

Wednesday Webinar: February 2019

Human Milk Oligosaccharides: Benefits for the breastfed infant and beyond

Presented by
Dr. Lars Bode, Associate Professor of Pediatrics

Press *6 to mute your line, #6 to unmute. Please do not press hold.
You can use the chat box for questions during the presentation.



COMMUNITIES AND HOSPITALS
ADVANCING MATERNITY PRACTICES

Upcoming CHAMPS 4-Hour Clinical Skills Trainings

- (4- hour) Anderson Regional Medical Center
 - Wednesday, **February 20th**, 2019 (morning session)
- Trainings are open to all CHAMPS hospitals and CHAMPS community partners. You can register for the trainings at CHEERequity.org/trainings



COMMUNITIES AND HOSPITALS
ADVANCING MATERNITY PRACTICES



Human Milk Oligosaccharides
Benefits for the breastfed infant and beyond

MOMI CORE

Lars Bode, PhD

**Larsson-Rosenquist Foundation
Mother-Milk-Infant Center of Research Excellence
University of California, San Diego**

Disclosures

Research in the Bode lab and the UC San Diego Mother-Milk-Infant Center of Research Excellence (LRF MOMI CORE) is currently supported by

- National Institutes of Health (NIH)
- National Science Foundation (NSF)
- Bill & Melinda Gates Foundation (BMGF)
- Family Larsson-Rosenquist Foundation (FLRF)
- Gerber Foundation (PI: Dr. Goran)

Dr. Bode receives travel reimbursements from Universities, foundations, and societies to speak at national and international grand rounds and conferences.



Disclosures

None of the work would be possible without amazing lab members as well as collaborators from across the US and around the world!



The Power of Human Milk

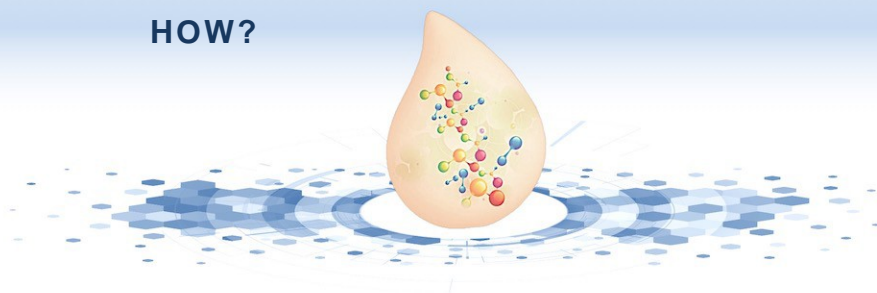
Saving Lives

“The deaths of 823,000 children and 20,000 mothers each year could be averted through universal breastfeeding, along with economic savings of US\$300 billion.”

Editorial Commentary, The Lancet - Breastfeeding Series 2016

WHY?

HOW?



Macromolecules in Human Milk

[g/L]

Protein

12

35

Fat

35

35

Lactose

65

45

Oligosaccharides

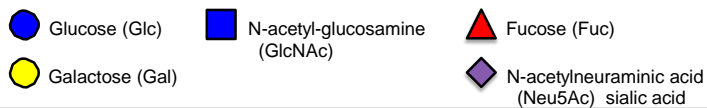
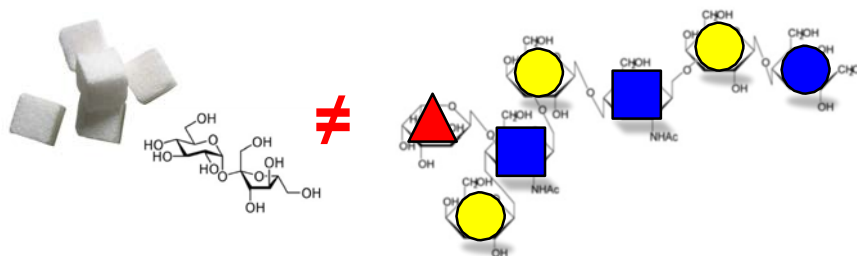
5-15 !

0.05

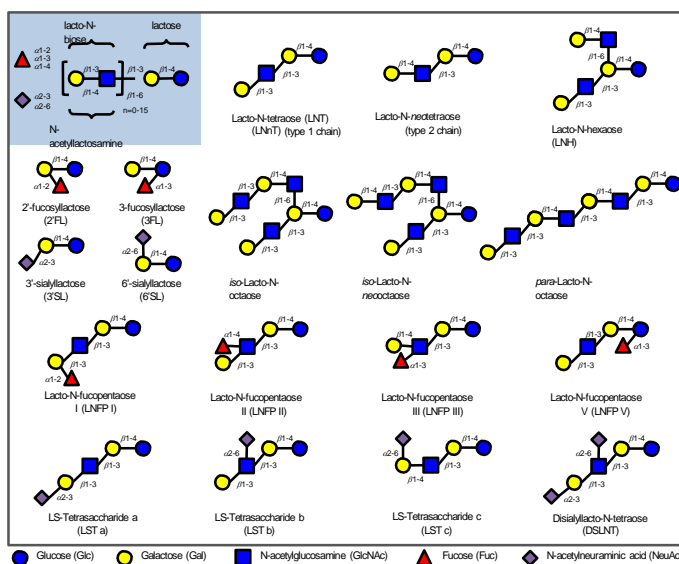


What are Human Milk Oligosaccharides (HMOs)?

Human Milk Oligosaccharides (HMOs) are Complex Sugars



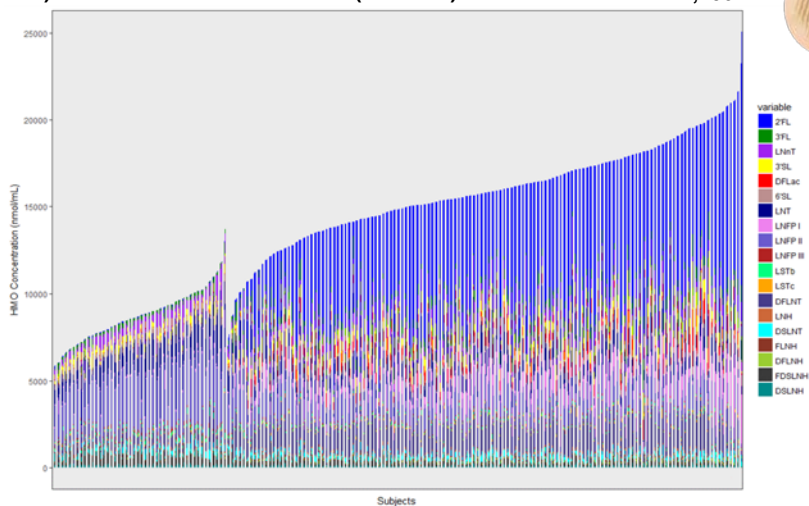
HMO Blueprint and Structural Diversity



150 – 200 different HMO

Personalized complex HMO composition (HMO "fingerprint")

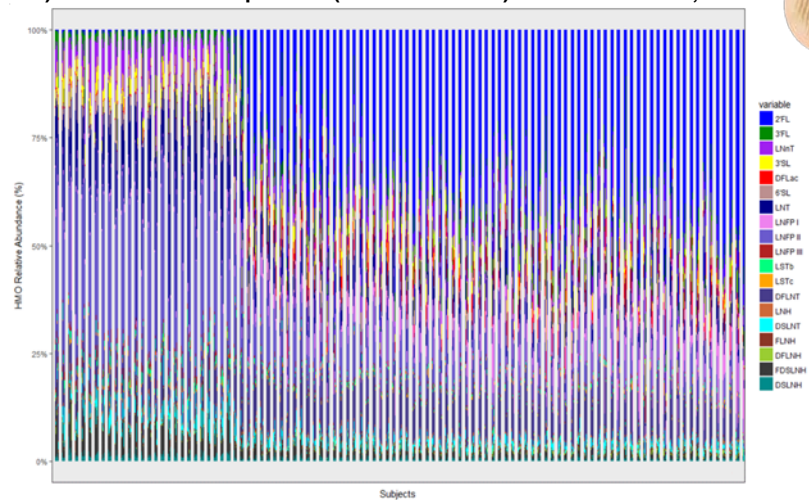
A) Absolute HMO concentration (nmol/mL) n=1,206



preliminary data from CHILD study cohort
(in collaboration with Dr. Meghan Azad)

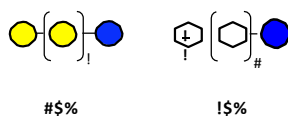
Personalized complex HMO composition (HMO "fingerprint")

B) Relative HMO composition (% of total HMOs) n=1,206

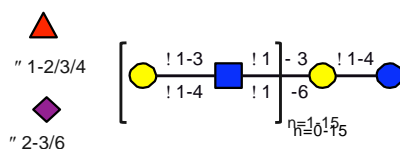


preliminary data from CHILD study cohort
(in collaboration with Dr. Meghan Azad)

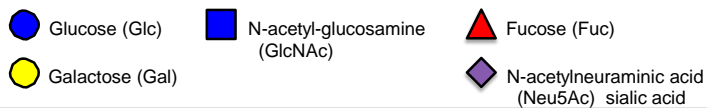
Oligosaccharides currently added to infant formula



...are structurally distinct from HMOs



Human milk oligosaccharides (HMO)



