Role and Importance of Human Milk Oligosaccharides


Role of Human Breast Milk

Breast-fed infants stay healthier than non-breast-fed infants

Benefits of breastfeeding

- **Short-term effects in infants**
- Lower incidence and severity of lower respiratory tract infections
- Lower risk of otitis media and diarrhea and protection against hospital admissions due to these disorders
- Lower risk of:
- Sudden infant death
- Atopic dermatitis in infants at risk
- Less constipation, gastroesophageal reflux
- Enterocolitis in preterm infants

Long-term effects in children

- Probable reductions in overweight/obesity and type 2 diabetes
- Fewer instances of allergies, eczema, and asthma
- Fewer childhood cancers, including leukemia and lymphomas
- Fewer instances of Crohn's disease and colitis
- Lower rates of respiratory illness
- Fewer speech and orthodontic problems
- Improved brain maturation & Increases intelligence
- Greater immunity to infection
- Better mother infant bonding

Breastfeeding provides immune benefits

Breastfeeding has many short-term and long-term benefits.[1-8]

- Breastfeeding is associated with a reduced risk of gastrointestinal and respiratory infections[4-8]
- Various components in human breast milk provide protection for the infant against pathogens and support the maturation of the immune system, including living cells, immunoglobulins and HMOs[3,8-11]

- Human Milk Oligosaccharides (HMOs)are an exciting and central area of research in infant nutrition.

- Scientific advances on HMOs are helping us know more about the role and importance of these essential components of Human milk

WHAT ARE HMOs ?

History of HMO DISCOVERY

- Human milk oligosaccharides (HMOs) are **specific bioactive compounds present in human milk.**[1]
- **The amount and variety of oligosaccharides** in human milk is unique and **not to be found in the milk of cows or other animals.**[2,3,4]
- Their discovery at the onset of the 20th century was driven by **the 7-fold increased mortality of non-breastfed infants** in a time of an alarmingly high overall infant mortality of 20-30%.[1]
- Even at that time, scientists recognised that these compounds in human milk **contribute to the protection of breastfed infants' health.**[1]

1 Kunz, Adv Nutr 2012; 2 Urashima et al. Adv Nutr 2012; 3 Ninonuevo et al. Pediatr Res 2008; 4 Ruhaak et al. Anal Bioanal Chem 2014


Discovery and History of HMOs

Discovery and History of HMOs

1900[1]

- Breastfed infants have a survival advantage
- Differences in the stool microbiota composition of breastfed and formula-fed infants discovered
- Mother's milk discovered to have an unidentified carbohydrate fraction

1930[1,2]

- Bifidogenic factor in human breast milk consists of oligosaccharides
- First individual HMOs characterised

1950-80s[1,2]

- Discovery and characterisation of the most abundant oligosaccharides in human breast milk

