

Bringing Synbiotic Interventions in Cancer to Practice: from bench to bedside

The UC Davis
Foods for Health Institute



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Associate Director, Human Studies Research

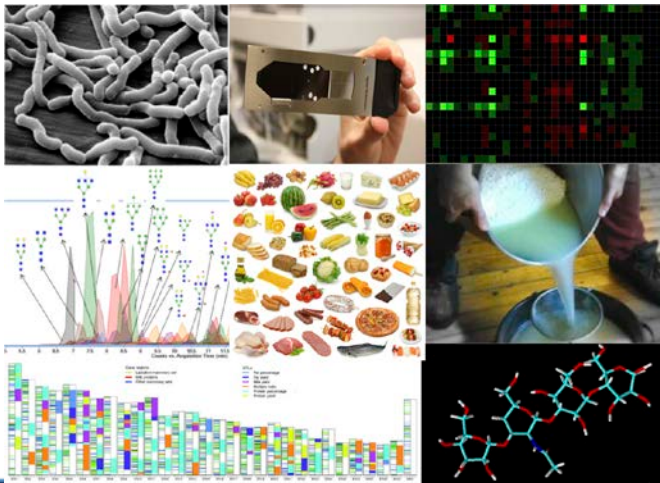
jensm@ucdavis.edu

<http://ffhi.ucdavis.edu>



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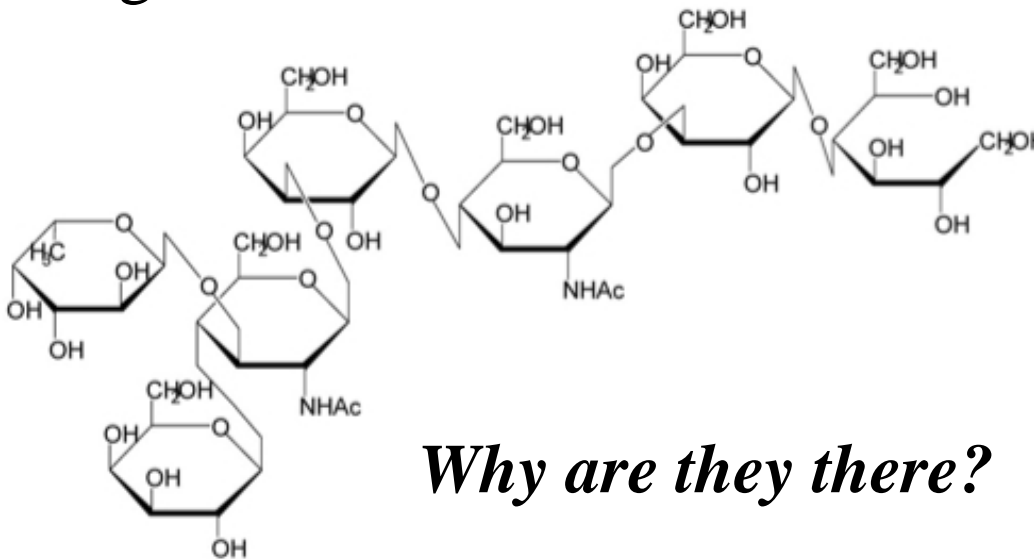
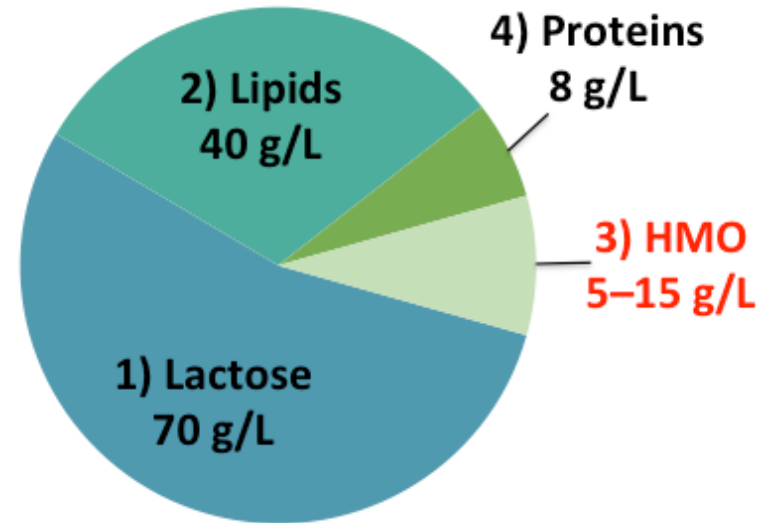
Translating Targets and Testing Efficacy to Personalize Diet & Health to Prevent Disease



Oligosaccharides are 3rd most abundant component in human milk

BUT

Humans do not have the enzymes to digest them!



Why are they there?



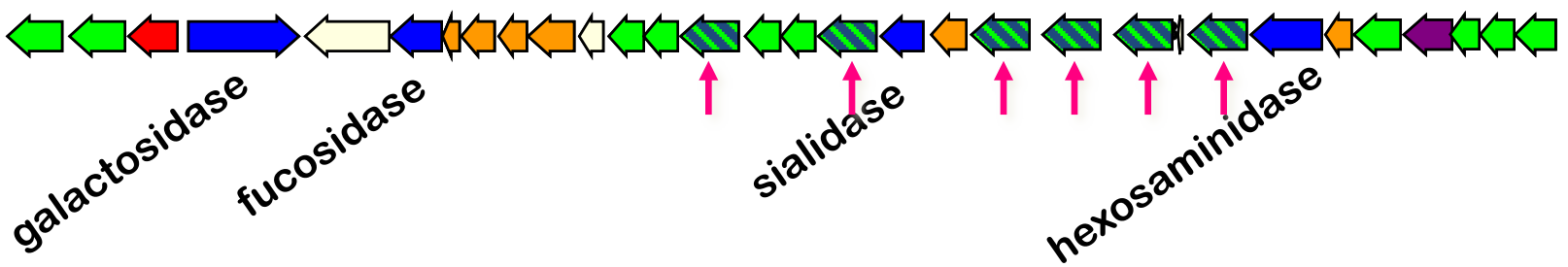
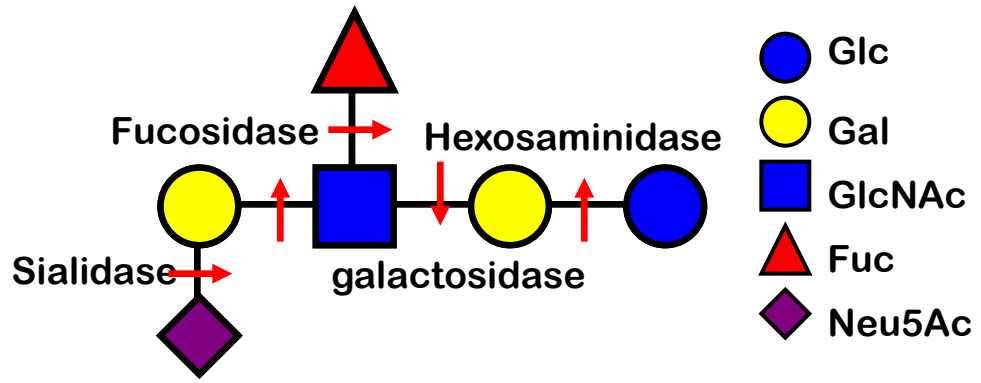
Bifidobacterium infantis