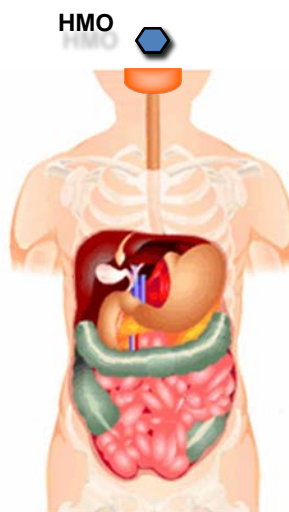
HMO Metabolism

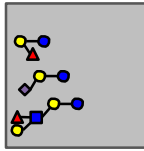
resistant to

- low pH
- pancreatic and brush border enzymes

small intestine:
>1% absorbed,
appear in the urine

colon:
bacterial degradation,
10-80% excreted w/ feces





Summary

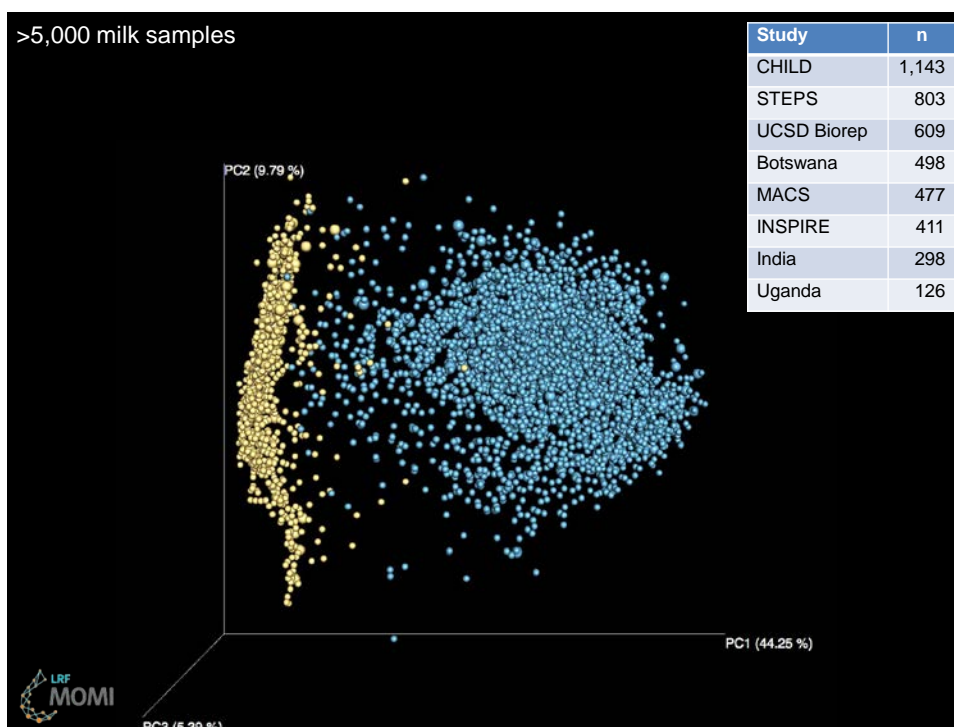
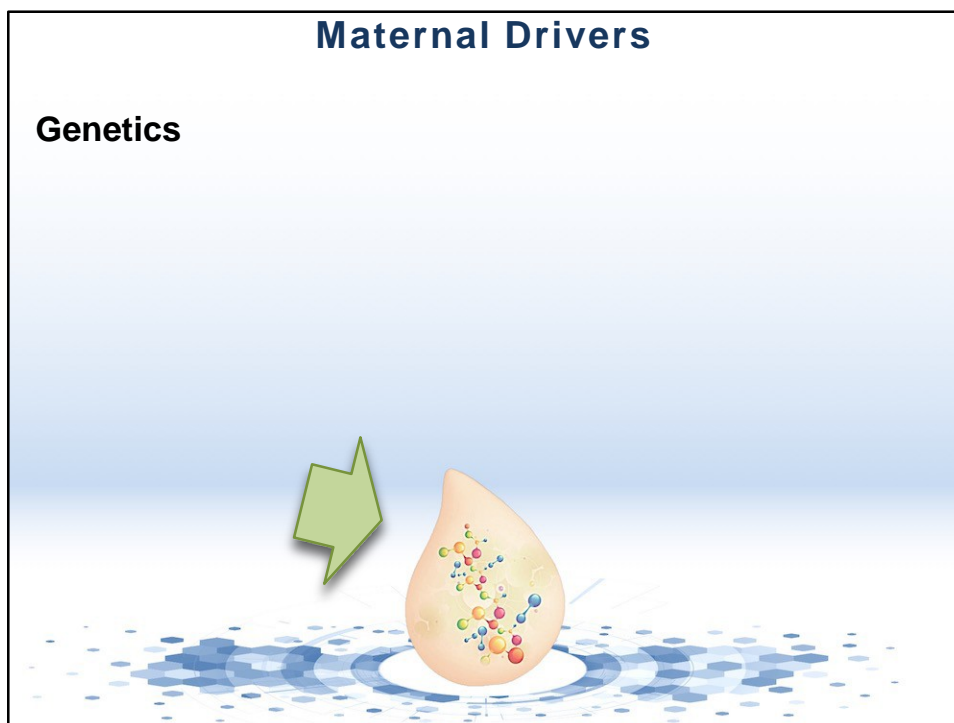
Summary

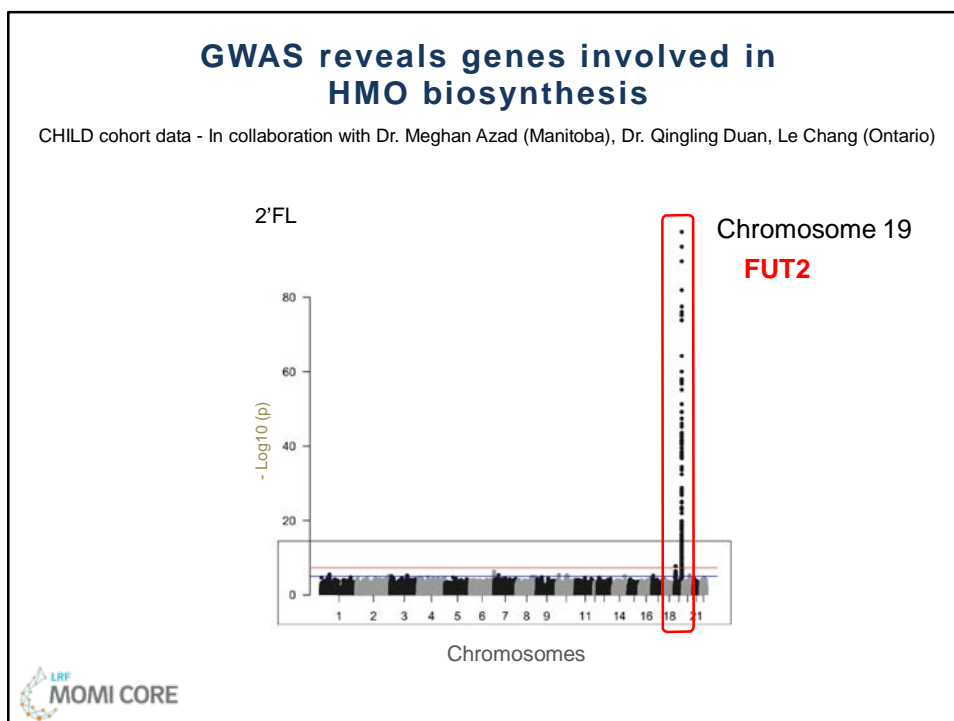
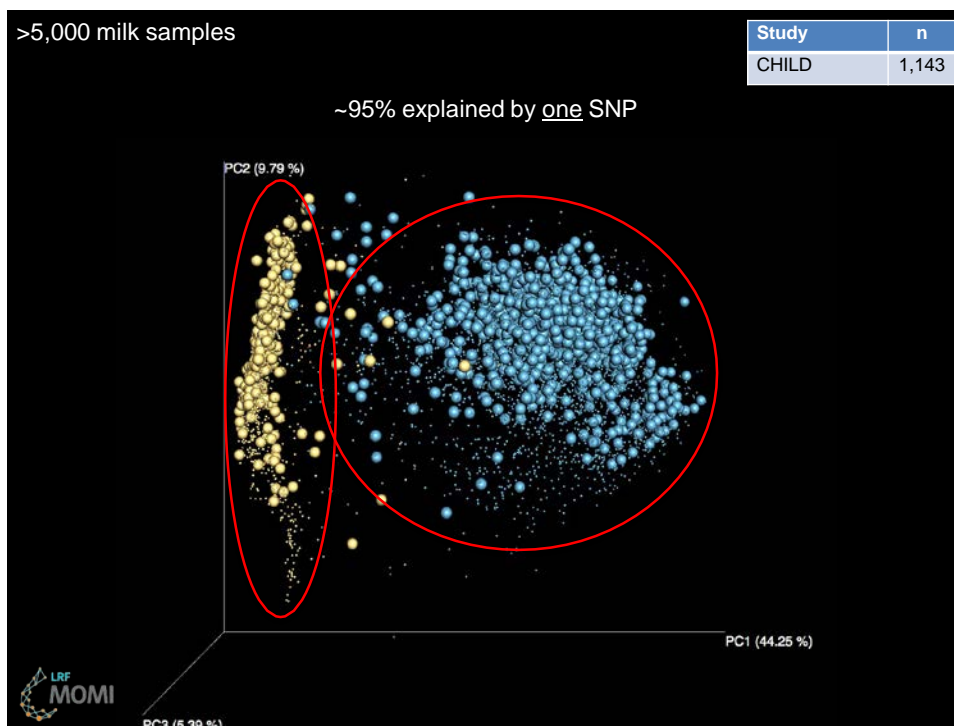
What are HMOs?

What are HMOs?

- third most abundant component in human milk
- composition follows basic blueprint
- more than 150 different HMOs identified
- inter- and intrapersonal differences in HMO composition
- infant formula oligosaccharides (GOS/FOS) structurally (and functionally) different from HMOs
- reach distal GI tract intact, but are also absorbed and reach systemic circulation and organs other than the gut

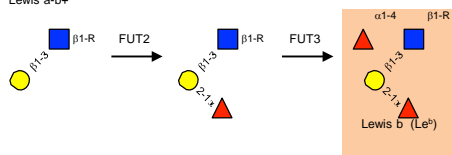
Which maternal factors contribute to variation in Human Milk Oligosaccharides (HMOs) composition?



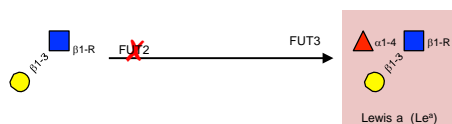


Structural Diversity and Genetics

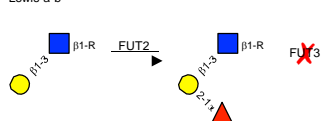
Group 1: Lewis-positive Secretor (Se+Le+)
Lewis a-b+



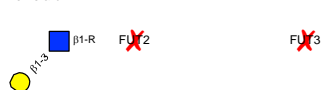
Group 2: Lewis-positive Nonsecretor (Se-Le+)
Lewis a-b-



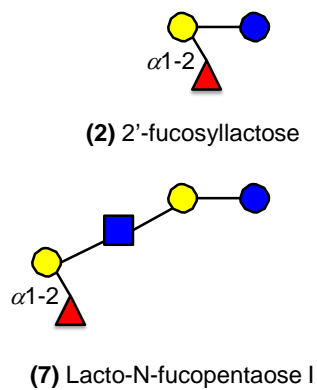
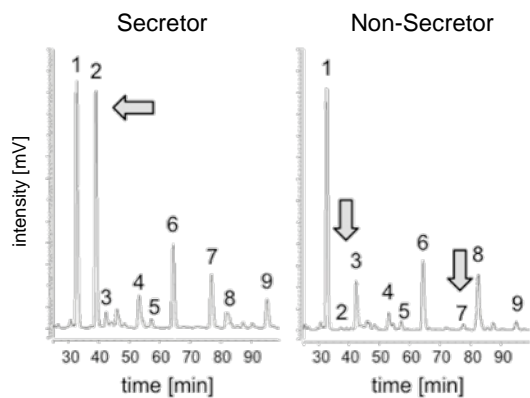
Group 3: Lewis-negative Secretor (Se+Le-)
Lewis a-b-

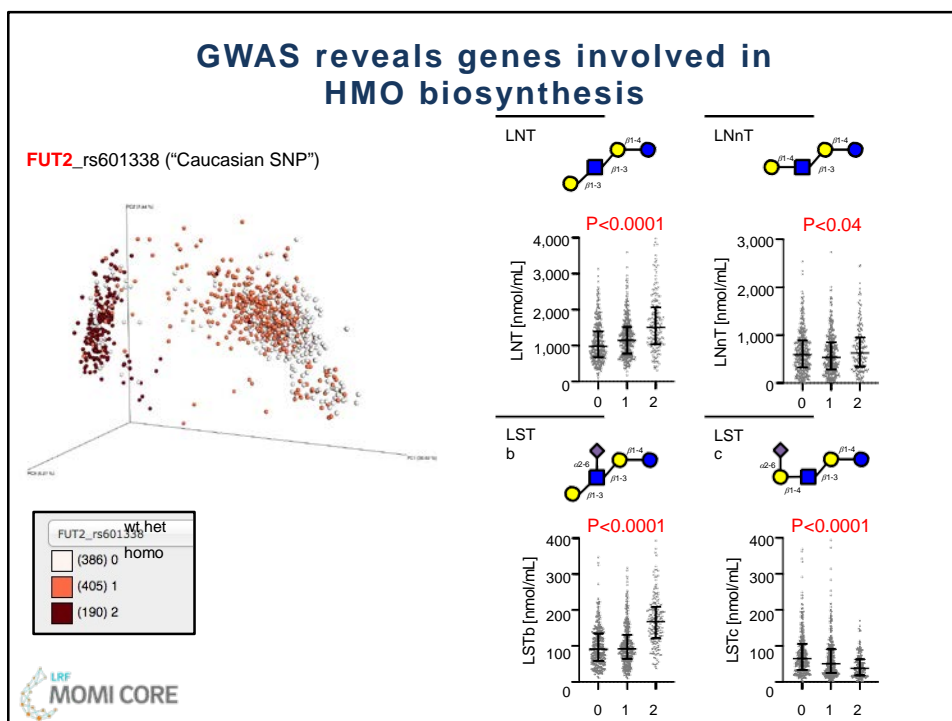
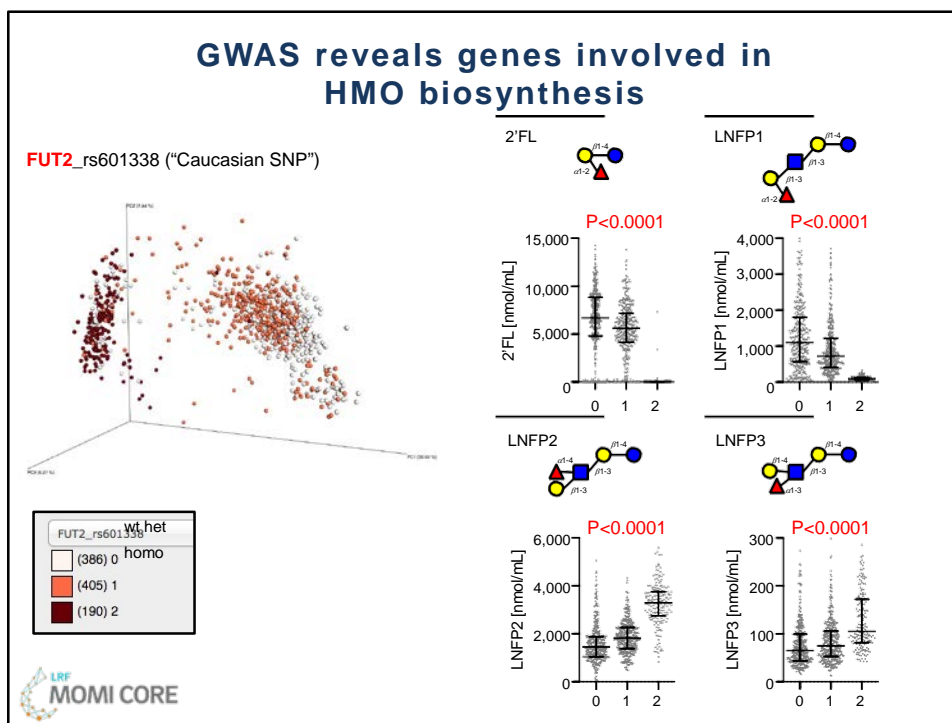