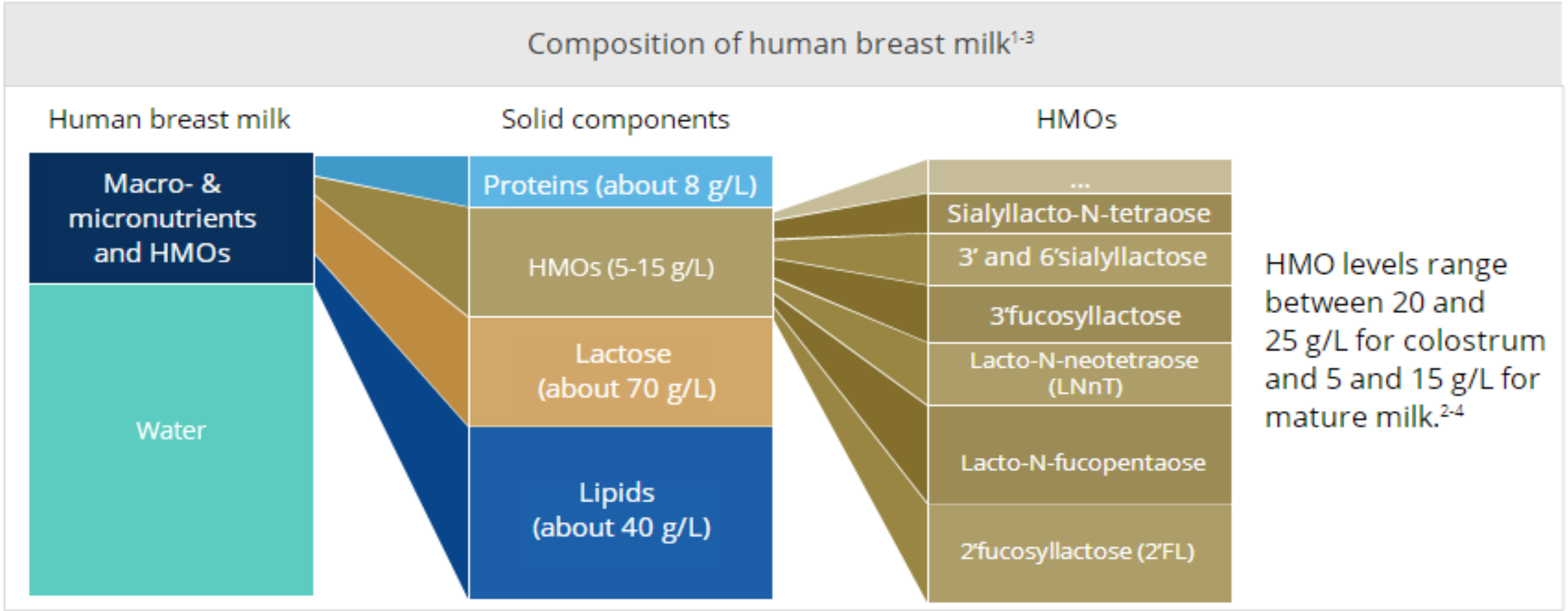
2000 onwards[2-4]

- Ongoing research on metabolic and biological benefits of HMOs in infants' and mothers' health


HMOs – The unique bioactive Component of Human Breast Milk
This section describes the structure and types of HMOs, the unique, bioactive component of human breast milk.

