Microbiome: DDW 2015 update

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**Financial Interest Disclosure**
(over the past 24 months)

Name: Dr. P Bercik

<table>
<thead>
<tr>
<th><strong>Commercial Interest</strong></th>
<th><strong>Relationship</strong></th>
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</thead>
<tbody>
<tr>
<td>Nestec Switzerland</td>
<td>Research support</td>
</tr>
<tr>
<td>Janssen Canada</td>
<td>advisory board</td>
</tr>
<tr>
<td>Forest Laboratories Inc Canada</td>
<td>advisory board</td>
</tr>
</tbody>
</table>
Speaker **David Morgan** perceives no conflict of interest with this presentation but has worked with or consulted for:

**Speaker Bureau:**
Pfizer, Merck, Astra Zeneca, Altana, Abbott, Janssen Ortho (JOI), Negma, Novartis, Scherring, Axcan, Wyeth, Proctor & Gamble, Solvay, Takeda, Johnson & Johnson, Forest Laboratories, Abbvie

**Consultant:**
Pfizer, Merck, Astra Zeneca, Altana, Abbott, Janssen Ortho (JOI), Negma, Novartis, Scherring, Axcan, Wyeth, Proctor & Gamble, Solvay, Ferring, Takeda, Johnson & Johnson, Shire, Kellog’s, Forest Laboratories, Abbvie, Astra, Apotex

**Research Funding:**
Heart and Stroke Foundation, Astra, JOI, Altana, Novartis, Pfizer, Negma, Aptalis,
CanMEDS Roles Covered:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Medical Expert</td>
<td>as <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS framework.</td>
</tr>
<tr>
<td>Communicator</td>
<td>as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.</td>
</tr>
<tr>
<td>Collaborator</td>
<td>as <em>Collaborators</em>, physicians effectively work within a healthcare team to achieve optimal patient care.</td>
</tr>
<tr>
<td>Manager</td>
<td>as <em>Managers</em>, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.</td>
</tr>
<tr>
<td>Health Advocate</td>
<td>as <em>Health Advocates</em>, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.</td>
</tr>
<tr>
<td>Scholar</td>
<td>as <em>Scholars</em>, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.</td>
</tr>
<tr>
<td>Professional</td>
<td>as <em>Professionals</em>, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.</td>
</tr>
</tbody>
</table>
OAG Post DDW (LA) 2006: Ulcerative Colitis

- Treatment
- Probiotics
  - Martinez (M1738)
    - Unstable Fecal Microbiota in UC
Metabolic profiles in IBD

- Stool samples (n=90) from 21 pediatric patients (in remission) and 69 first-degree relatives

- Samples analysed by 16S sequencing (Illumina HiSeq) and mass spectrometry (Q-TOF Premier): enterotypes and metabotypes based on their microbiota and metabolomic profile.

- Multivariate models incorporating gender, ethnicity, mode of delivery, anti-TNF therapy and family

- The IBD-associated enterotype had increased Lachnospiraceae (Blautia, [Ruminococcus]) and decreased Ruminococcaceae (Faecalibacterium, Ruminococcus)
The metabolome refers to the complete set of small-molecule chemicals found within a biological sample. The Human Metabolome Database (HMDB) is currently the most complete and comprehensive curated collection of human metabolite and human metabolism data in the world. It contains records for more than 2180 endogenous metabolites.
- Gender, age, race identification
- Biorythmic processes analysis
- Obesity-linked responses analysis
- Dietary sources classification
- Intake amount estimation
- Metabolizer types identification

**METABOTYPE CRITERIA:**
- Presence-Absence of Metabolites
- Concentration Levels
- Ratios between Metabolites’ levels
- Profiling of Metabolites’ sets

- Environmental conditions deduction
- Biological signals interpretation
- Geographic origins control
- Chemotaxonomical analysis
- Diseases determination
- Intoxication sources identification
- Doping detection
Metabolic profiles in IBD

- Enterotype and metabotype were associated with disease state \((p<10^{-6})\) and with one another.

- Family status had a statistically significant effect on metabotype in healthy individuals \((p=0.008)\)

<table>
<thead>
<tr>
<th>Metabotype</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>0</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>UC</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-IBD</td>
<td>30</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

\(p = 1 \times 10^{-6}\)

- #3: reduced levels of glutamate, tryptophan, and tyrosine
- #2: reduced valine and phenylalanine

#1010 Jacobs et al. Disease-associated enterotypes and metabotypes in families with pediatric inflammatory bowel disease
Metabolic profiles in IBD

The bacterial metabolomic profile appears to have higher predictive value for IBD than the genetic predisposition.