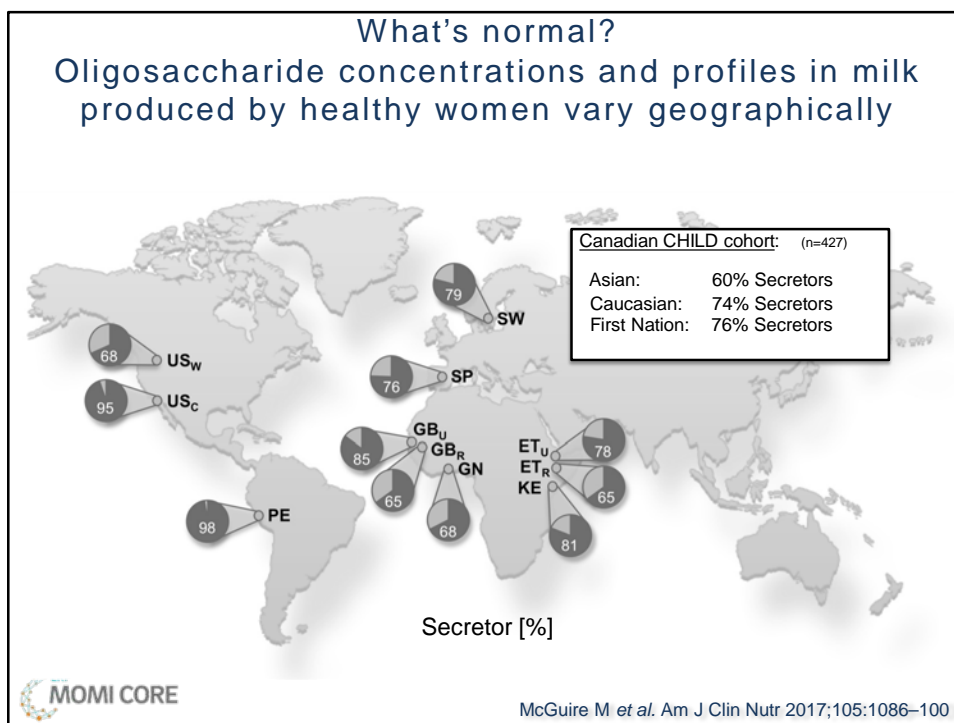
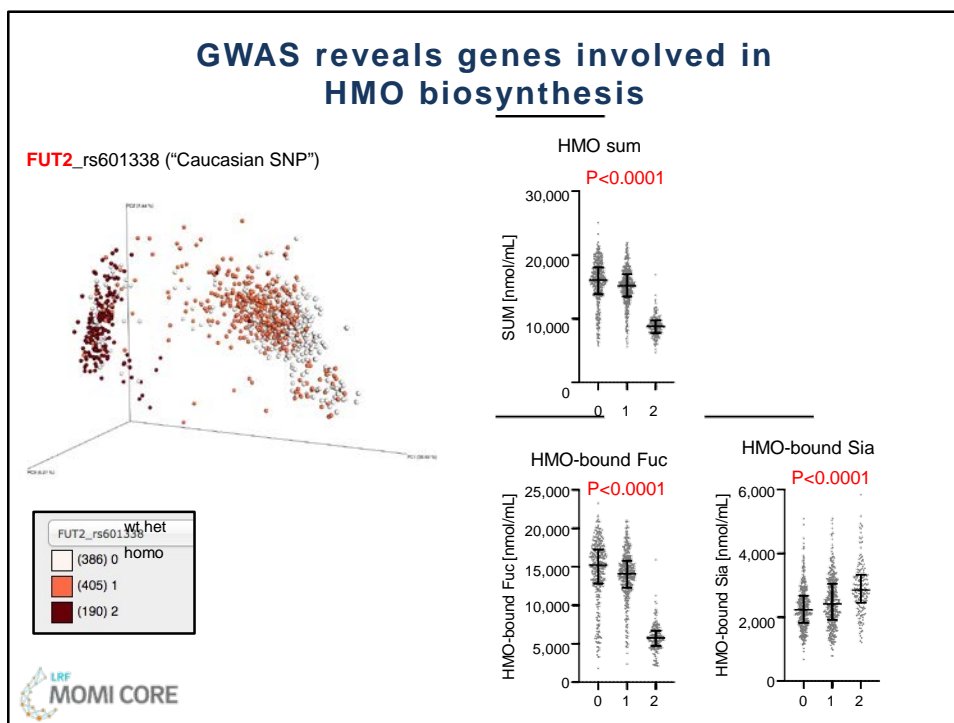
Group 4: Lewis-negative Nonsecretor (Se-Le-)
Lewis a-b-



Structural Diversity and Genetics







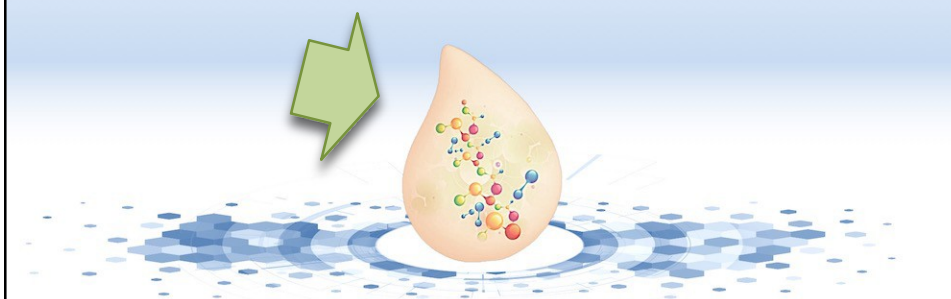
Maternal Drivers

Genetics

- Secretor/Lewis
 - other?
- genomics, transcriptomics, HMO-mics
- *in silico* pathway modeling
 - validation through *in vitro* enzyme characterization and manipulation

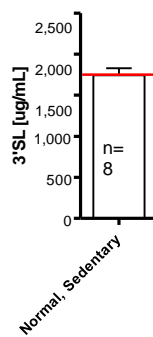
Environment

- diet



Maternal Drivers of HMO Composition

Diet and exercise alter mouse milk oligosaccharide concentration
(3'-sialyllactose, 3'SL)



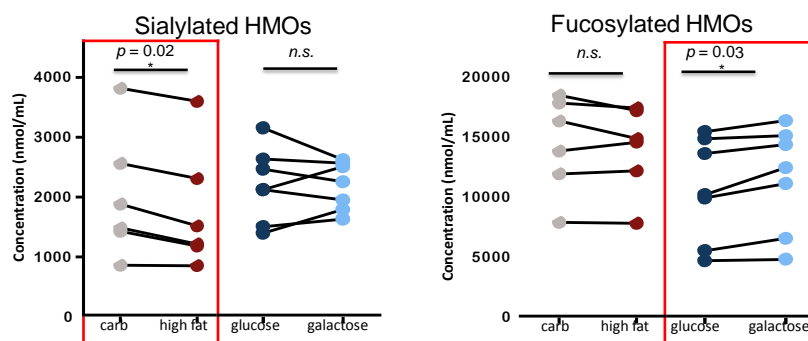
less sialylated HMO on high fat diet



In collaboration with Dr. Kristin Stanford, Ohio State University

Maternal Drivers of HMO Composition

Maternal diet alters HMO composition



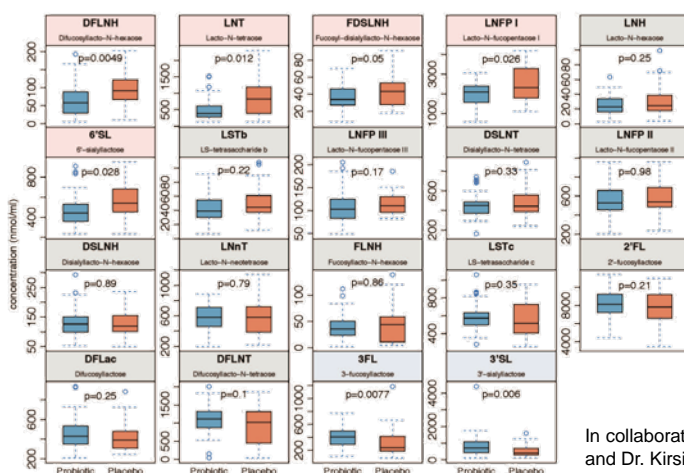
less sialylated HMO on high fat diet



In collaboration with Dr. Morey Haymond, Dr. Mahmoud Mohammad, and Dr. Kjersti Aagaard, Baylor College of Medicine

Maternal Drivers of HMO Composition

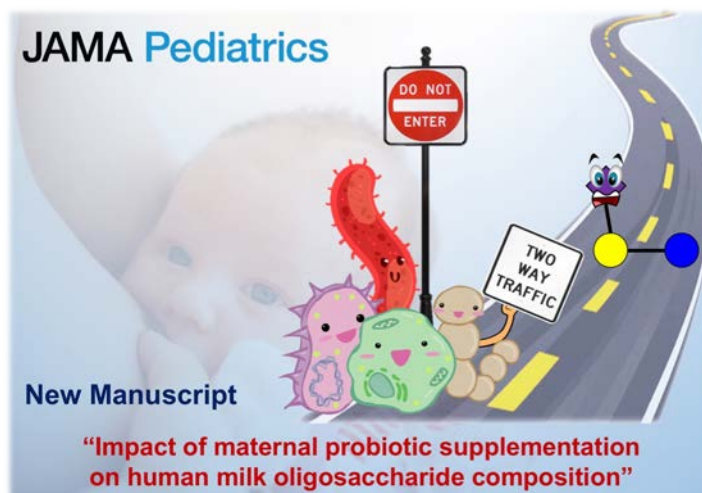
Maternal use of probiotics during late pregnancy is associated with variation in HMO composition



In collaboration with Dr. Antti Seppo and Dr. Kirsi Järvinen-Seppo, University of Rochester



Seppo A et al. JAMA Pediatrics (In Press)



Maternal Drivers

Genetics

- Secretor/Lewis
 - other?
- genomics, transcriptomics, HMO-mics
- *in silico* pathway modeling
 - validation through *in vitro* enzyme characterization and manipulation