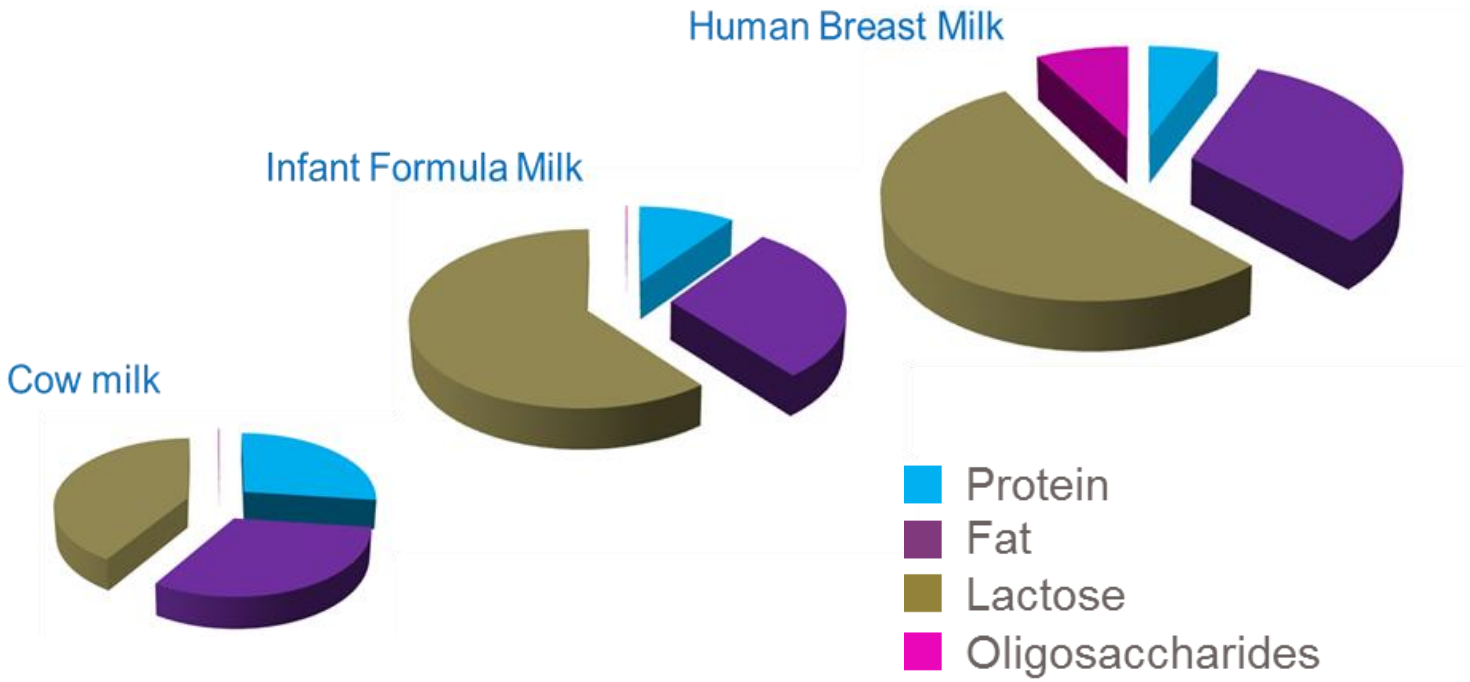
Composition of Human Breast Milk

Synthesised by the mammary gland, HMOs are the third most abundant component of human breast milk, after lactose and lipids.[1-3]



HMO, human milk oligosaccharide.

Human Milk VERSUS INFANT FORMULA COMPOSITION TODAY



The content and quality of macronutrients including that of protein of infant formulae is well adapted to human milk.

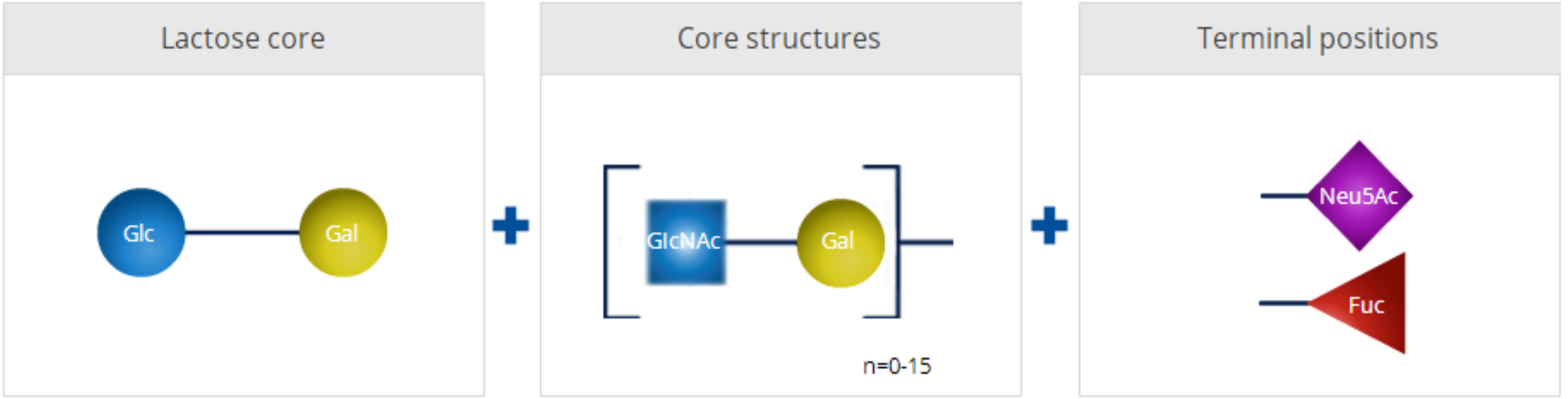
However, infant formulae do not currently contain human milk identical oligosaccharides.

Does this GAP matter?

Structure of HMOs

The structure of HMOs is unique and determines their biological functions.[1-3]

Glc	Gal	GlcNAc	Fuc	Neu5Ac
Glucose	Galactose	N-acetylglucosamine	Fucose	Sialic acid



Between the lactose core and the terminal position, the structure can be elongated or branched to create small or large HMOs.[2]

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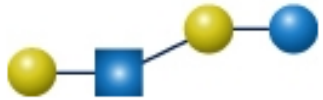
Glc	Gal	GlcNAc	Fuc	Neu5Ac
Glucose	Galactose	N-acetylglucosamine	Fucose	Sialic acid