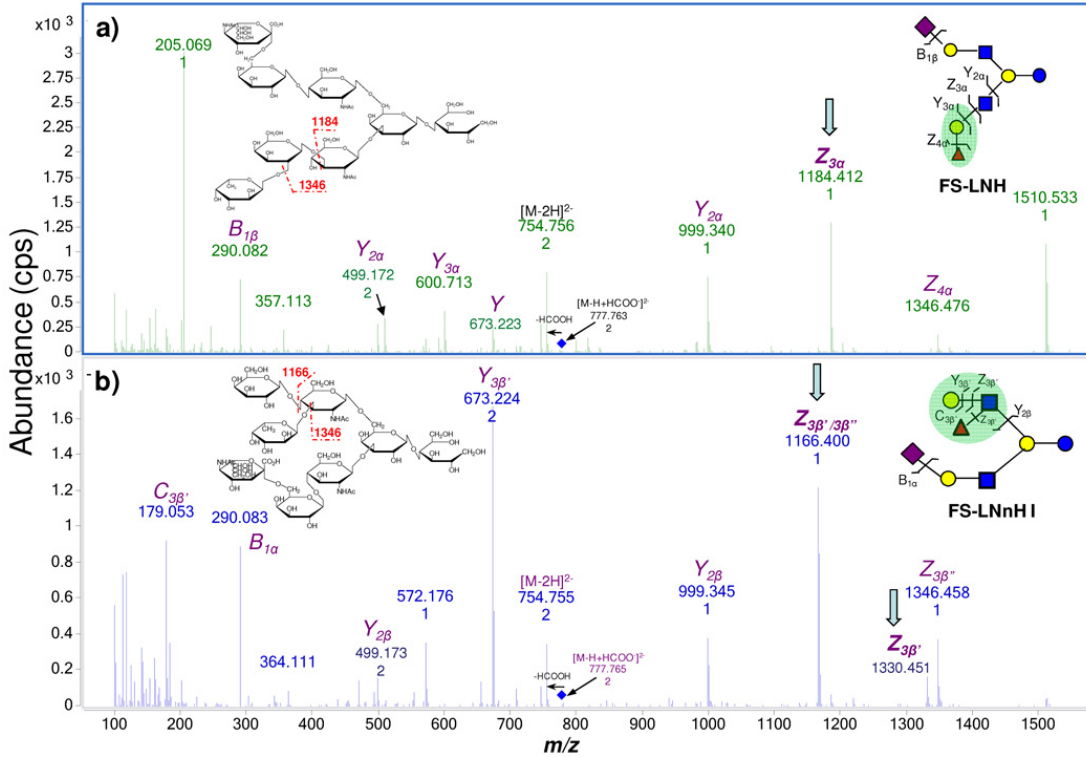
Oligosaccharides unique to milk select specific *Bifidobacteria infantis* to colonize and dominate the intestinal microbiome of infants



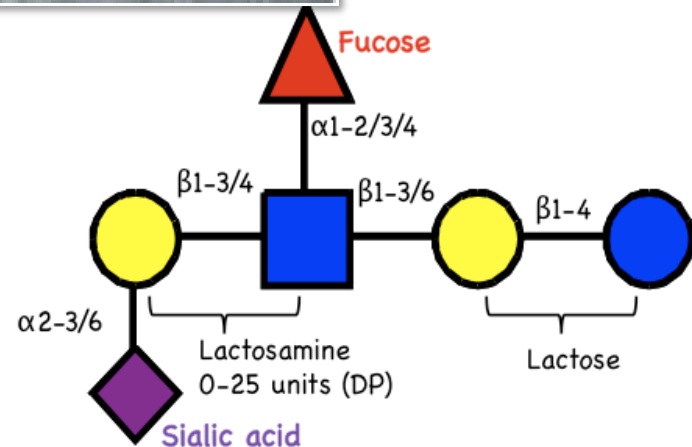
David Mills
Food Sci, V&E



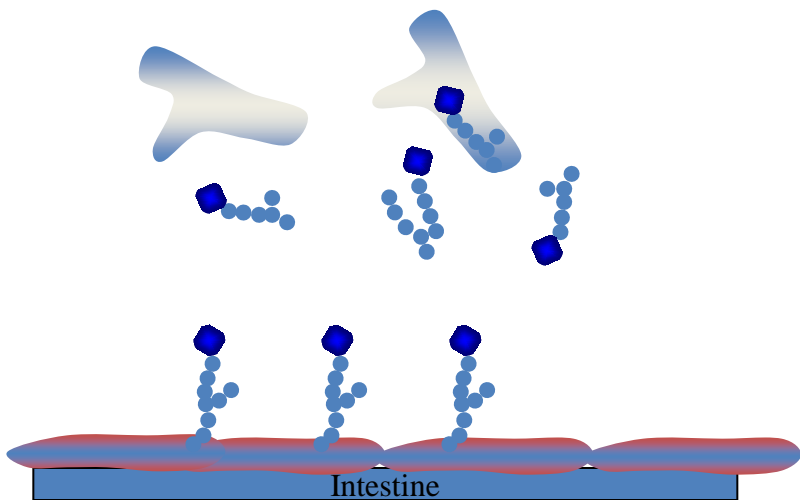
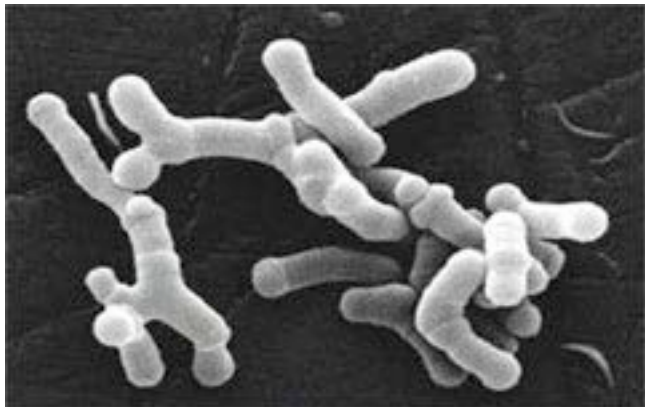
- Characterization of HMO: development of novel analytical technologies and methods



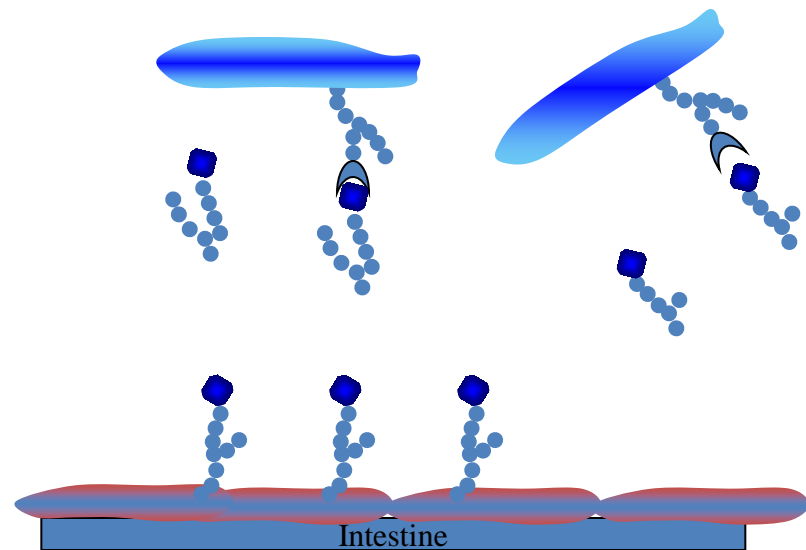
Carlito Lebrilla
Chemistry



Functions of Free Oligosaccharides in Milk



As food for beneficial bacteria
(Prebiotics)