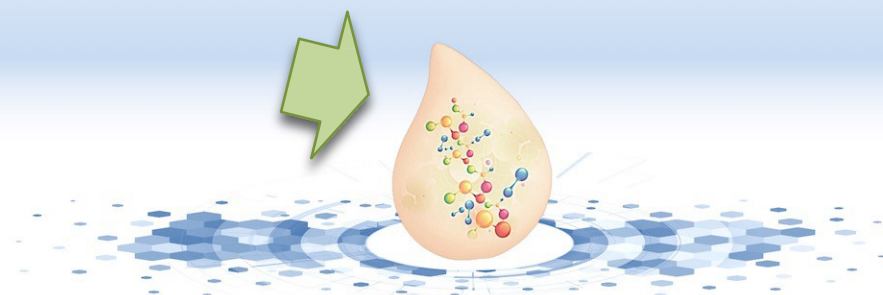
Environment

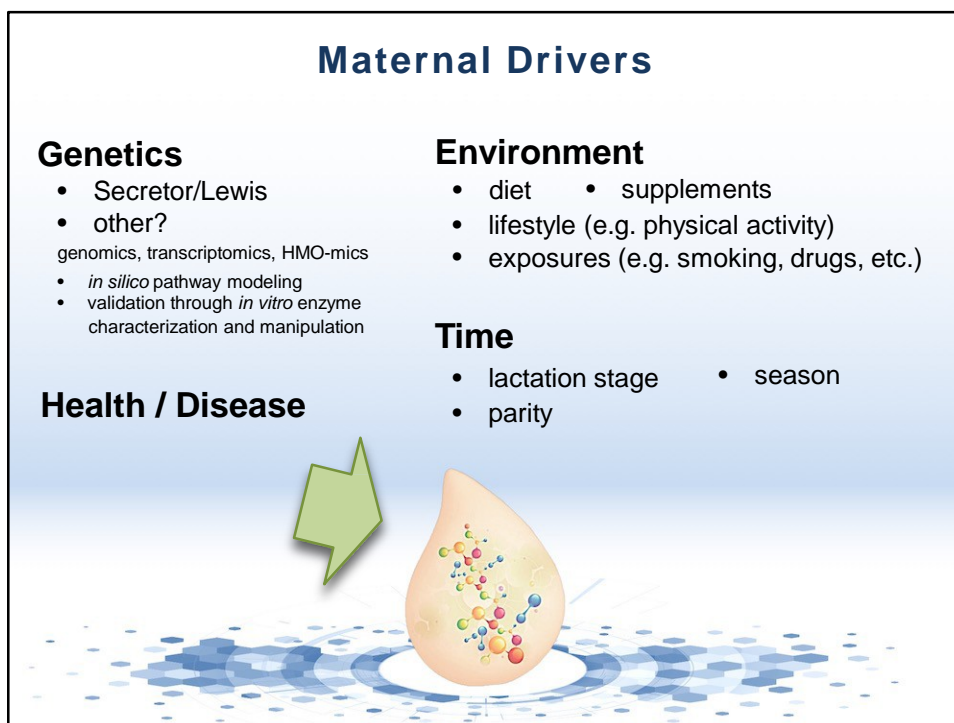
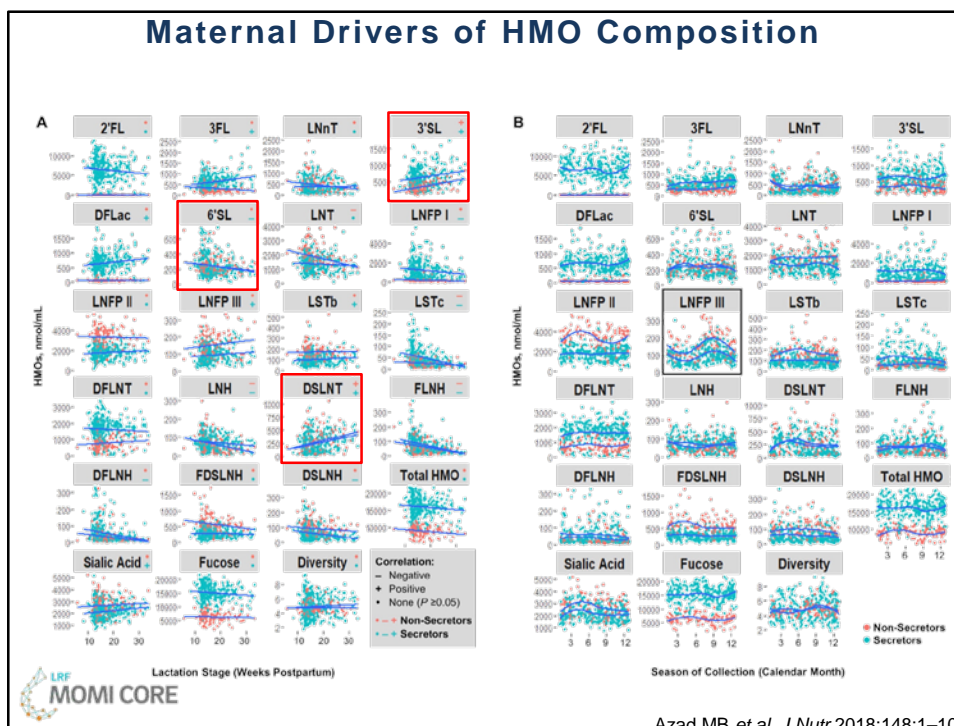
- diet
- supplements
- lifestyle (e.g. physical activity)
- exposures (e.g. smoking, drugs, etc.)

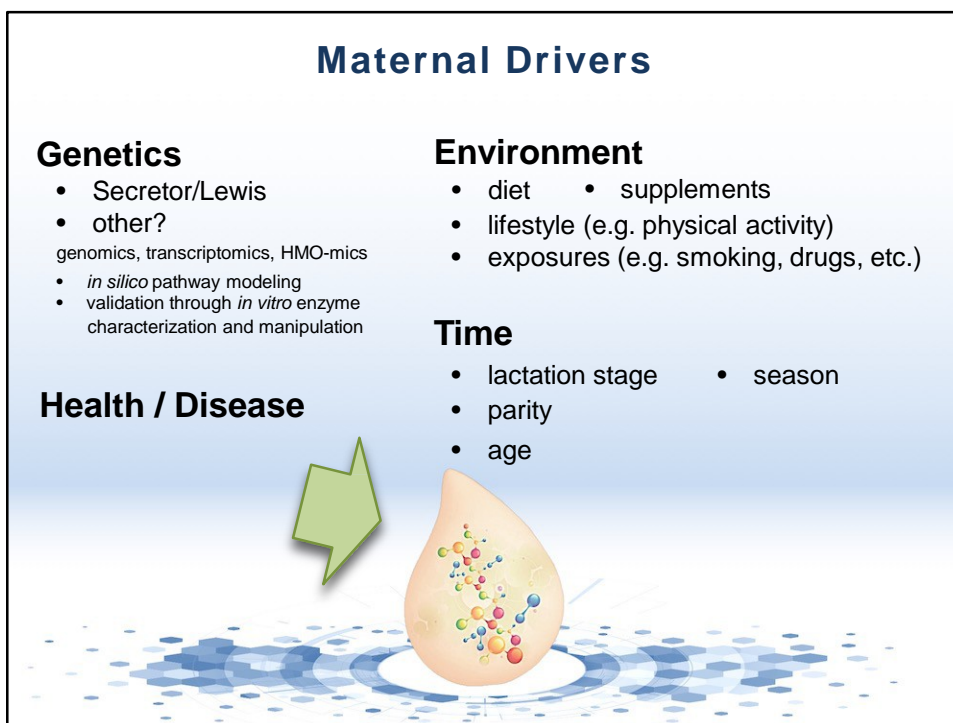
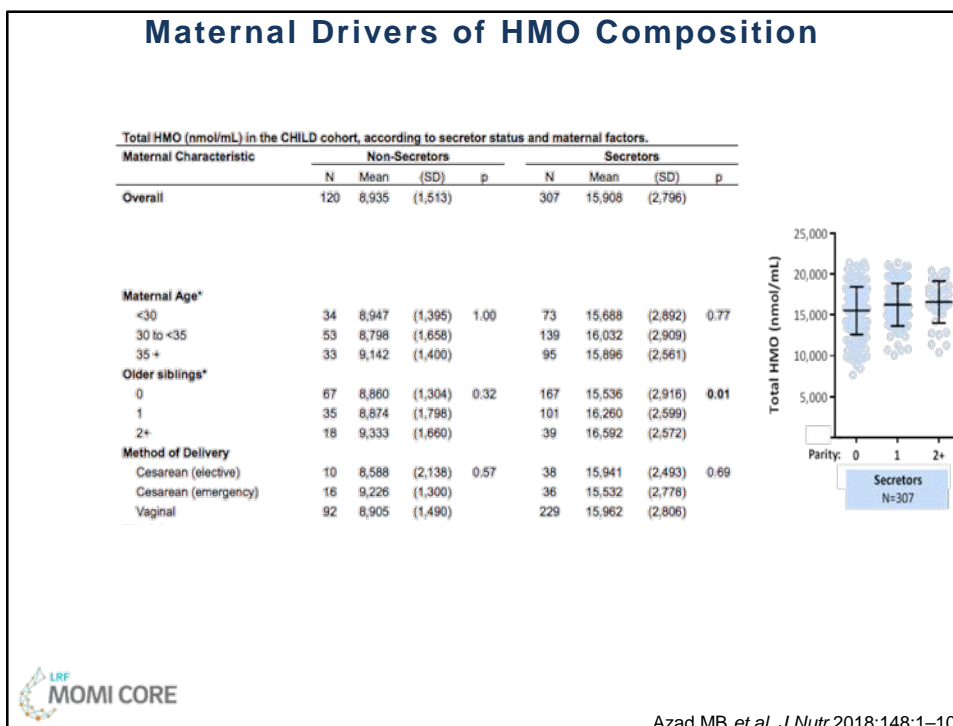
Time

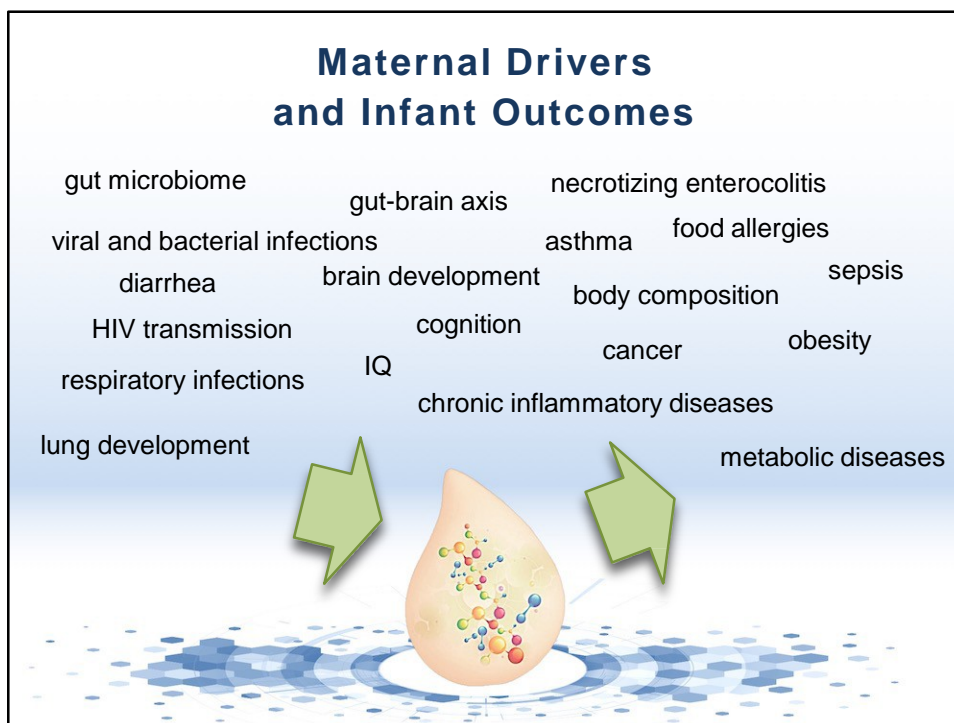
- lactation stage

Health / Disease




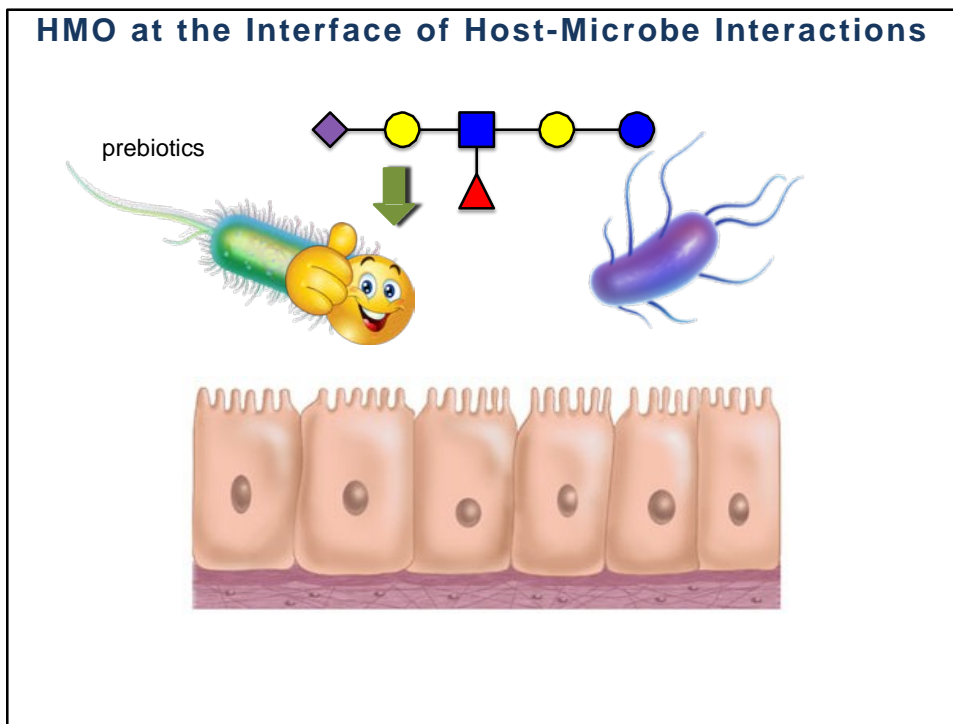






What are Human Milk Oligosaccharides (HMOs) doing?