Small HMOs

Examples

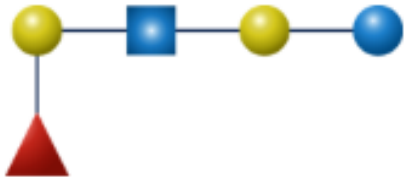
2'FL (trisaccharides)



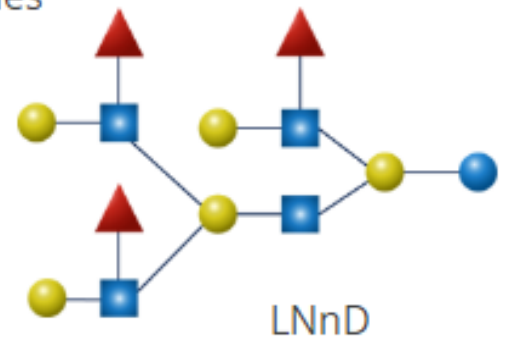
LNnT (tetrasaccharides)

Complex HMOs

Examples



LNFP I



LNnD

Small HMOs, such as 2'FL and LNnT, are among the most common HMOs.[2,5]

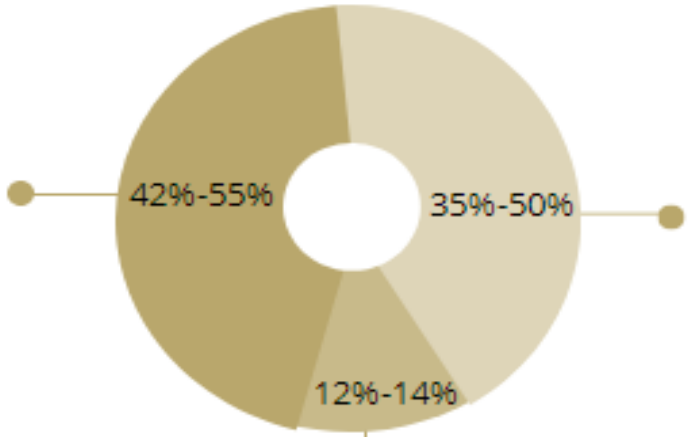
2'FL, 2'fucosyllactose; HMO, human milk oligosaccharide; LNFP I, lacto-N-fucopentaose I; LNnD, lacto-N-neodecaose; LNnT, lacto-N-neotetraose.

HMO Categories

More than 150 HMOs have been identified so far, which are classified into 3 different categories[1-4]:

Non-fucosylated HMOs

- Neutral
- Addition of N-acetylglucosamine or galactose at the terminal position
- Examples: LNnT



Fucosylated HMOs

- Neutral
- Addition of fucose at the terminal position
- Example: 2'FL

Sialylated HMOs

- Acidic in nature
- Addition of a sialic group at the terminal position
- Example: 3'SL