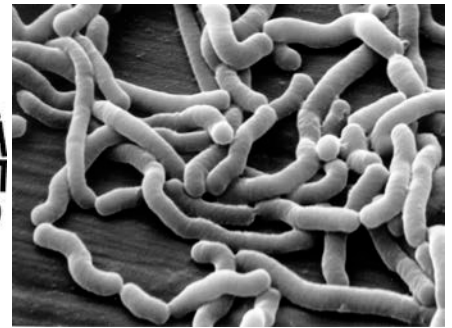


Prevent adhesion
of pathogenic bacteria

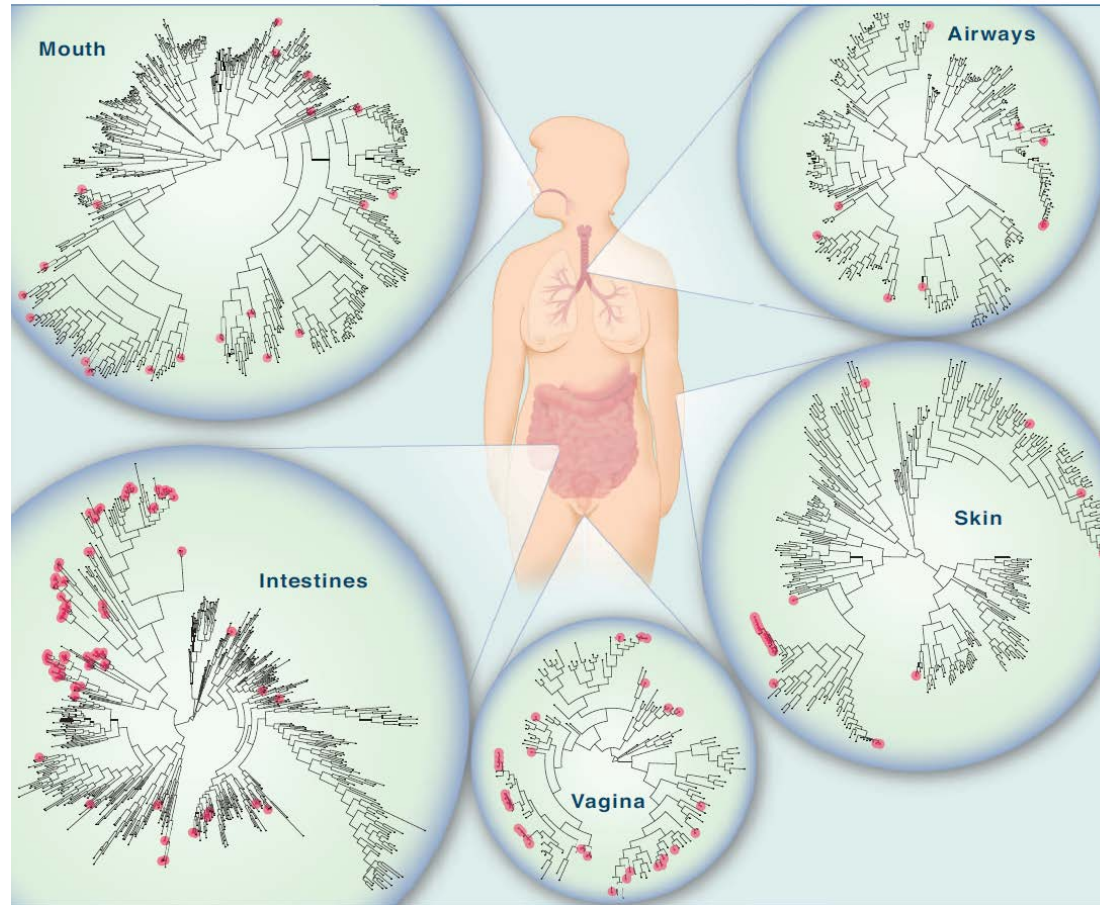
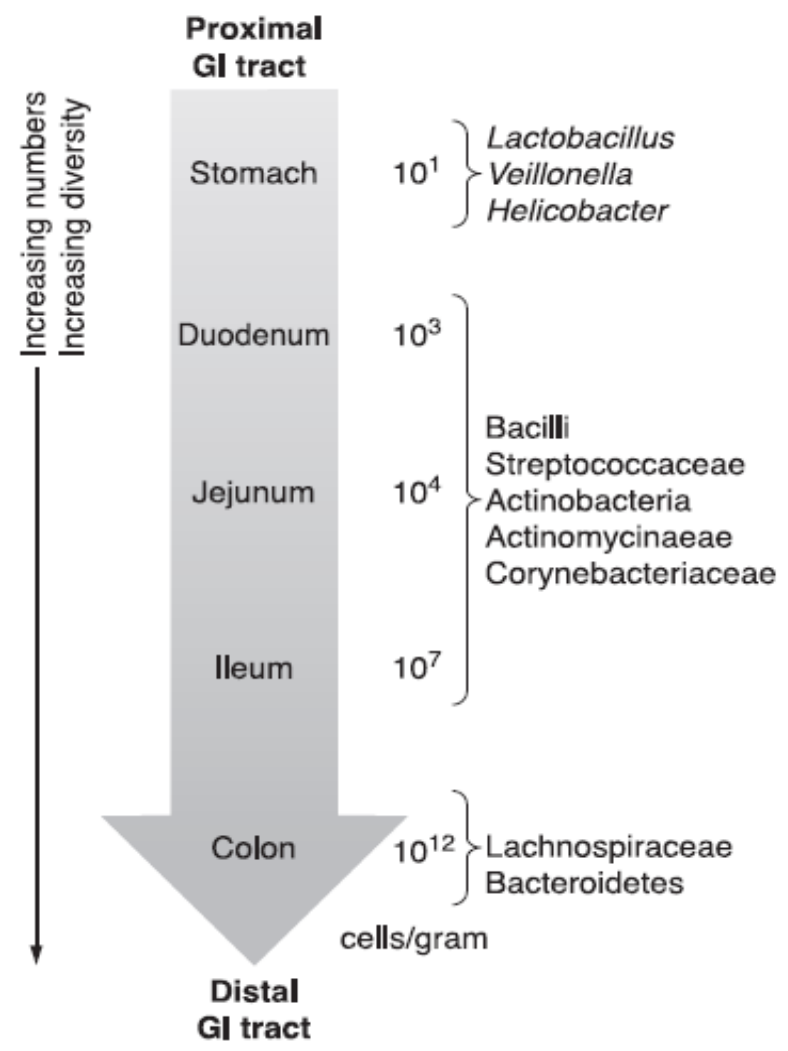
Premature Infants

