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

The UC Davis Foods for Health Institute

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

Oligosaccharides are 3rd most abundant component in human milk

**BUT**

Humans do not have the enzymes to digest them!

1) Lactose 70 g/L
2) Lipids 40 g/L
3) HMO 5–15 g/L
4) Proteins 8 g/L

Why are they there?
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

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?
In the proximal GI tract:
- **Stomach**: $10^1$
  - *Lactobacillus*  
  - *Veillonella*  
  - *Helicobacter*
- **Duodenum**: $10^3$
  - Bacilli
  - *Streptococcaceae*  
  - *Actinobacteria*  
  - *Actinomycinaceae*  
  - *Corynebacteriaceae*
- **Jejunum**: $10^4$
- **Ileum**: $10^7$
- **Colon**: $10^{12}$
  - *Lachnospiraceae*  
  - *Bacteroidetes*

Increasing numbers towards the distal GI tract.

Function of GI 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

Does Gut Dysbiosis Influence the Etiology of Cancer?
GI Dysbiosis in CRC

- 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?
Improving QoL during RT

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>VSL#3</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-induced enteritis &amp; colitis</td>
<td>52%</td>
<td>32%</td>
<td><em>P</em> &lt; 0.001</td>
</tr>
<tr>
<td>Grade 3 or 4 diarrhea</td>
<td>55%</td>
<td>1.4%</td>
<td><em>P</em> &lt; 0.001</td>
</tr>
<tr>
<td>Daily bowel movements</td>
<td>14.7 ± 6</td>
<td>5.1 ± 3</td>
<td><em>P</em> &lt; 0.05</td>
</tr>
</tbody>
</table>

What’s in VSL#3

B. *Infantis* Soluble Proteins

![Graph showing Mannitol Flux](image)

**Graph Legend**
- **IL-10 deficient**
- **IL-10 deficient + BiCM**

**Images**
- IFNγ
- IFNγ + BiCM

*Ewaskchuk, Am. J. Physiol. Gastrointestinal Liver Physiol. 2008*
B. Infantis Soluble Proteins

How to Hone B. *infantis* Functions?

Synbiotics
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
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
FFHI Synbiotics Approach

- **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