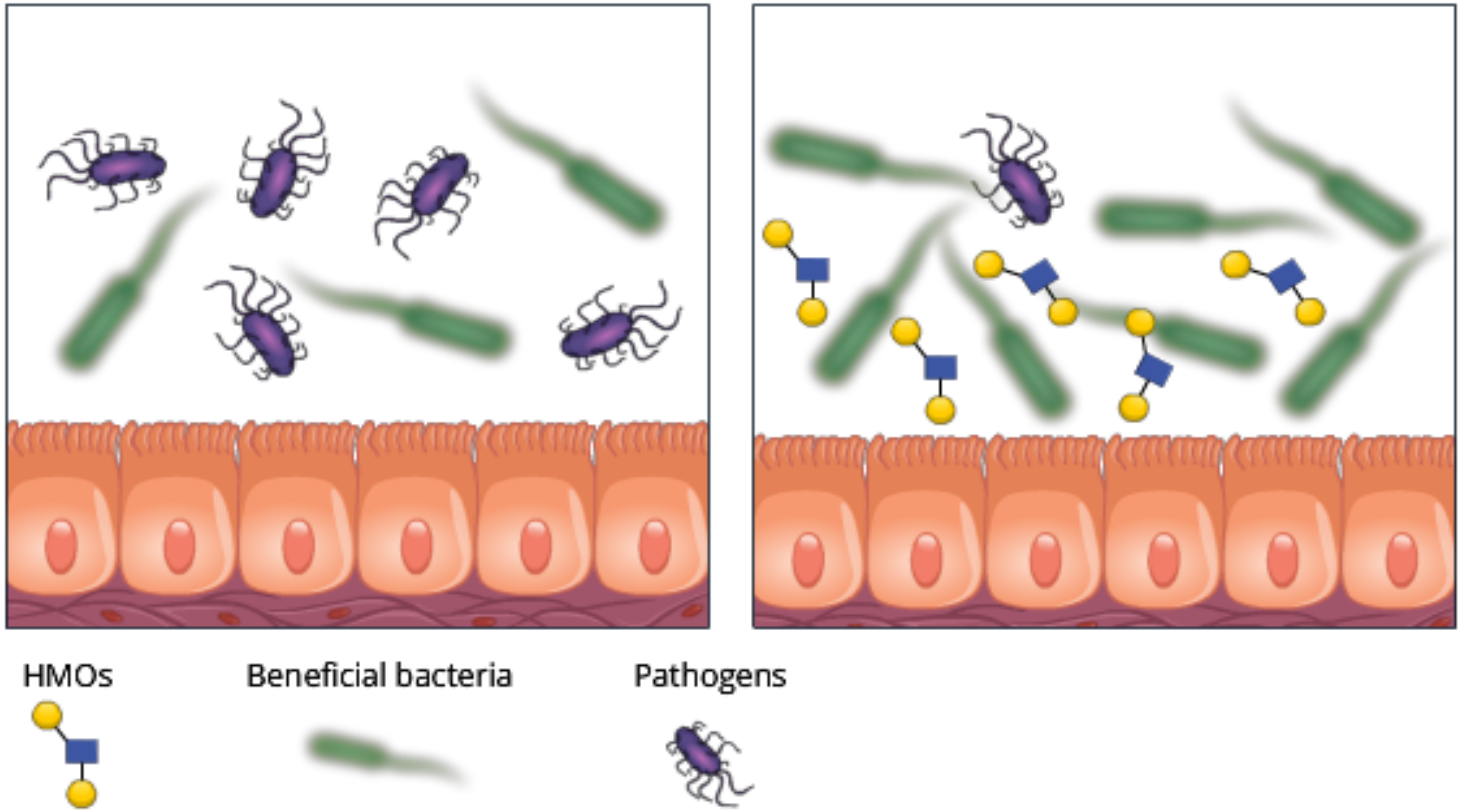
Neutral HMOs account for more than 75% of the total HMOs in human breast milk.[2,3]

2'FL, 2'fucosyllactose; 3'SL, 3'sialyllactose; HMO, human milk oligosaccharide; LNnT, lacto-N-neotetraose.


How HMOs support immunity in 4 ways?

HMOs support Immunity

HMOs promote the growth of beneficial bacteria.[1-3]