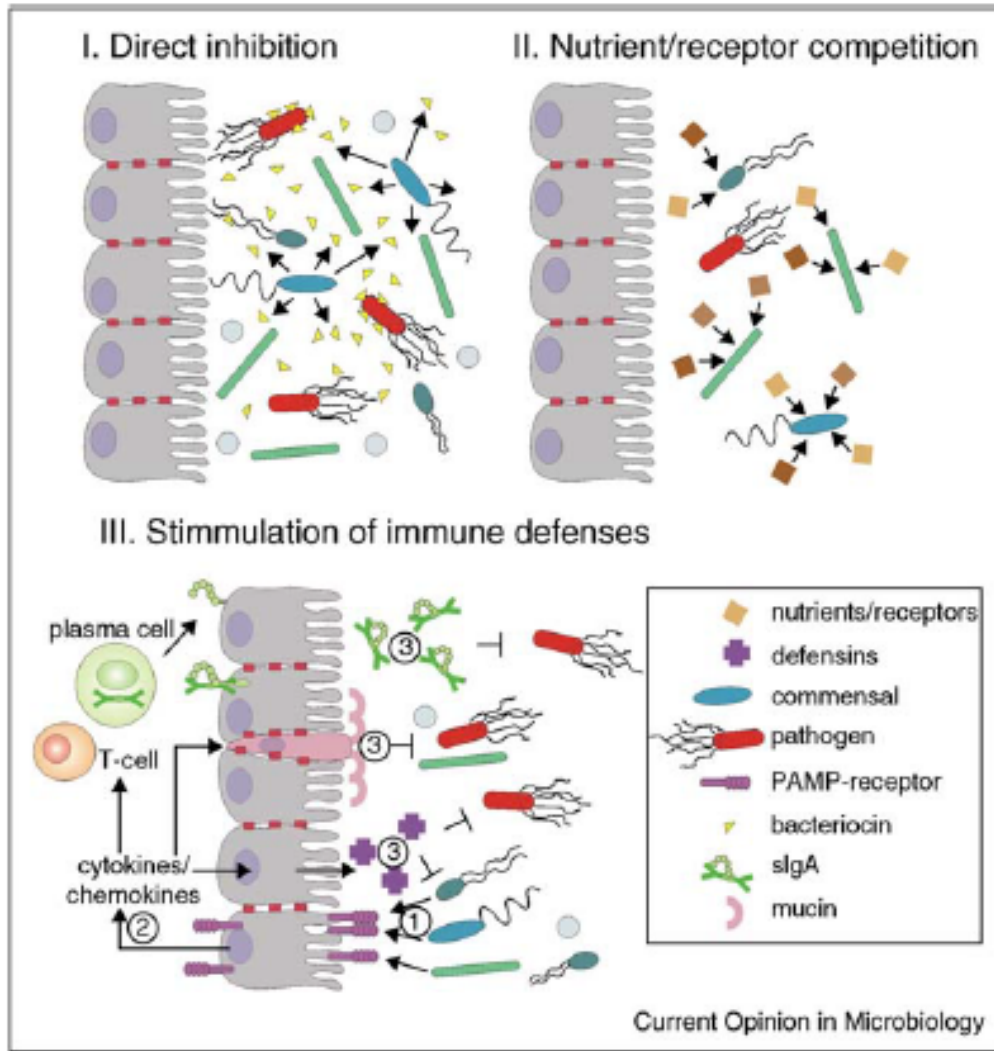
Necrotizing Enterocolitis

Combination of Human milk
oligosaccharides plus
Bifidobacteria longum
subsp. infantis protection,
growth



Function of “Normal” Adult Microbiota?





Immune

- Barrier fortification
- tight junction regulation
- Immune system development

Metabolic

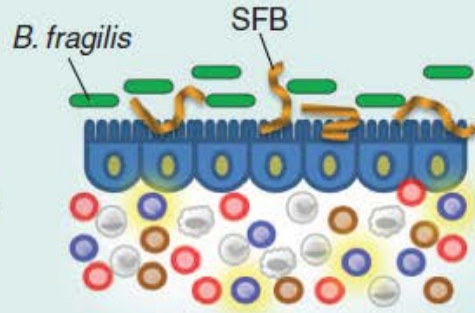
- Synthesize vitamins
- Ferment non-digestible carbohydrates
- Produce SCFA
- Salvage energy
- Facilitate ion absorption
- Metabolize dietary carcinogens

Human microbiome

Human genome

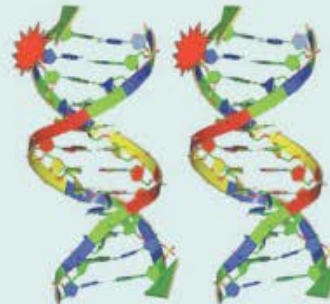
T_H17/Treg profile

A

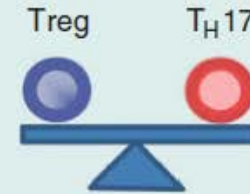


Healthy
microbiome

+

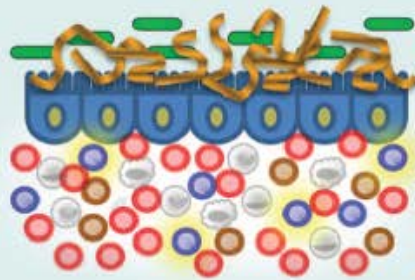


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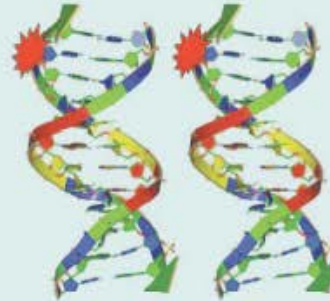
Health

B

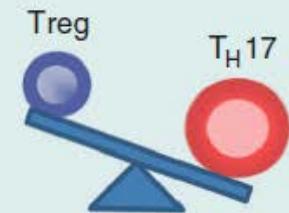


Dysbiosis
(increased pro-
inflammatory
bacteria)

+

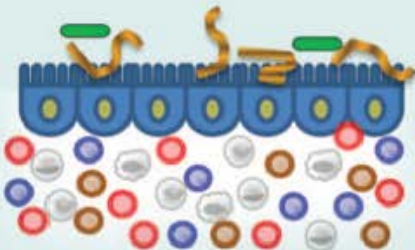


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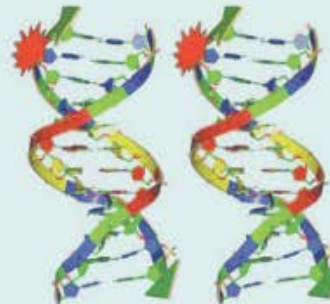
Disease

C

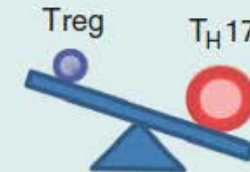


Dysbiosis
(decreased anti-
inflammatory
bacteria)