#1010 Jacobs et al. Disease-associated enterotypes and metabotypes in families with pediatric inflammatory bowel disease
Microbiota and recurrence of Crohn’s disease

• 141 mucosal samples from 34 Crohn’s patients at resection (baseline) and from the ileum and anastomosis at colonoscopy 6 and/or 18 months post-op.

• 28 control samples: 12 colonic samples from healthy patients (healthy controls) and 16 ileal and anastomosis samples from 8 patients with colon cancer (surgical controls)

• Mucosal microbiota 16S ribosomal profiling performed using the MiSeq Illumina.

• Patients post-op treated with metronidazole ± thiopurine ± adalimumab
Microbiota and recurrence of Crohn's disease

#264 Wright et al. What Causes Recurrence of Crohn's Disease After Intestinal Resection? A Prospective Evaluation of Microbiota, Smoking and Anti-TNF Therapy. Results from the POCER Study.
Microbiota and recurrence of Crohn’s disease

• Crohn’s disease was associated with reduced bacterial diversity when compared to healthy controls BUT NOT surgical controls (Shannon Diversity).

• Bacterial composition (beta diversity) differed significantly between Crohn’s disease and both healthy (p=0.024) and surgical (p=0.038) controls.

• The profiles within Crohn’s patients changed over time, but did not differ significantly between those with and without endoscopic recurrence.

→ No specific bacterial signature to predict recurrence.
Microbiota and recurrence of Crohn’s disease

- Recurrence associated with increased Proteus (p=0.019) and decreased genera from the Firmicutes phylum including Faecalibacterium (p=0.004).

- No effect of anti-TNF on microbial composition

Surgical resection alone may be responsible for some, but not all, of the taxonomic differences observed in patients following intestinal resection in Crohn’s disease
Microbiota and colon CA

#208 O’Keefe. Colonic Metabolites and Cancer Risk

Courtesy of Stephen JD O’Keefe, Pittsburgh, USA
Microbiota and colon CA

• Products of bacterial metabolism:

• Possibly harmful:
  – H₂ and H₂S
  – Secondary bile acids
  – Toxins and pro-inflammatory metabolites

• Possibly beneficial:
  – SCFA: mainly butyrate
  – Methane
  – Polyphenols et vitamins
  – Anti-inflammatory metabolites

#208 O’Keefe. Colonic Metabolites and Cancer Risk

Courtesy of Stephen JD O’Keefe, Pittsburgh, USA
Microbiota and colon CA

- 20 African-American adults (Pittsburgh) admitted to the hospital for 2 wks and kept on African diet
- 20 African adults kept in a camp (Africa) on Western (American) diet for 2 wks
- Coloscopy before and after

#208 O’Keefe. Colonic Metabolites and Cancer Risk

Courtesy of Stephen JD O’Keefe
• In 2 weeks there was an up-regulation of certain biomarkers related to colon CA: Ki67 proliferation marker, CD68+ cells and intra-epithelial lymphocytes

• American diet decreased butyrate levels by 50% and increased the secondary bile acids level by 400 %

#208 O’Keefe. Colonic Metabolites and Cancer Risk  Courtesy of Stephen JD O’Keefe
Microbiota and colon CA

- There was a significant change in the gut microbiota profiles
- Increase in *Bilophila wadsworthia* (bile acid metabolism)
- Decrease in *Desulfo bacter hydrogenophilus* (sulphate reducer)

There appears to be a strong association between diet, microbiota and risk factors of colon CA
Microbiota and colon CA

• The Yup’ik people from Southwest Alaska have one of the highest reported prevalence of colon cancer (>100:100,000) in the world.

• Their diet is dominated by fish, marine and land mammals, and is severely deficient in fruit, vegetables & grains.