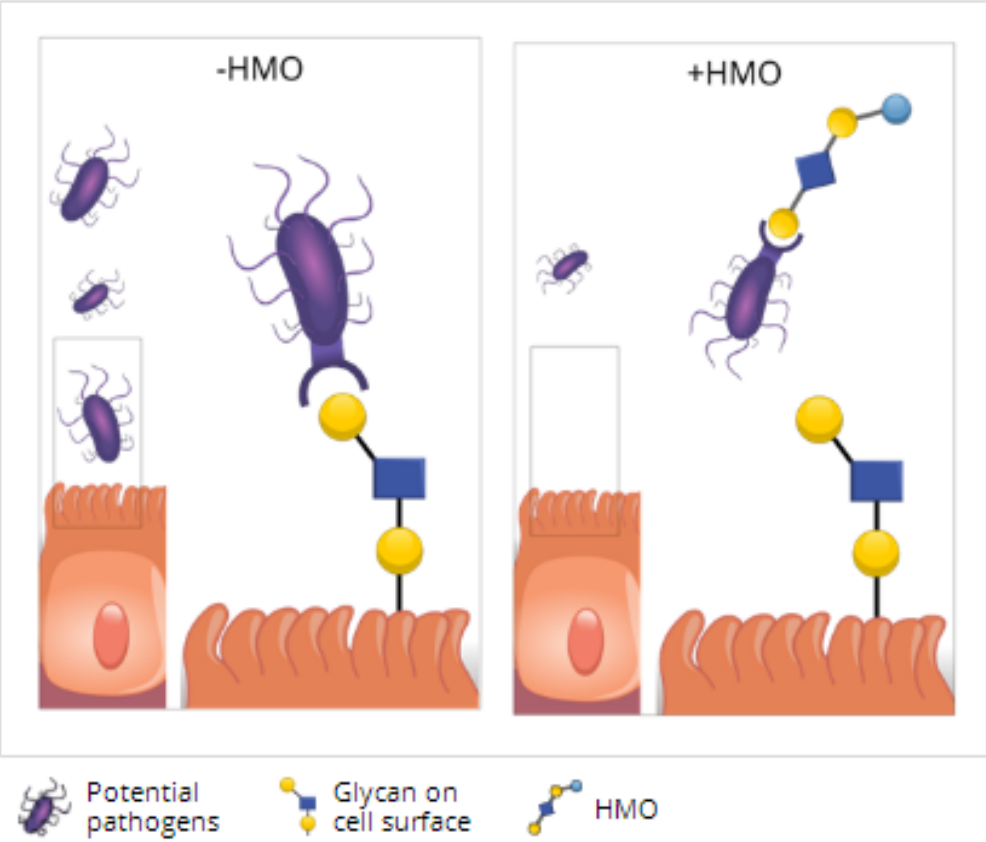
- HMOs serve as metabolic substrates for specific beneficial bifidobacteria and provide them with a growth advantage over potential pathogens[3,4]
- HMOs do not allow the growth of potentially pathogenic strains of Enterobacteriaceae, *Escherichia coli* and Clostridia[4,5]

Adapted from Bode, Glycobiology, 2012.

HMO, human milk oligosaccharide.

HMOs support Immunity

HMOs prevent bacterial adhesion in the gut.[1-4]



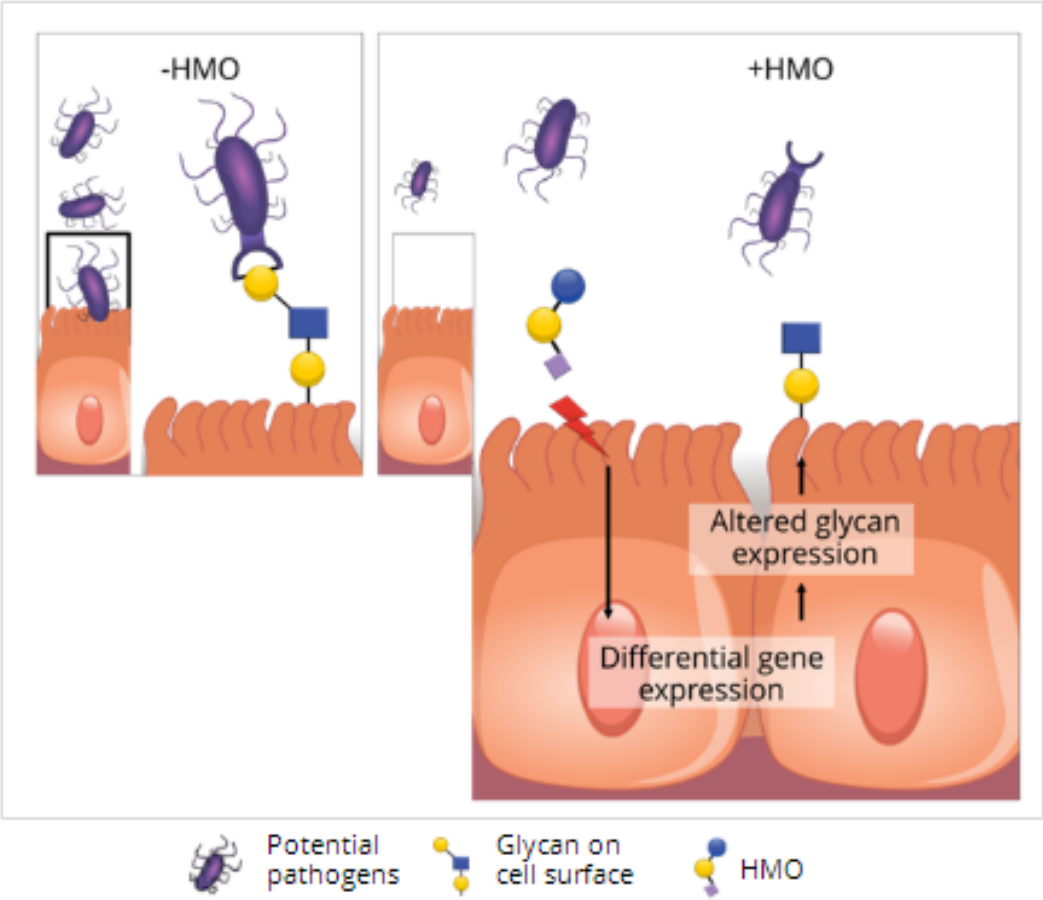
- HMOs in the gut may act as soluble decoy receptors for pathogens[1,2]
- This helps in preventing pathogen adherence to the intestinal wall and reduces their ability to infect the infant[1-5]