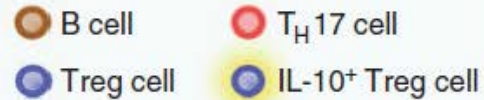
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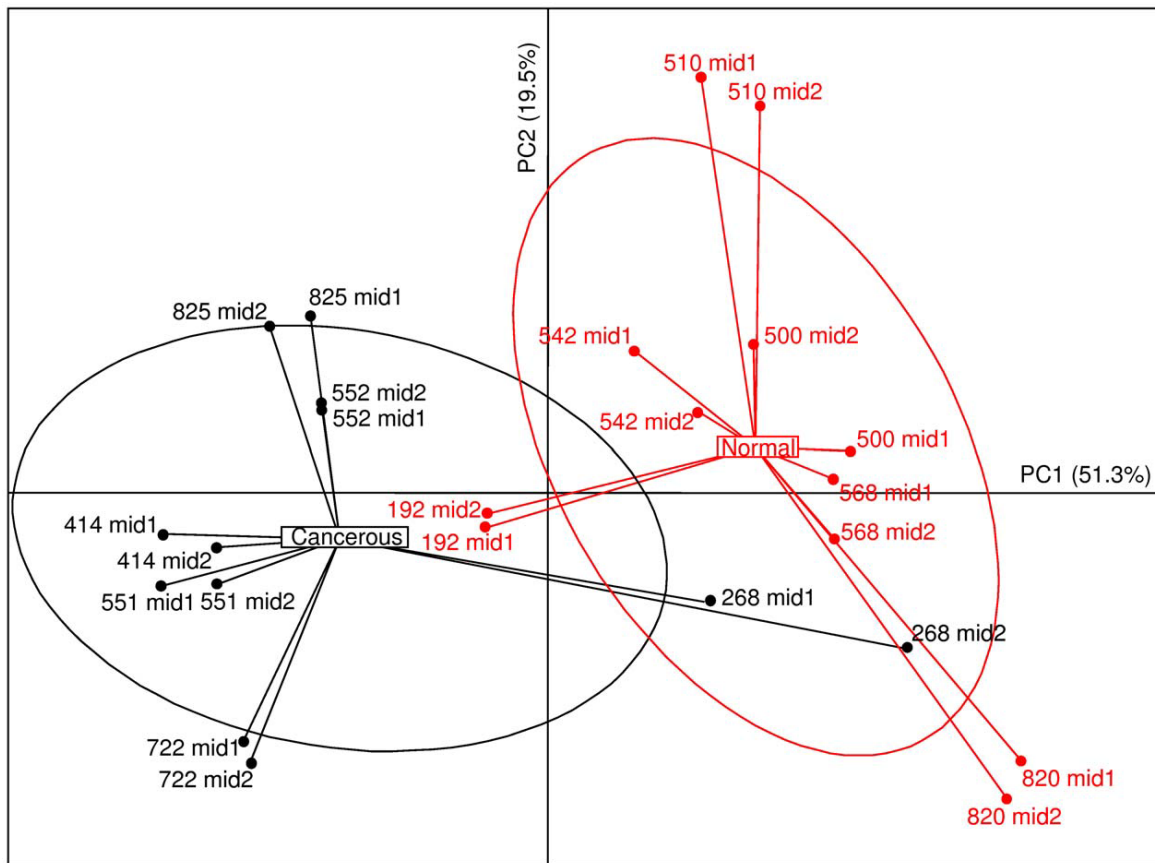
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Disease



Does Gut Dysbiosis Influence the Etiology of Cancer?



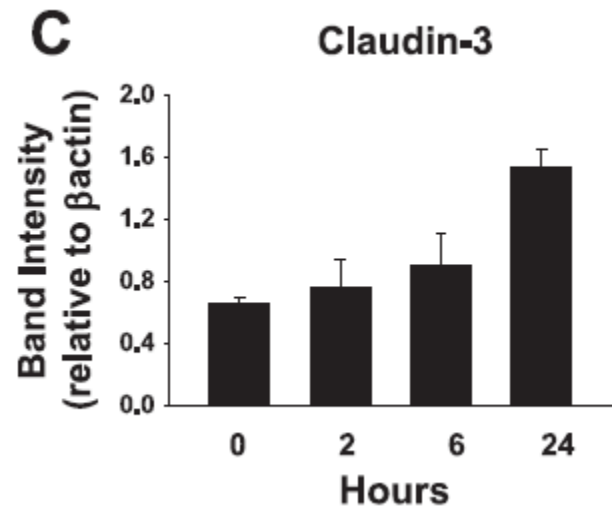
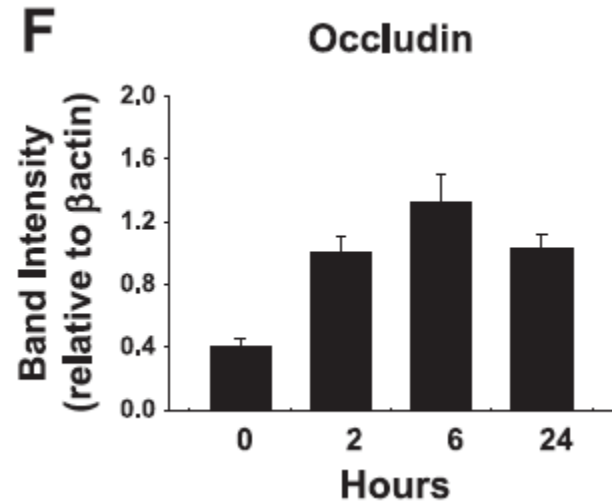
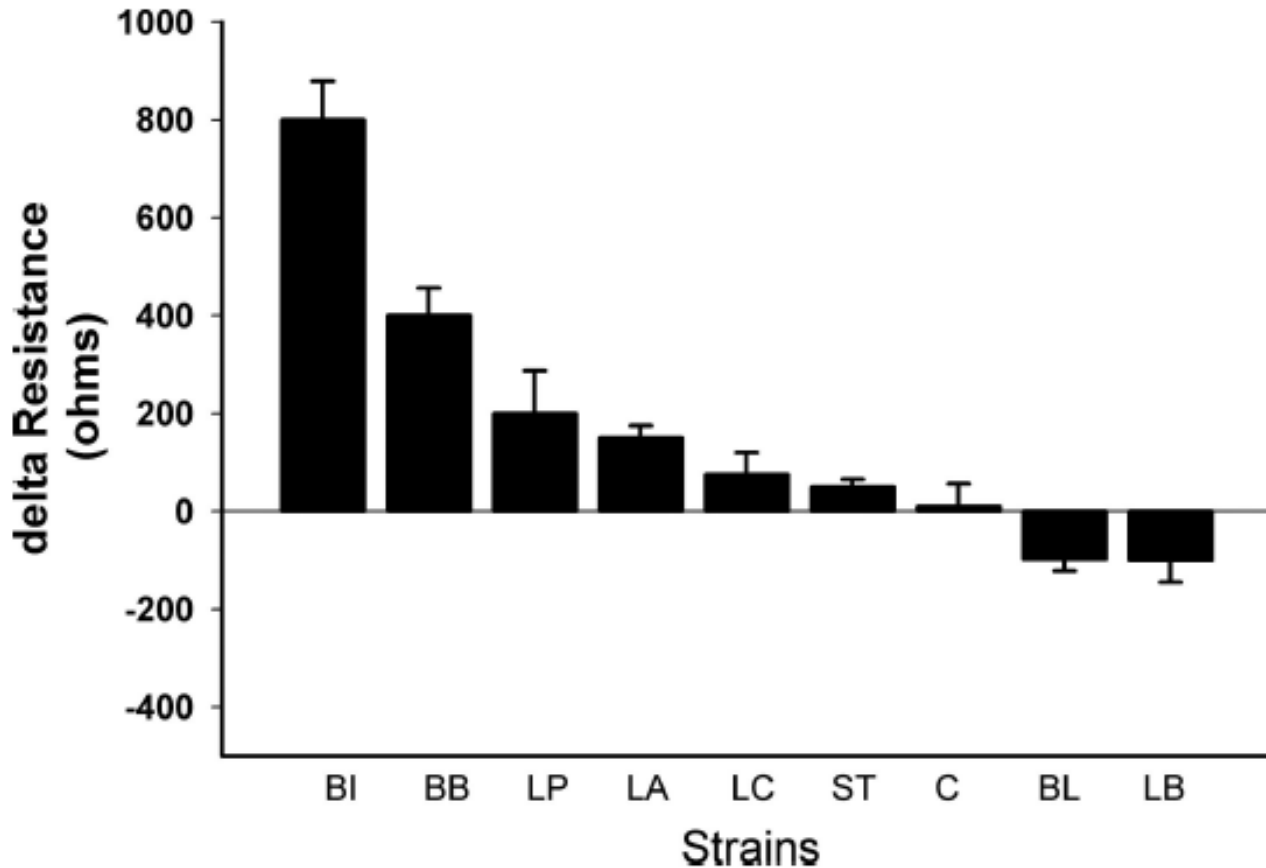
- Pyroseq identified bacterial genera differentiates CRC and healthy controls
- qPCR levels of *Bacteroides/Prevotella* group 5-fold higher in CRC vs. control
- Immunohistochemistry, TH17 reactive cells significantly higher in normal mucosa of cancer patients vs. not detected in healthy controls

How to Modulate Gut Microbiota to Improve Cancer Etiology?