 UC San Diego



HMO as Prebiotics

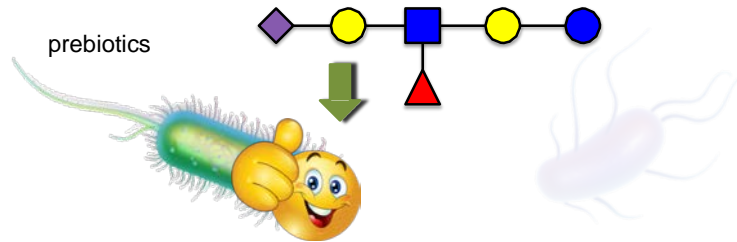
This slide details HMOs as prebiotics. It features the same HMO structure and microbial interaction diagram as the first slide. A portrait of Dr. Karsten Zengler from UCSD is included on the right. Below the diagram, the text "Shaping microbial community development" is followed by a bullet point: "structure-specific effects of HMO ex vivo (infant feces)".

Three specific HMO structures are shown with their corresponding glycosyltransferase enzymes:

- Lacto-N-tetraose (LNT) (type 1 chain)**: Structure with a yellow circle, blue square, and yellow circle. Enzyme: β 1-3
- 2'-fucosylactose (2FL)**: Structure with a yellow circle, blue square, and yellow circle. Enzyme: α 1-2
- 3'-sialyllactose (3SL)**: Structure with a yellow circle, blue square, and yellow circle. Enzyme: α 2-3

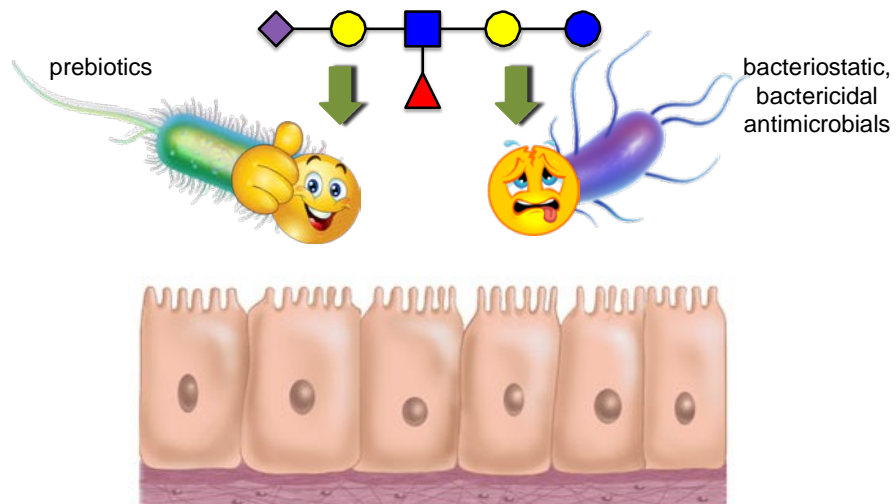
Below these structures are two glycan motifs: a yellow circle with a blue circle attached to its top, labeled "#5%", and a blue circle with a yellow circle attached to its top, labeled "15%".

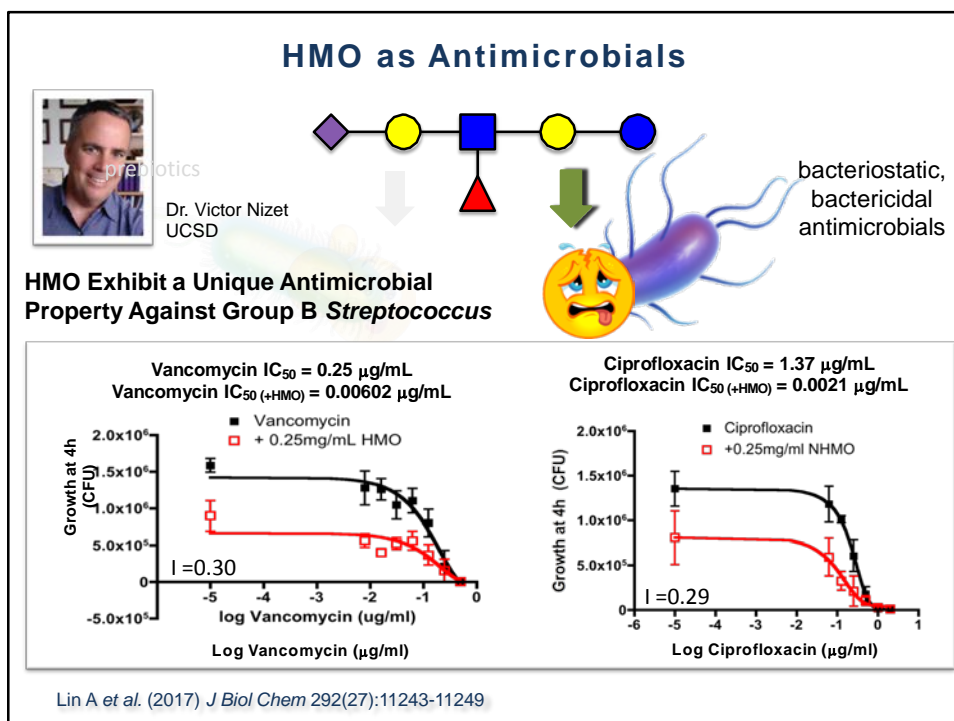
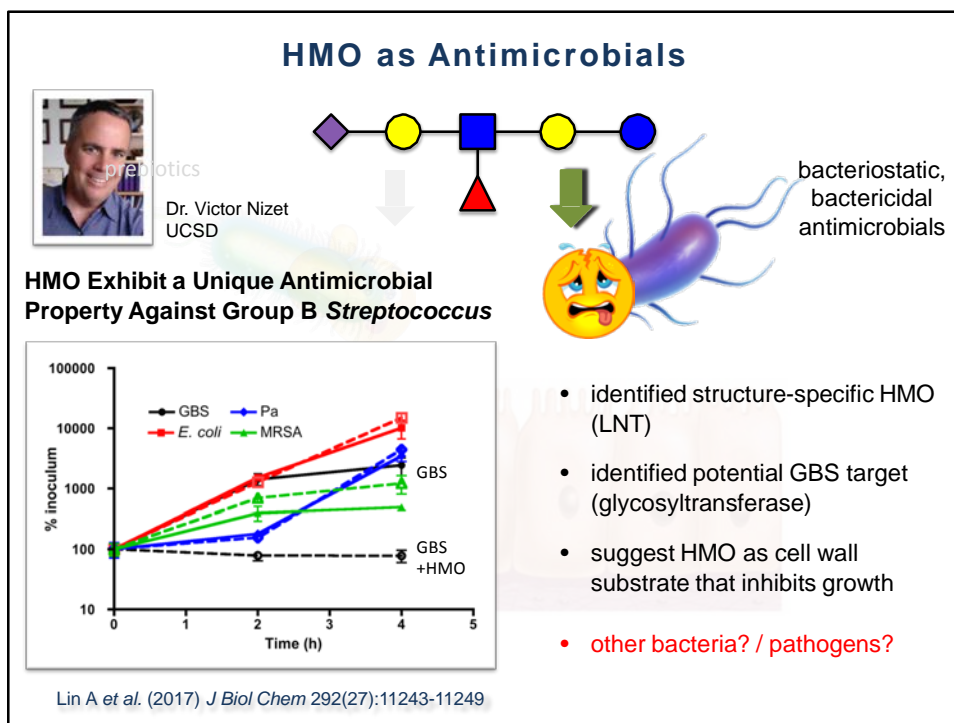
HMO as Prebiotics

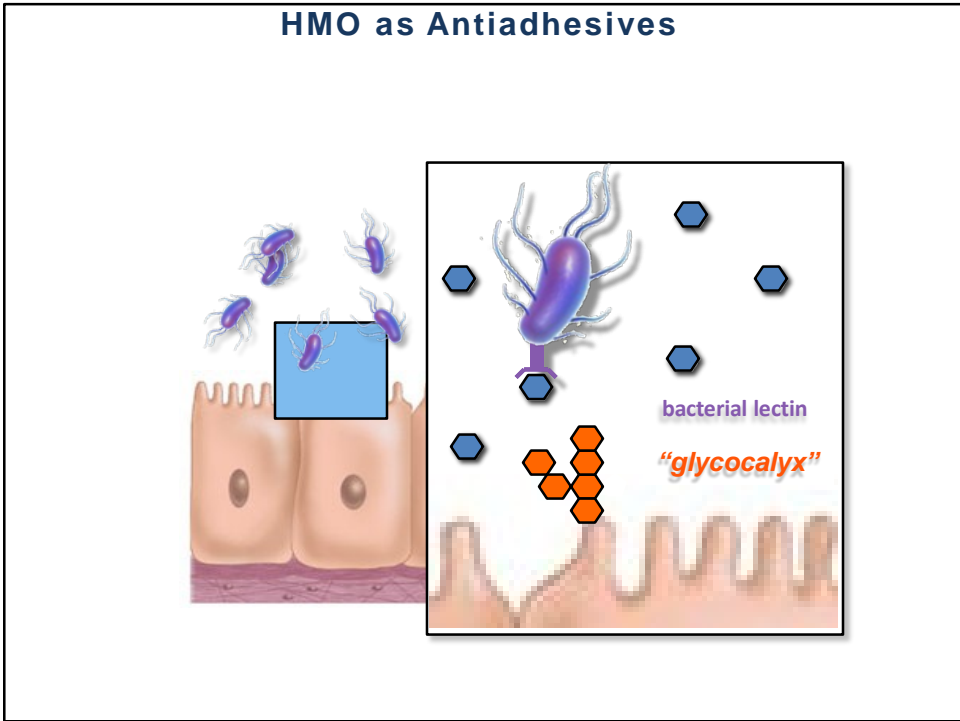
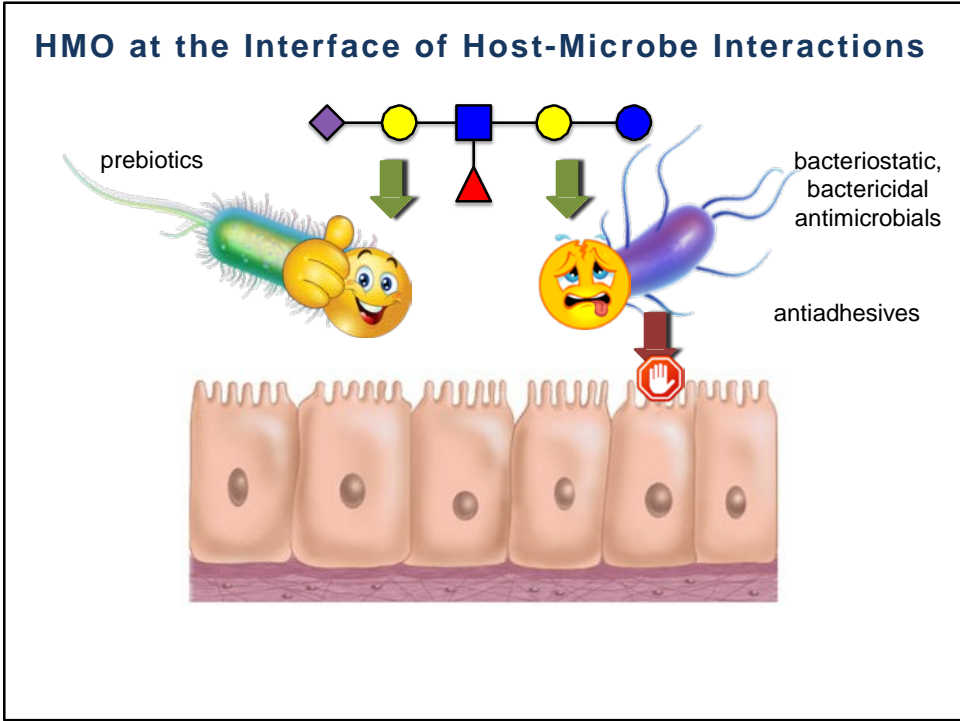


