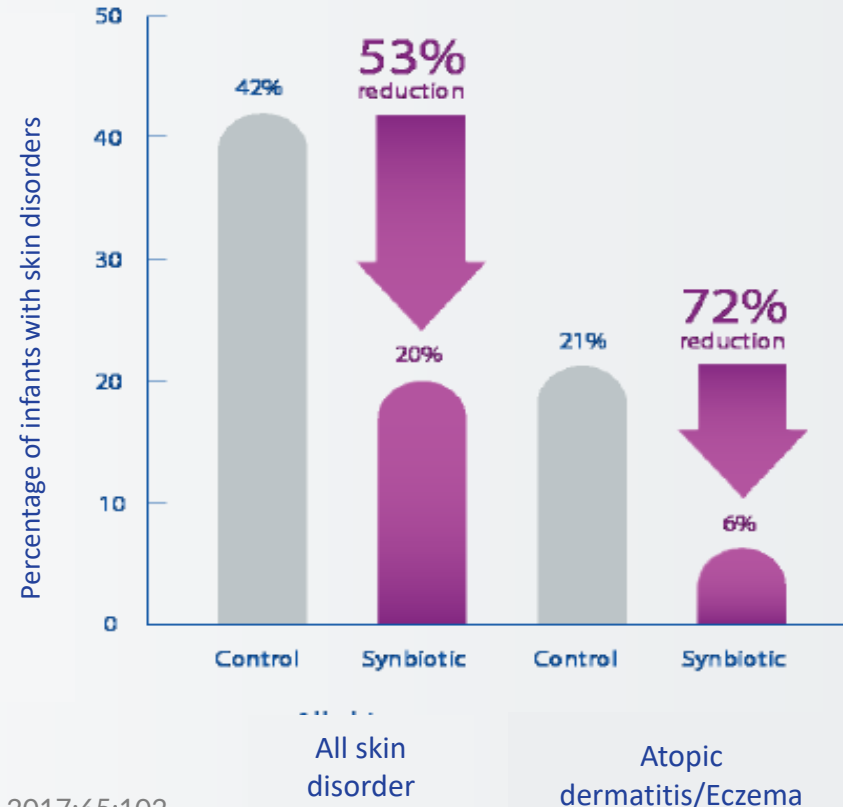
## SUPPORTING INFORMATION

# SYNEO HAS BEEN SHOWN TO MODULATE THE BALANCE OF GUT MICROBIOTA AND THE POTENTIAL TO REDUCE THE DEVELOPMENT OF ATOPIC DERMATITIS/ECZEMA <sup>1,2</sup>

Restores delayed colonization of bifidobacteria in C-section delivered infants, bringing levels closer to that of vaginally born and breastfed (p=0.001)<sup>1</sup>



Has potential to reduce the development of atopic dermatitis/eczema in C-section delivered infants (p=0.037) <sup>1</sup>



1. Chin ChuaM, et al. JPGN, 2017;65:102

# OUTLOOK

- Early life gut microbiota disruption(DYSBIOSIS) can impact immune & Allergy development.
- Risk factors contributing to allergy prevalence are : Family history of allergy, C/S, Antibiotic use in infancy and pollution.
- Human milk is our reference for nutritional solutions for dietary prevention and management of allergy in infants.
- Bioactive compounds beyond macro and micronutrients in human milk are key influencers in gut microbiota and immune development of infants.( HMOS and live bacteria like bifidobacteria )
- Recent innovation in IF inspired by HM research :
- **SYNEO™**, Nutricia's patented combination of prebiotic oligosaccharides and probiotic strain **with synergistic effect to target gut microbiota dysbiosis and helps allergy management in infants.**