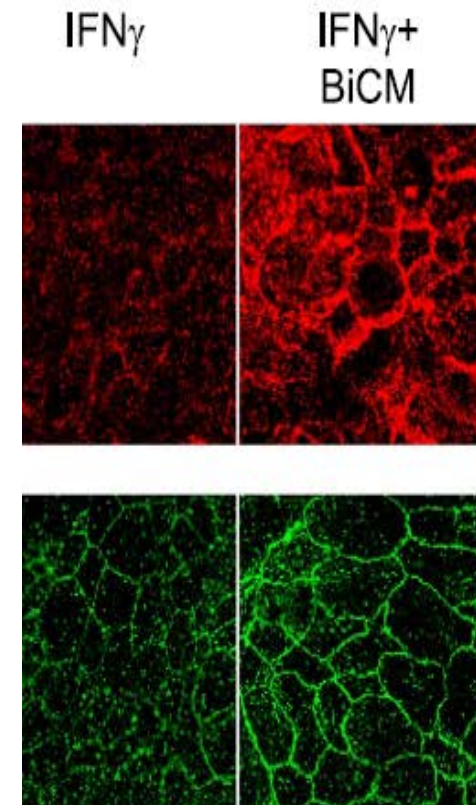
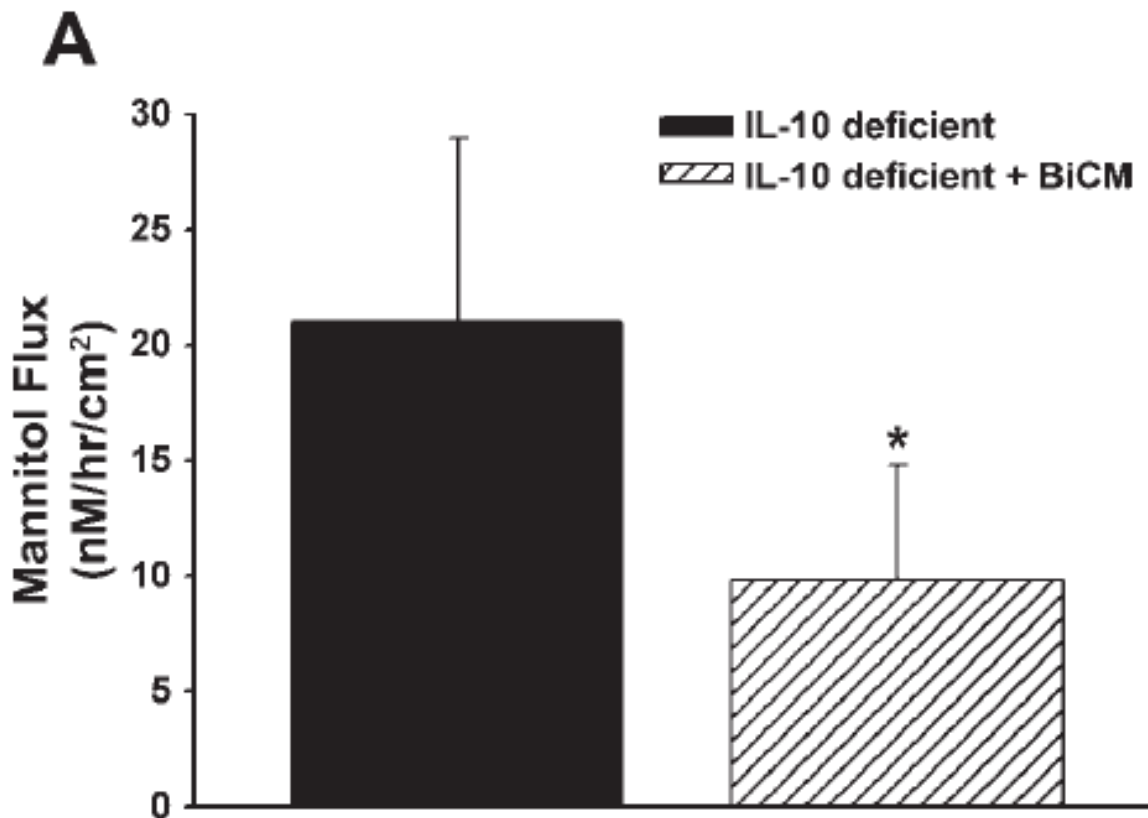
- Double-blind, placebo-controlled trial, n = 490
- Adjuvant postoperative radiation therapy after surgery for sigmoid, rectal, or cervical cancer, randomized, VSL#3 (4.5×10^{11}) or placebo starting from the first day of RT

| Outcome | Placebo | VSL#3 | Significance |
|--------------------------------|--------------|-------------|--------------|
| RT-induced enteritis & colitis | 52% | 32% | $P < 0.001$ |
| Grade 3 or 4 diarrhea | 55% | 1.4% | $P < 0.001$ |
| Daily bowel movements | 14.7 ± 6 | 5.1 ± 3 | $P < 0.05$ |