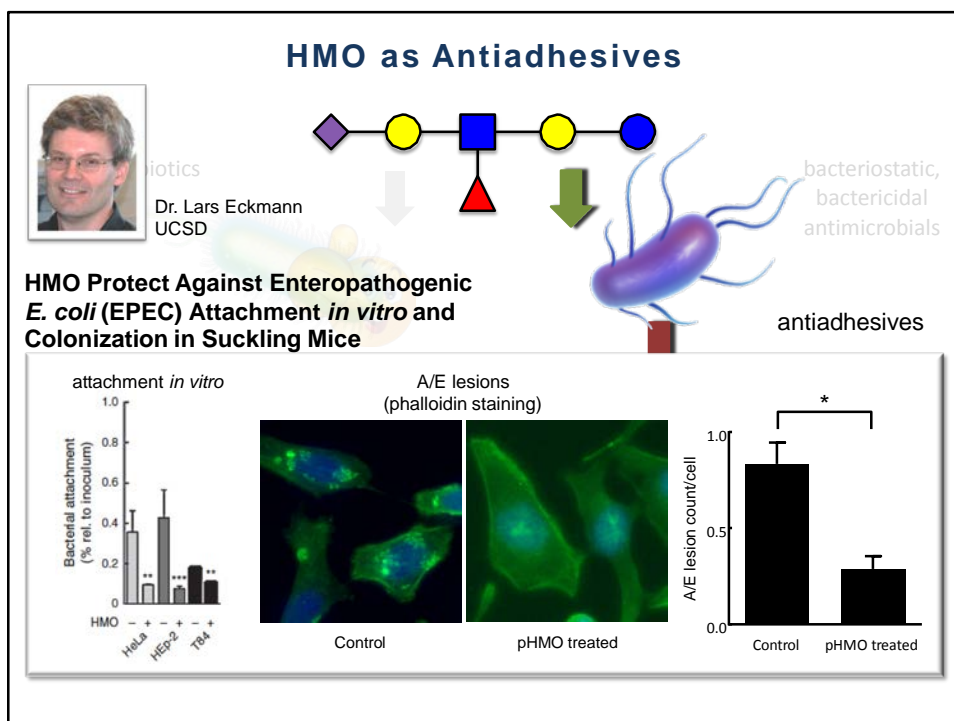
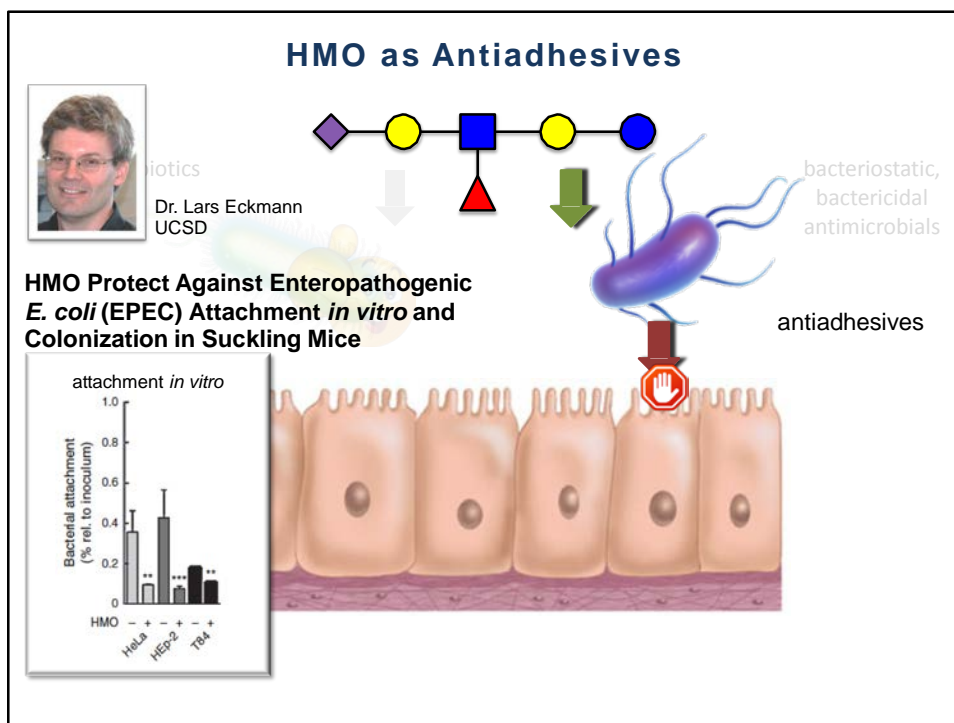
- prebiotic effects of HMOs are **structure-specific**!
 - different HMOs have different effects on microbial communities
 - mixture of HMOs vs individual HMOs?
 - short- and long-term consequences?
(DOHaD: Developmental Origins of Health and Disease)

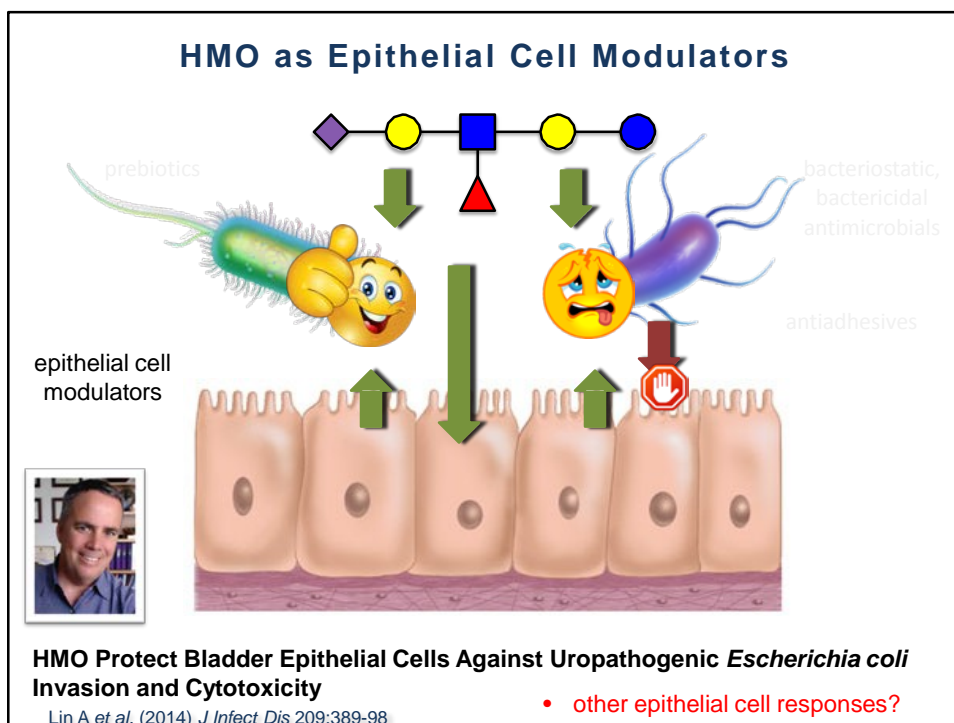
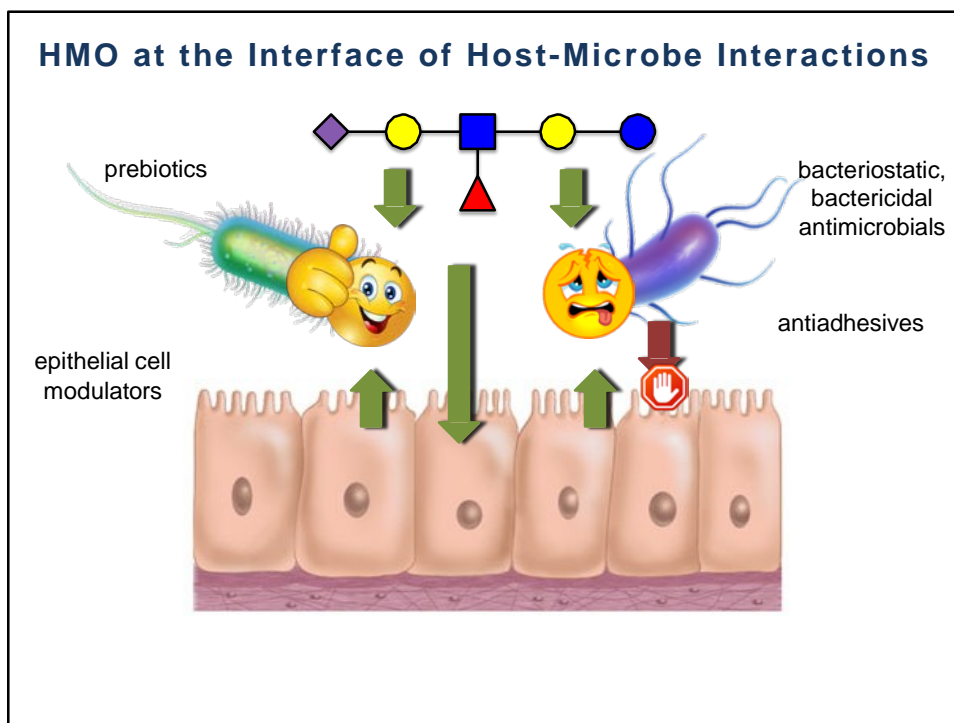
HMO at the Interface of Host-Microbe Interactions