• Fecal samples from 10 healthy Yup’ik people, 12 low risk of CA rural Africans and 12 high risk African Americans (Pittsburgh) were tested for SCFA and bile acids by HPLC-MS.
#508 Sevco et al. Association Between Low Fecal Short-Chain Fatty Acids, High Fecal Bile Acids and the High Colon Cancer Risk of the Yup'ik Alaska Native People

## Microbiota and colon CA

<table>
<thead>
<tr>
<th>Population</th>
<th>Acetic Acid</th>
<th>Propionic Acid</th>
<th>Butyric Acid</th>
<th>Deoxycholic Acid</th>
<th>Lithocholic Acid</th>
</tr>
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<tbody>
<tr>
<td>Yup'ik</td>
<td>68.0*</td>
<td>11.3**</td>
<td>9.1**</td>
<td>201.6*</td>
<td>68.1*</td>
</tr>
<tr>
<td>Native Africans</td>
<td>123.6</td>
<td>31.1</td>
<td>21.6</td>
<td>7.3</td>
<td>1.8</td>
</tr>
<tr>
<td>African Americans</td>
<td>60.6</td>
<td>11.0</td>
<td>11.1</td>
<td>37.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>
Microbiota and colon CA

The extremely high colon cancer risk seen in the Yup’ik Alaska Native population may be a consequence of their high fat, low fiber diet mediated by increased fecal secondary bile acid levels and SCFA deficiencies.
Microbiota and IBS

• Non-systematic review of the literature

• 18 case controls studies

• Evaluating 782 subjects

• All studies positive showing differences in microbiome between IBS and healthy controls
## Microbiota and IBS

<table>
<thead>
<tr>
<th>Author</th>
<th>Controls</th>
<th>IBS</th>
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</thead>
<tbody>
<tr>
<td>Jalanka-Tojuinen</td>
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<td>23</td>
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<tr>
<td>Matto</td>
<td>27</td>
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<td>Majkonen</td>
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<tr>
<td>Codling</td>
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<td>Rajilic-Stojanovic</td>
<td>46</td>
<td>62</td>
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<td>Saulnier</td>
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<tr>
<td>Malinen</td>
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<tr>
<td>Rigsbee</td>
<td>22</td>
<td>22</td>
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<tr>
<td>Lyra</td>
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<td>Kassinen</td>
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<td>Krogius-Kurikka</td>
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<td>Maccaferri</td>
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<tr>
<td>Duboc</td>
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</tr>
<tr>
<td>Carroll</td>
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<tr>
<td>Chassard</td>
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<tr>
<td>Durban</td>
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</tr>
</tbody>
</table>

#579 Moayyedi P. IBS: Is it Caused by Dysbiosis? Courtesy of P. Moayyedi
Microbiota and IBS

- 50% of studies stated diversity *increased* in IBS
- 50% of studies stated diversity *decreased* in IBS

#579 Moayyedi P. IBS: Is it Caused by Dysbiosis? Courtesy of P. Moayyedi
Bacteria altered in IBS: no clear signature

- Bacteroides fragilis
- Bacteroides ovatus
- Bacteroides uniformis
- Bacteroides caccae
- Prevotella ruminicola
- Clostridium difficile
- Faecalibacterium prausnitzii
- Clostridium leptum
- Clostridium difficile
- Bifidobacterium breve
- Ruminococcus callidus
- Clostridium nexile
- Prevotella oralis
- Clostridium cellulosi
- Bacteroides vulgaris
- Clostridium orbiscindens
- Bacteroides stercoris
- Clostridium symbiosum
- Bacteroides intestinalis
- Bacteroides stercoris
- Lactobacillus salviarius
- Clostridium thermosuccinogenes
- Eubacterium rectale
- Bifidobacterium breve
- Ruminococcus gnavus
- Bacillus cereus
- Ruminococcus bromii
- Bifidobacterium adolescents
- Bacteroides salyersiae
- Prevotella tannerae
- Prevotella tannerae
- Lactobacillus buchnerri
- Ruminococcus lactis
- Enterococcus faecium

increased
decreased

#579 Moayyedi P. IBS: Is it Caused by Dysbiosis? Courtesy of P. Moayyedi
Microbiota and IBS

- There are controversial results on microbial signatures in IBS, likely due to low numbers of subjects studied (chance) and different methods used.

- It is likely the altered function of the microbiota which contributes to gut dysfunction in IBS.

#579 Moayyedi P.  IBS: Is it Caused by Dysbiosis?
Take home message

- Microbiota seems to play an important role in many GI diseases, including IBD and colon CA
- However, the exact mechanisms underlying its effects are still unknown
- Bacterial metabolome may be more important than the bacterial profiles
- The currently available data should be scrutinized with “healthy scepticism”
Thank you