Adapted from Bode, Glycobiology, 2012.

HMO, human milk oligosaccharide.

HMOs support Immunity

HMOs assist gut barrier function.[1-3]



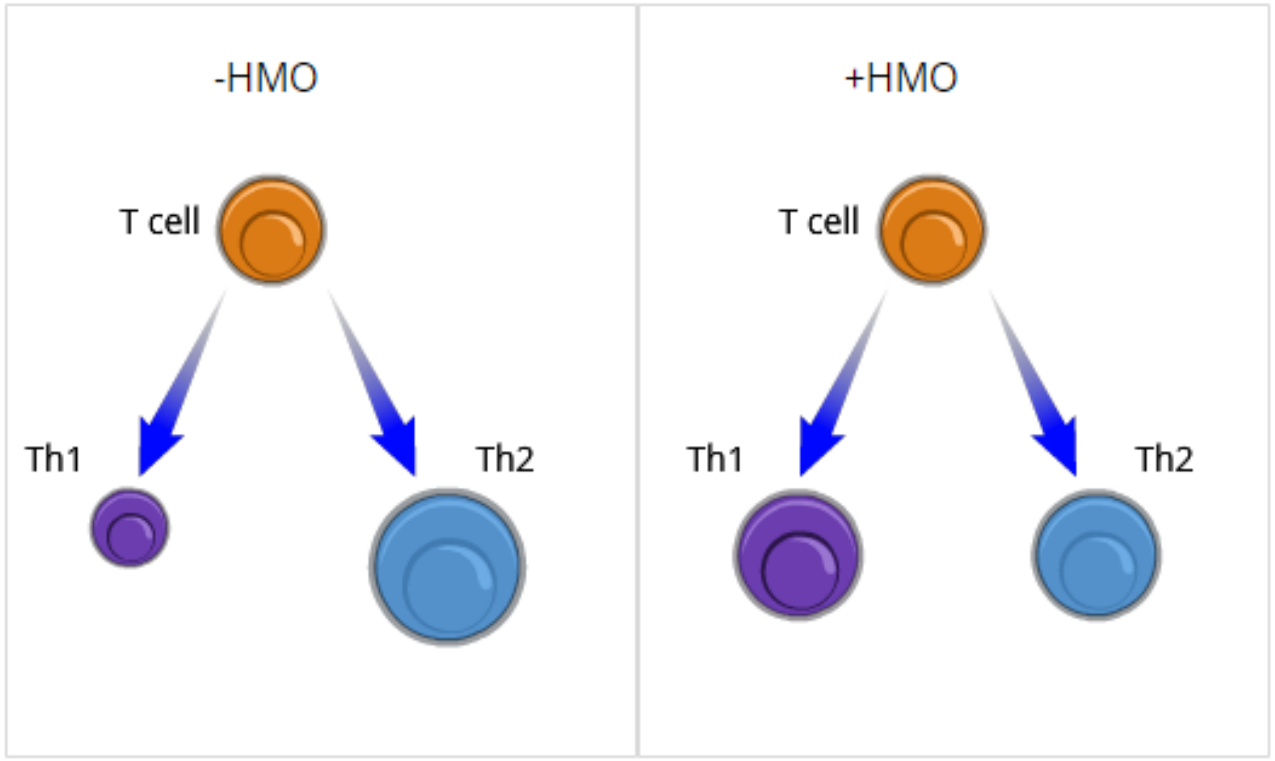
Adapted from Bode, Glycobiology, 2012.