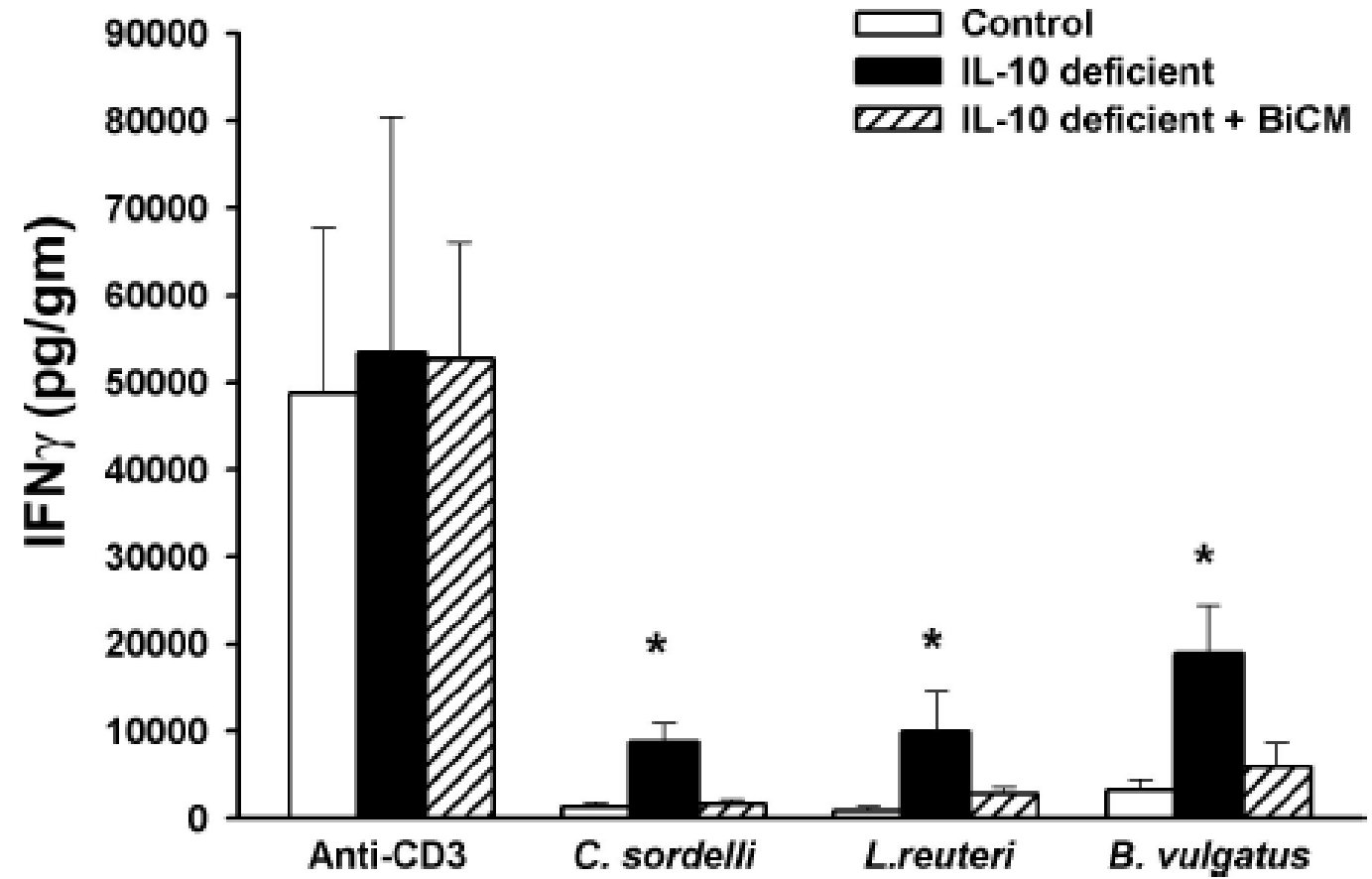
What's in VSL#3



B. *Infantis* Soluble Proteins



B. Infantis Soluble Proteins



How to Hone *B. infantis* Functions?