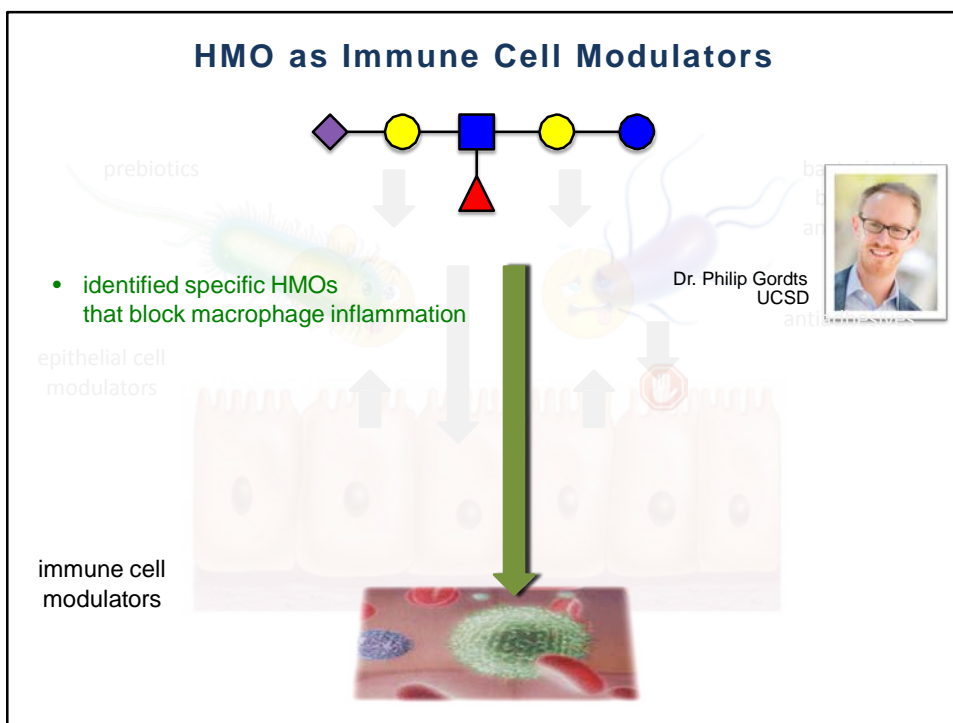
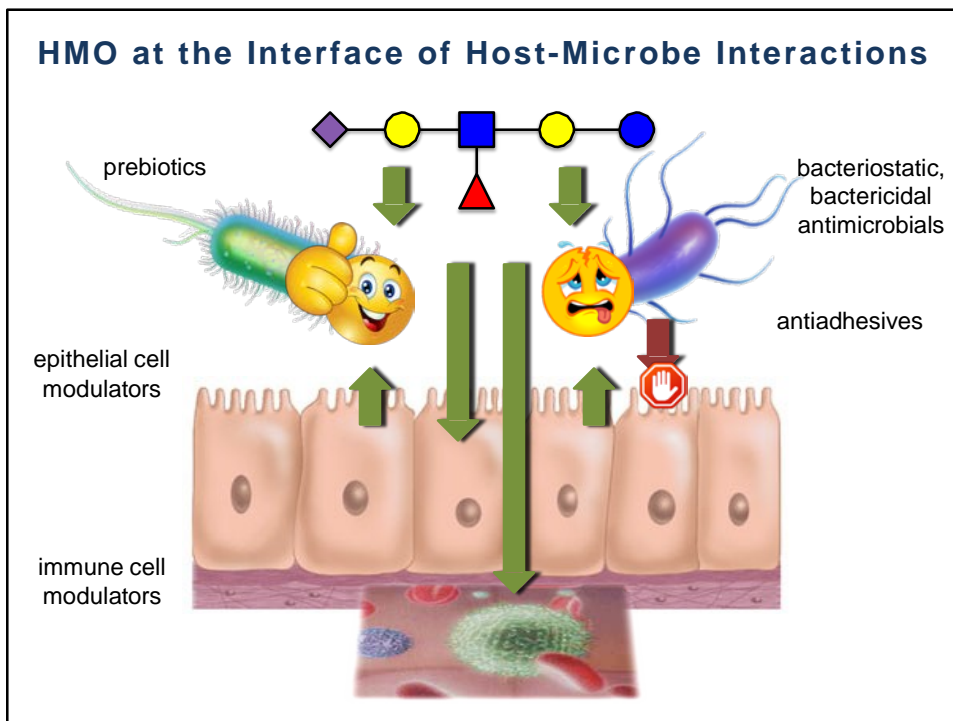


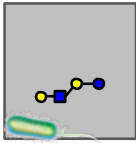











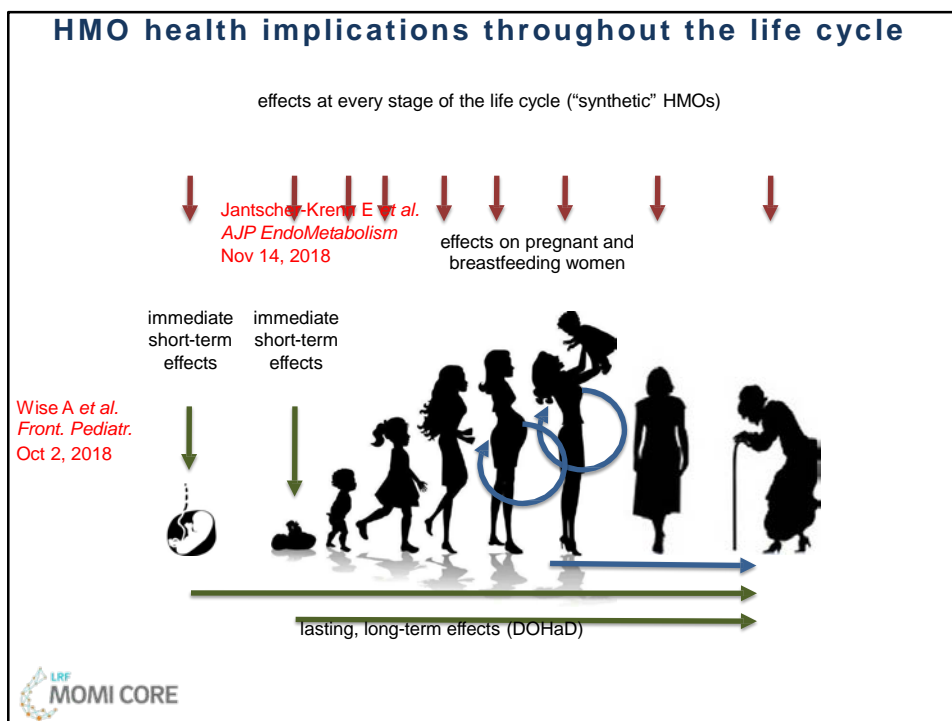


Summary

What are the potential benefits of HMOs?

- indirect effects on the infant (through effects on the microbiome)
 - prebiotic
 - anti-microbial
 - anti-adhesive
- direct effects on the infant
 - epithelial cell response modulators
 - immune cell response modulators
- multiple potential other mechanisms
- health implications throughout the life cycle





Necrotizing Enterocolitis (NEC) in the Preterm Infant

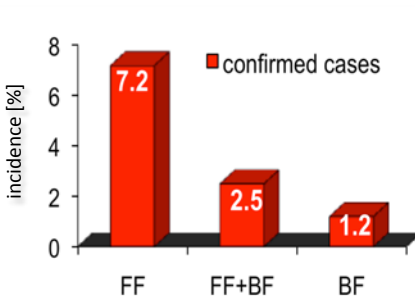


Necrotizing Enterocolitis

N Engl J Med 2011

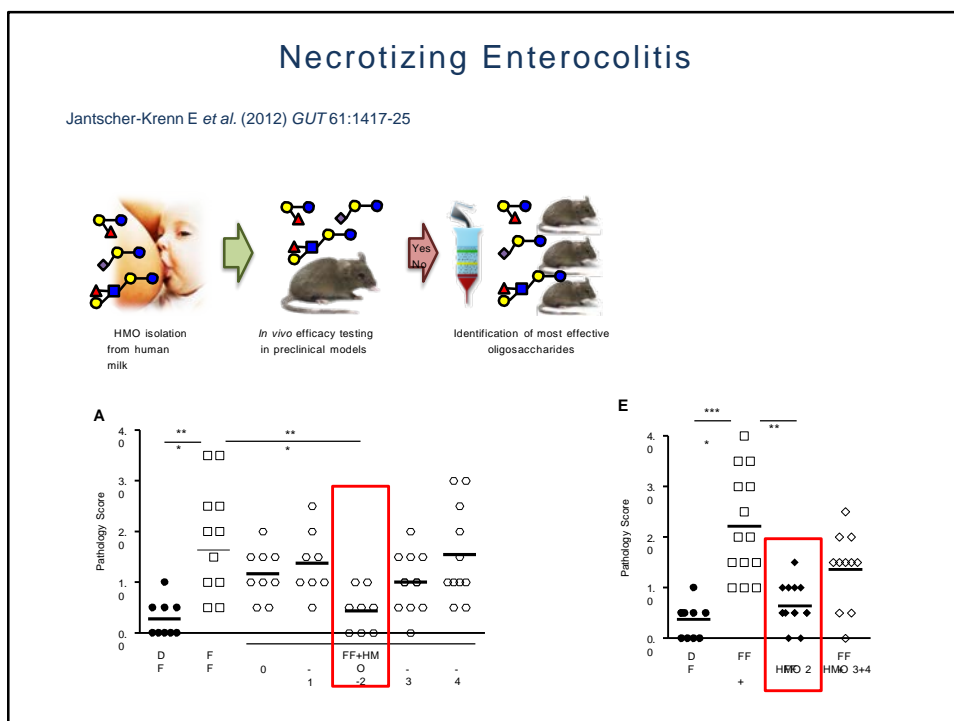
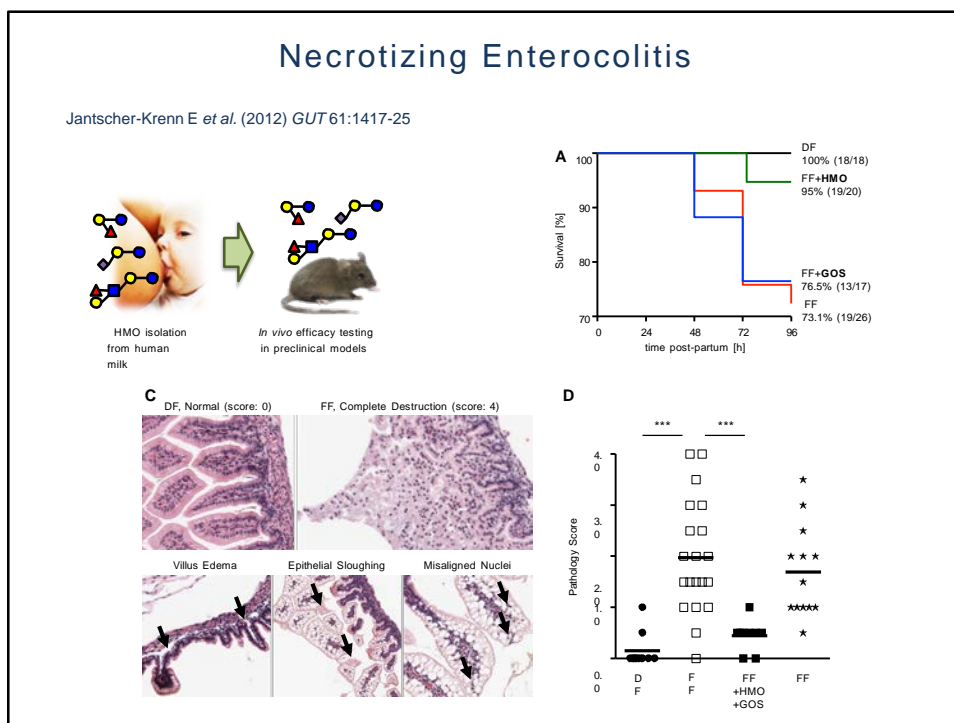


- one of the most common and fatal GI disorders in preterm infants
- ~5% of all VLBW infants (<1,500g)
- high mortality (>25%)
- ~6- to 10-fold higher risk in formula-fed infants (FF) compared to breast-fed infants (BF)



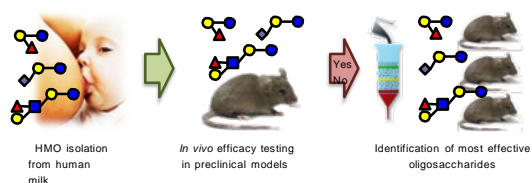
**HMOs?
which one?**

Lucas A and Cole TJ (1990) *Lancet* 336: 1519-1523



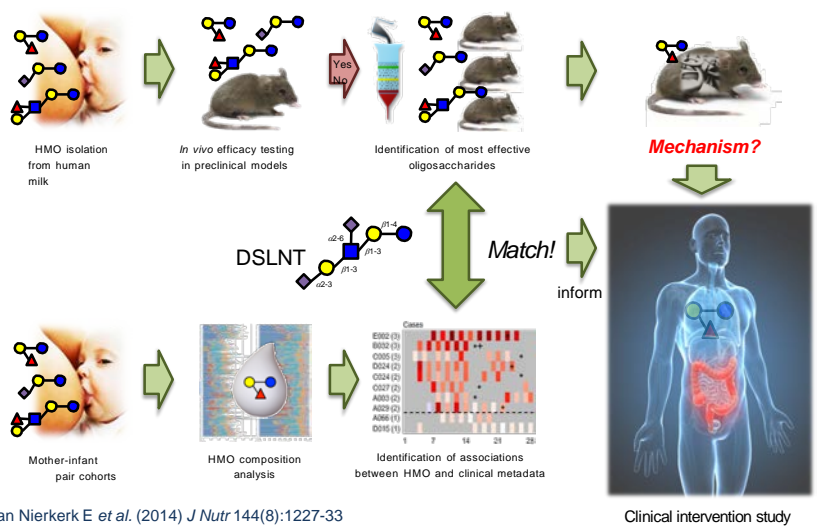
Necrotizing Enterocolitis

Jantscher-Krenn E *et al.* (2012) *GUT* 61:1417-25
 Yu H *et al.* (2014) *Angew Chem Int Ed Engl.* 53(26):6687-91
 Autran CA *et al.* (2016) *Br J Nutr* 116(2):294-9
 Yu H *et al.* (2017) *J Org Chem.* 82(24):13152-13160