HMO, human milk oligosaccharide.

- HMOs may directly interact with gut epithelial cells and modulate their glycan expression on intestinal cell surface[1-3]
- Modulating their glycans can be an alternative mechanism to prevent pathogen attachment to the host cell, therefore strengthening the gut barrier[1]

HMOs support Immunity

HMOs directly modulate the immune system.[1]



- The infant's innate immune system is highly unbalanced towards Th2 response favouring allergic reactions.[2,3]
- HMOs may help promote a shift towards a balanced Th1/Th2 response and drive immune maturation.[1-3]

Adapted from Bode, Glycobiology, 2012.

HMO, human milk oligosaccharide; Th, T helper cell.

Conclusion

5 Things to remember

- HMOs are unique bioactive oligosaccharides naturally found in human breast milk.
- HMOs are the third most abundant component of human breast milk, after lactose and lipids, with levels ranging between 5 and 15 g/L in mature milk.
- HMOs are synthesised by the mammary gland, and more than 150 different HMOs have been identified, which can be categorised as fucosylated, non-fucosylated and sialylated HMOs.
- Small HMOs, including 2'FL and LNnT, are among the most common oligosaccharides in human breast milk.
- HMOs support immunity by promoting the growth of beneficial bacteria, preventing bacterial adhesion in the gut, assisting gut barrier function and directly modulating the immune system.

2'FL, 2'fucosyllactose; HMO, human milk oligosaccharide; LNnT, lacto-N-neotetraose.

Variations in the composition and amount of HMOs in breast milk

- The oligosaccharide amount and composition in human milk varies[1,2,4]
  - between individuals (interpersonal variation)
  - diurnally
  - by infant gestational age
  - over the course of lactation
  - with the mother's nutritional status.
- The most extreme interpersonal variations are based on women's secretor and Lewis blood group status that is determined by genetic factors.[1,2]

1 Bode et al. Adv Nutr 2012; 2 Goehring et al. Plos One 2014; 4 Morrow et al. J Nutr 2005

Summary : HMO structure

- Scientists have identified more than 200 HMOs in human milk.
- The monosaccharide building blocks of HMOs are: glucose, galactose, N-acetyglucosamine, fucose and the sialic acid N-acetylneuraminic acid.
- The lactose core is elongated by one or more of 4 monosaccharides: galactose, N-acetyglucosamine, fucose and N-acetylneuraminic acid.
- Concentrations of total and specific oligosaccharides in human milk mainly depend on genetic factors such as the mother's secretor status and Lewis blood group and time of lactation.
- 2'FL is by far the most abundant HMO with in average 3 g /L (around 30% of total HMOs) in the milk of Se+ women (80% of women worldwide).
- 2´FL belongs to the neutral oligosaccharides that account for a total of more than 75% of the total HMOs.

HMOS DO NOT NOURISH – ARE THEY A WASTE OF ENERGY ?

"Breast milk, the sole source of nourishment for newborns, has been under intense selective pressure over millions of years of evolution to meet the infant's needs to grow and survive"[1]

De Leoz *et al*. 2015

BUT :

- 10 % of the 500 calories a lactating woman burns each day to make milk, is spent synthesizing large amounts of different oligosaccharides[2], which have no nutritive role.

➔HMOs must have bioactive functions of high relevance for the infant's healthy development and well-being.

1 De Loez et al. J Proteome Res 2015; 2 Nelson 2014 http://ucdavis.edu/ucdavis-today/2014/july/25-breast-milk.html

Summary : HMO Content in human milk

- HMOs are, after lactose and lipids, the third largest solid component in human milk with 10-15 g/L.
- The HMO fraction is quantatively larger than that of protein (which is typically around 8 g/L); HMOs can therefore be considered a key component of breast milk.
- HMOs are generally regarded to be non-digestible by the infant's gut due to lack of human production of the necessary enzymes.
- Despite not nourishing the infant, HMOs take up 10% of the total calories needed for breast milk production.
- Evolution suggests that this alone means that HMOs must serve an important function

THANK YOU


HAPPY