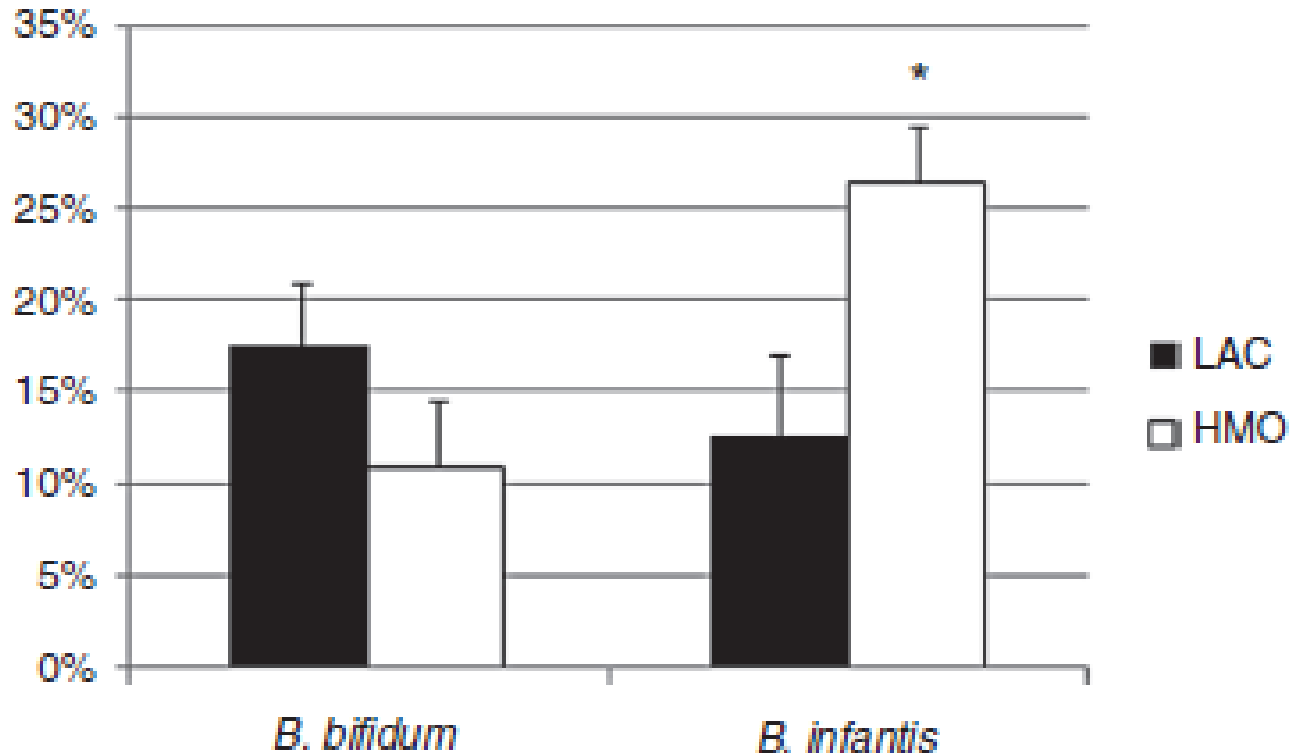
Synbiotics

HMO grown *B. Infantis* Binding

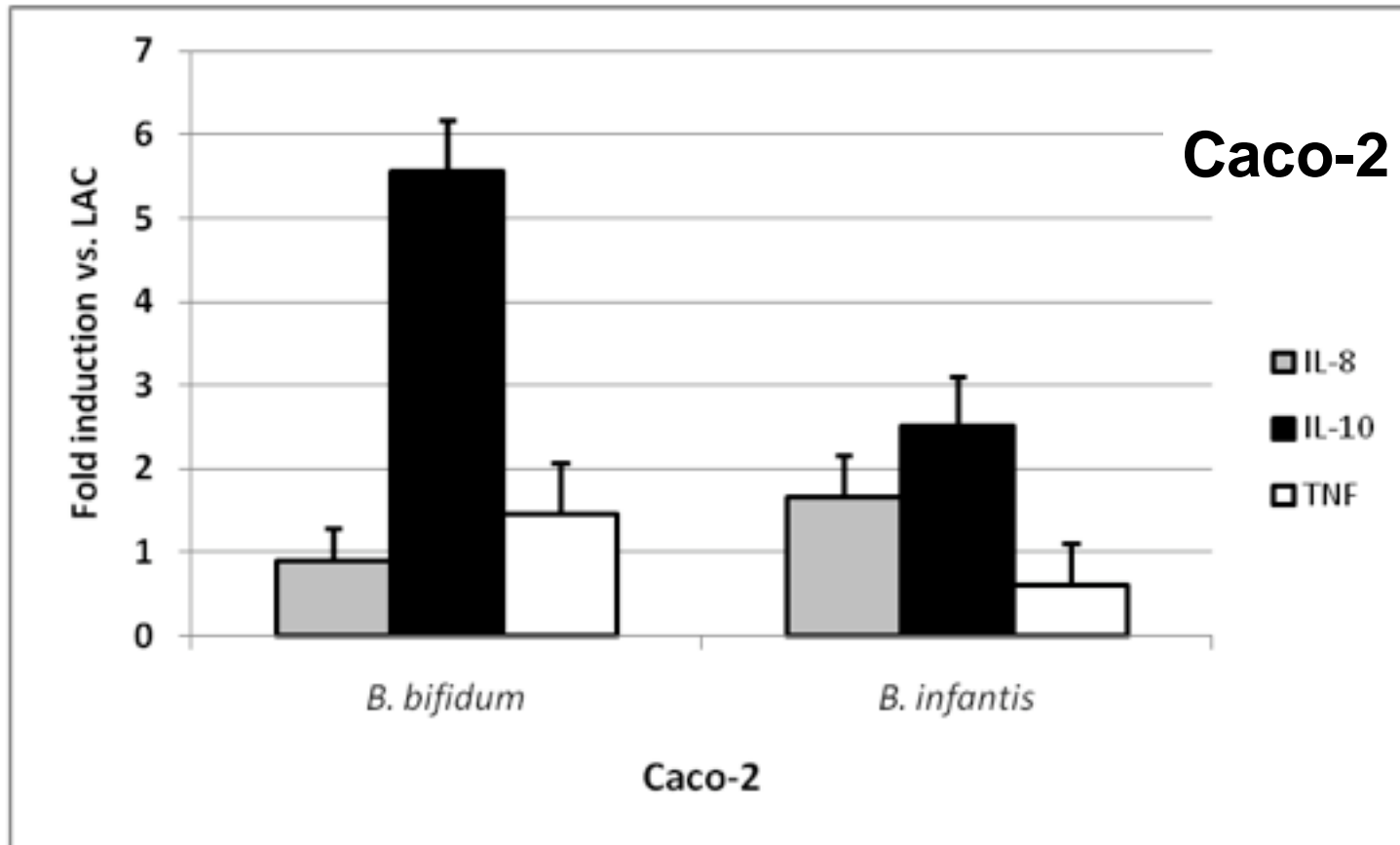


Helen
Raybould
Vet School

HT-29



HMO-grown *B. infantis* adheres better to intestinal cells

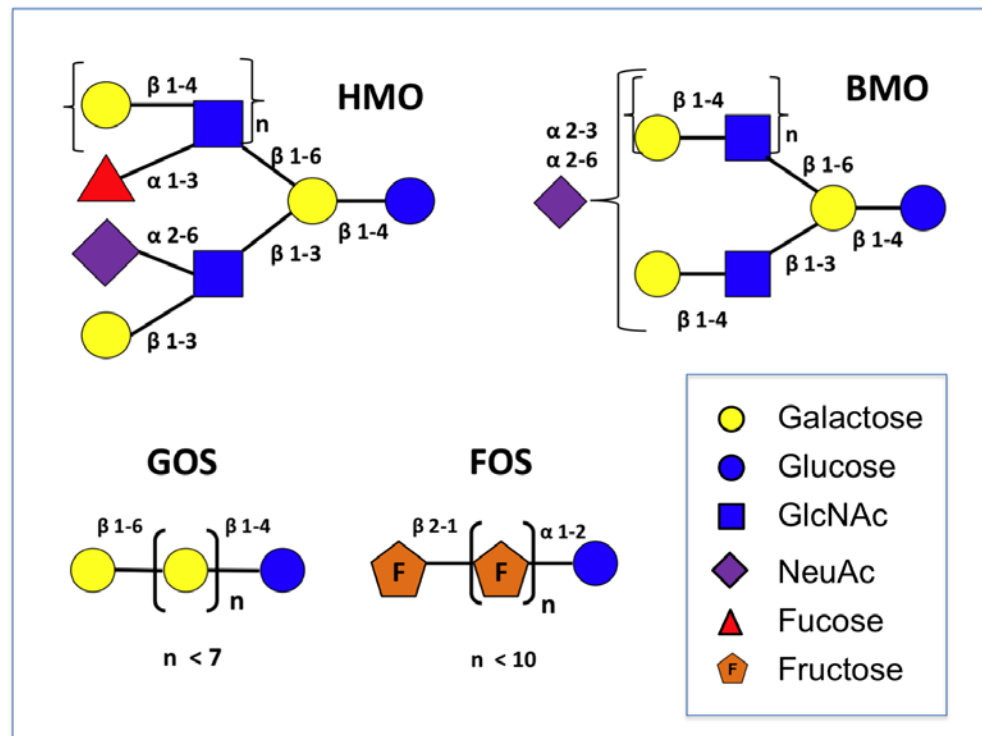


HMO-grown *Bifidobacteria* modulate inflammatory signaling molecules: net anti-inflammatory

- Bovine milk oligosaccharides (BMO):
Translating the benefits of human milk to children, adults, the elderly, cancer patients, ...



Daniela Barile
Food Science



Food grade, pilot scale equipment and facilities for:

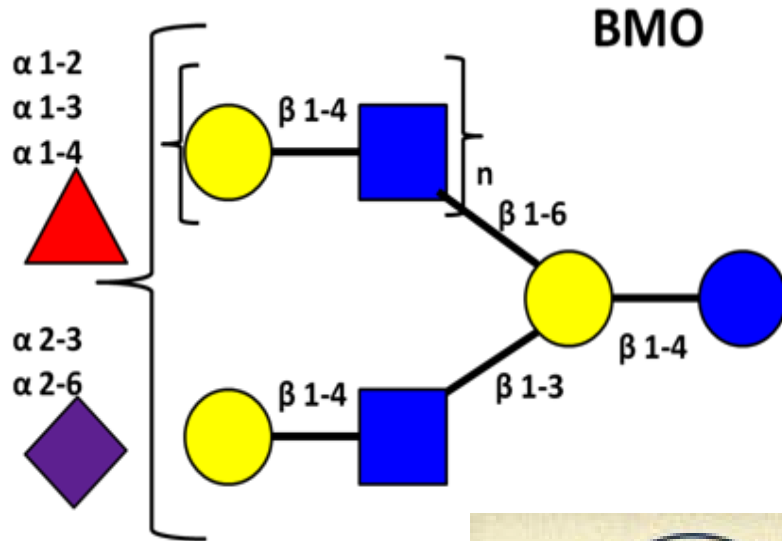
- Testing out new food formulations
- Processing new streams
- Bioactives separation



Daniela Barile
Food Science



Do BMO modulate an adult intestinal microbiota?



- Fecal microbiota Δ
- Metabolomic analyses
- “Well-being”
- Targeting intestinal health



Jennifer Smilowitz
FFHI



Carolyn Slupsky
Nutrition



Daniela Barile
Food Science



Dairy Research Institute

- Improving gut function in cancer patients undergoing Cancer therapy to improve quality of life and increase efficacy of treatment. (RISE, Mucosal Immunity)
- Sensory testing: formulations of bioactives-enriched ice cream



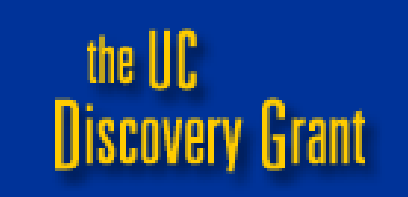
Ralph de Vere White
UCD Cancer Center



- **Safe**--owing 100 million years of testing
- **Selectivity**--leveraging evolutionary relationship *B. infantis* and milk oligosaccharides
- **Effective**-- adheres to epithelial cells, non-motile
- **Translation**--lower incidence of NEC, rotavirus infants
- **Physical Protection**--Prevents pathogens from invading, don't translocate
- **Immune Regulation**--Modulates innate & shapes adaptive immune systems
- **Anti-inflammatory**--Lower regional inflammation



Acknowledgements



National Institute of Allergy and Infectious Diseases
National Institutes of Health



BILL & MELINDA GATES foundation