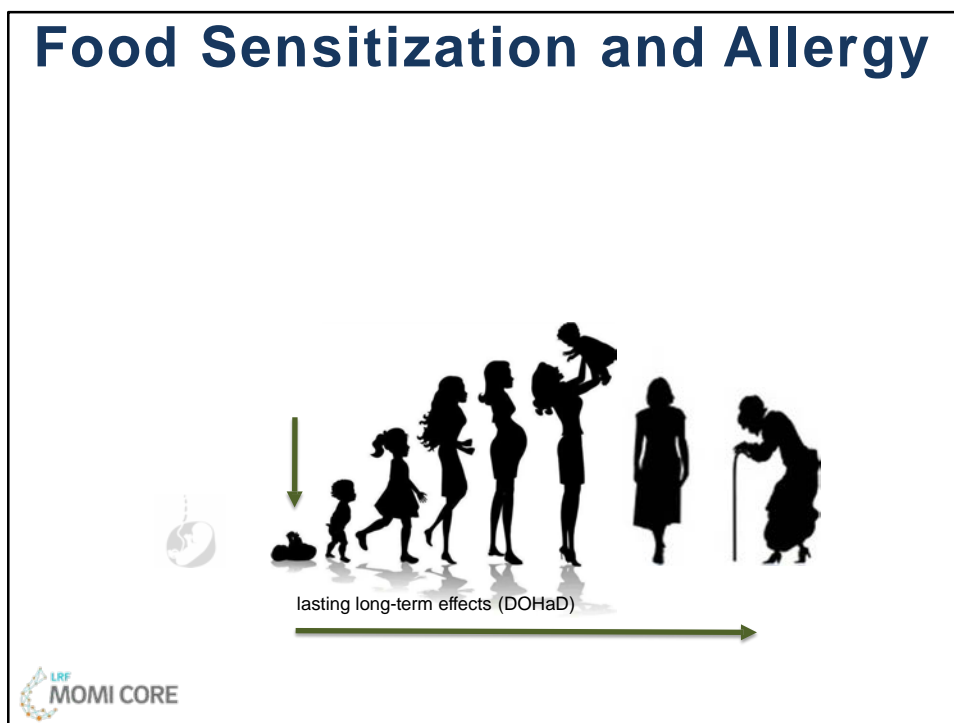
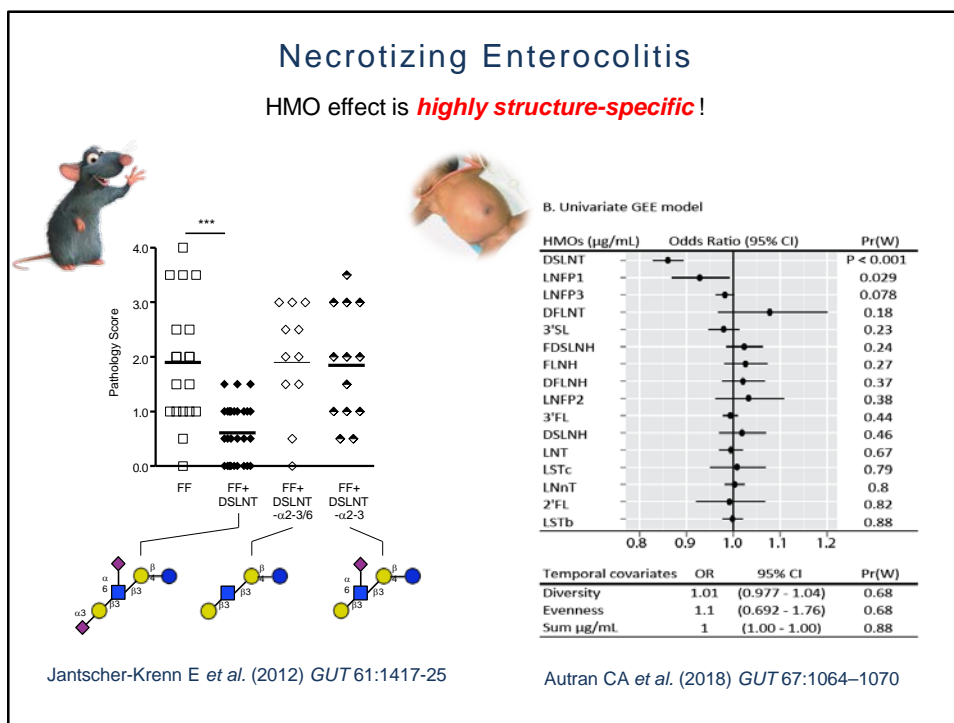


Necrotizing Enterocolitis

Jantscher-Krenn E *et al.* (2012) *GUT* 61:1417-25
 Yu H *et al.* (2014) *Angew Chem Int Ed Engl.* 53(26):6687-91
 Autran CA *et al.* (2016) *Br J Nutr* 116(2):294-9
 Yu H *et al.* (2017) *J Org Chem.* 82(24):13152-13160





Van Nierkerk E *et al.* (2014) *J Nutr* 144(8):1227-33
 Autran CA *et al.* (2018) *GUT* 67:1064–1070

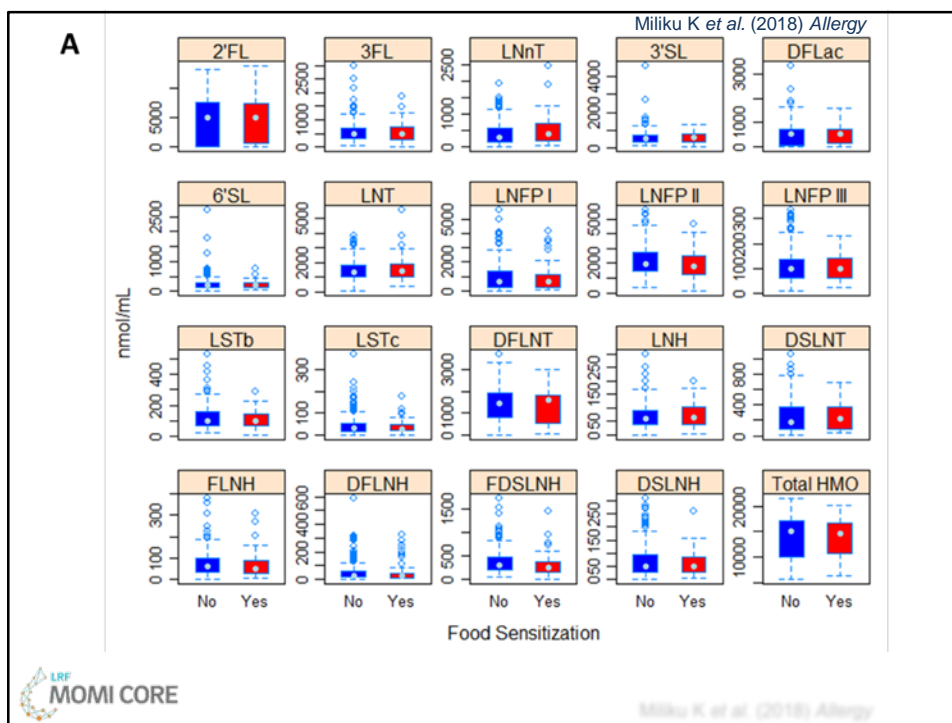


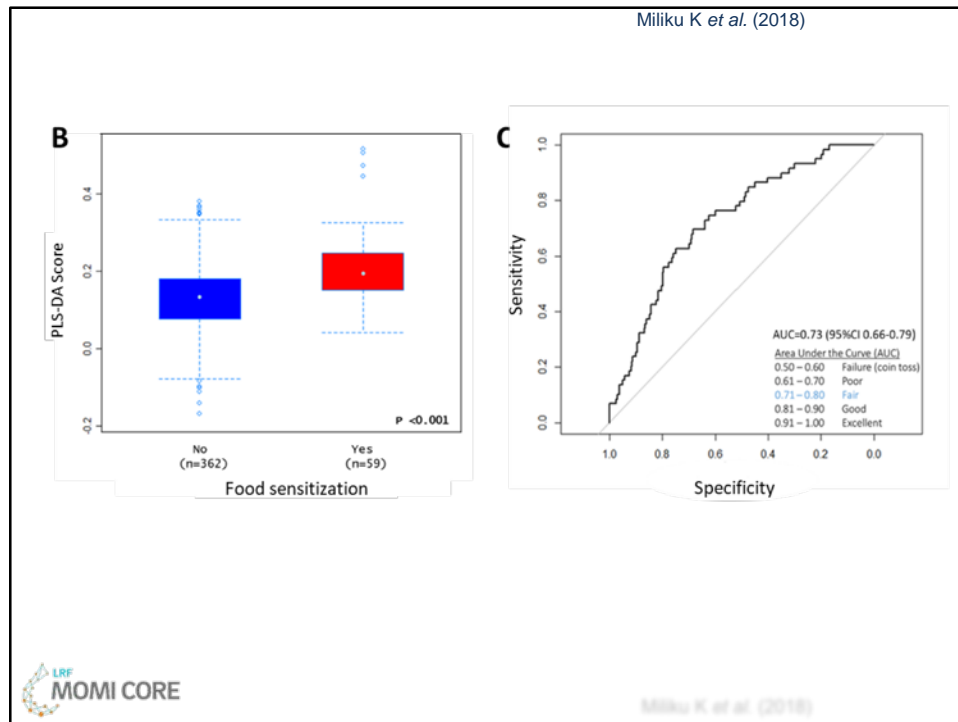
Letter to the Editor

Human milk oligosaccharide profiles and food sensitization among infants in the CHILD Study

Kozeta Miliku, Bianca Robertson, Atul K. Sharma, Padmaja Subbarao, Allan B. Becker, Piuskumar J. Mandhane, Stuart E. Turvey, Diana L. Lefebvre, Malcolm R. Sears, The CHILD Study Investigators, Lars Bode, Meghan Azad  ... See fewer authors 

First published: 18 May 2018 | <https://doi.org/10.1111/all.13476>





Individual HMOs or HMO profiles?

What we've learned so far...

What we've learned so far...

- **sometimes specific individual HMOs are effective**
 - effects are highly structure-specific
 - dose-response effect
 - mechanisms likely receptor-mediated (host and/or microbe)
- **sometimes specific mixtures (composition profiles) are effective**
 - relative abundance of HMOs, ratio of HMOs
 - mechanisms likely indirect through shaping microbial communities, microbial metabolites, and/or direct on host (immune system and other)

What is the 'optimal' Human Milk Oligosaccharide (HMO) composition?



Is there an 'optimal' Human Milk Oligosaccharide (HMO) composition?

Infant
(genetics)

Environment

Time

Geographic Location

Personalized, Context-dependent Composition



Conclusion

- HMOs are the third most abundant component of human milk
- maternal (genetic and environmental) factors driving variation in complex HMO composition not fully understood
- combination of preclinical, cohort and clinical studies required to fully assess effects, functions and potential claims
- sometimes individual HMOs are effective; sometimes complex mixtures of HMOs in specific relative abundancies are required (personalized?)
- HMOs benefit the breastfed infant and potentially the fetus
- HMOs may have potential long-term effects (DOHaD)
- HMOs may benefit maternal health
- HMOs serve as template for novel therapeutics way beyond the first 1,000 days



UC San Diego



Larsson-Rosenquist Foundation
Mother-Milk-Infant
Center of Research Excellence

www.bodelab.com

www.milk.ucsd.edu

lbode@ucsd.edu

