Microbiome-based approach to personalized medicine

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Director, Edmonton FMT program
University of Alberta
Nov 3, 2018
Objectives

• Review the microbiome in IBD
• Discuss manipulation of the microbiome through fecal microbiota transplantation (FMT) for therapeutic effect from both the theoretical and clinical standpoint
• Examine utility of microbial signatures in precision medicine
IBD pathogenesis

Dysbiosis

Over 200 genes associated with IBD
NOD2, ATG16, IL-23R

Luminal microbial antigens and adjuvants
Genetic susceptibility
Environmental triggers
Immune response

Increased pro-inflammatory cytokines – TNFα, IFNγ, IL-6
Decrease in regulatory immune cells

NSAIDS, smoking, diet
Intestinal microbiome

• Dysbiosis in itself is insufficient to cause IBD
• Most studies examine stool microbiome
  • Differs from mucosal microbiome
• Most studies focus on bacteria
  • Intestinal microbiome includes fungiome and virome
• Most studies focus on composition analysis using 16S rRNA
  • Does not provide strain level detail or function information
• Few studies are longitudinal in nature or take diet/medications into consideration
1. Intestinal (fecal) microbiome in IBD
IBD microbiome

• Reduced diversity and altered composition
• Alteration may precede the development of IBD
• Dysbiosis may lead to metabolic pathway disruption and increased inflammation
  • Reduced short chain fatty acid production
  • Increased relative abundance of *Desulfovibrio* and *Bilophila wadsworthia* in UC → Increased H$_2$S production
  • *Reduced relative abundance of Faecalibacterium prausnitzii* in UC and CD: anti-inflammatory properties
IBD microbiome

• Bacteriophages may play a role in intestinal dysbiosis and inflammation
• Increased abundance of *Aspergillus clavatus* and *Cryptococcus neoformans* are seen in active inflammation
• CD more unstable microbiome compared to UC
• Active vs quiescent CD have different microbiome
• Ileal CD has different microbiome compared to colonic CD
2. Manipulation of microbiome through FMT in IBD
FMT is highly effective for recurrent Clostridioides difficile infection (RCDI)
Fecal microbiota transplantation (FMT) for IBD

• Tempting to extrapolate from RCDI
  • IBD is much more complicated than RCDI

• Concurrent IBD and RCDI
  • FMT is as effective at treating RCDI in IBD and non-IBD patients
  • Effect of FMT on IBD is somewhat unpredictable
    • Improvement: 20-30%
    • Exacerbation: 15-20%
### 4 RCT: FMT vs control in mild to moderate UC

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>N (FMT: control)</td>
<td>48 (23:25)</td>
<td>75 (38:37)</td>
<td>81 (41:40)</td>
<td>73 (38:35)</td>
</tr>
<tr>
<td>Control</td>
<td>Autologous stool</td>
<td>Water</td>
<td>Saline</td>
<td>Autologous stool</td>
</tr>
<tr>
<td>Biologics</td>
<td>no</td>
<td>permitted</td>
<td>no</td>
<td>permitted</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Remission (SCCAI ≤ 2 + and ≥ 1 point reduction in Mayo endo score) @ wk 12</td>
<td>Remission (Mayo score &lt; 3 + Mayo endo score=0) @ wk 7</td>
<td>Steroid free remission + endoscopic response or remission (total Mayo &lt; 2 + endoscopic Mayo reduction by ≥1 point) @ wk 8</td>
<td>Steroid free remission (Mayo ≤ 2 + endo Mayo ≤ 1) @ week 8</td>
</tr>
</tbody>
</table>
## Differences in FMT protocols

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery route</strong></td>
<td>Nasoduodenal tube</td>
<td>enema</td>
<td>Colonoscopy + enema</td>
<td>Colonoscopy + enema</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>2 Rx</td>
<td>weekly x 6 weeks</td>
<td>5 Rx/week x 8 weeks</td>
<td>3 Rx</td>
</tr>
<tr>
<td><strong>Donor stool wt/Rx</strong></td>
<td>120 g</td>
<td>8 g</td>
<td>37.5 g</td>
<td>50 g (colonoscopy) 24 g (enema)</td>
</tr>
<tr>
<td><strong>FMT processing</strong></td>
<td>Aerobic</td>
<td>Aerobic</td>
<td>Aerobic</td>
<td>Anaerobic</td>
</tr>
<tr>
<td><strong>Fresh vs frozen</strong></td>
<td>Fresh</td>
<td>Fresh + frozen</td>
<td>Frozen</td>
<td>Frozen</td>
</tr>
<tr>
<td><strong>FMT additive</strong></td>
<td>Nil</td>
<td>Nil</td>
<td>Glycerol</td>
<td>Glycerol</td>
</tr>
<tr>
<td><strong># Stool donor</strong></td>
<td>Single</td>
<td>Single</td>
<td>Pooled (3-7)</td>
<td>Pooled (3-4)</td>
</tr>
<tr>
<td><strong>Clinical response</strong></td>
<td>7/23 (30%) vs 5/25 (20%), p=0.51</td>
<td>9/38 (24%) vs 2/37 (5%), p= 0.03</td>
<td>11/41 (27%) vs 3/40 (8%), p= 0.02</td>
<td>12/38 (32%) vs 3/35 (9%), p&lt; 0.01</td>
</tr>
</tbody>
</table>
# Systematic review: FMT in UC remission

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Donor transplant</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>7</td>
<td>23</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Moayyedi 2015</td>
<td>9</td>
<td>38</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>Paramsothy 2017</td>
<td>11</td>
<td>41</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Costello 2017</td>
<td>12</td>
<td>38</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>140</td>
<td></td>
<td>137</td>
</tr>
<tr>
<td>Total events</td>
<td>39</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.00; \chi^2 = 1.70, df = 3 (P=.64); I^2 = 0$

Test for overall effect: $Z = 3.63 (P=.0003)$

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Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody
Systematic review: safety profile

• Overall well tolerated
• Self limited GI complaints
• Worsening colitis: 3/140 in FMT group vs 4/137 in placebo group
Microbial changes following FMT for UC

<table>
<thead>
<tr>
<th>Study and sequencing type</th>
<th>Bacterial changes in UC patients relative to donors</th>
<th>Bacterial changes associated with response</th>
<th>Bacterial changes associated with nonresponse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossen et al.\textsuperscript{38}</td>
<td>↑Bacteroidetes, Bacilli, Proteobacteria and Clostridium clusters IX and XI ↑Clostridium clusters IV, XIVa and XVIII No difference in diversity</td>
<td>↑Diversity in responders post-FMT ↑Clostridial clusters IV, XIVa and XVIII ↓Bacteroidetes</td>
<td>No change in diversity post-FMT</td>
</tr>
<tr>
<td>Phylogenetic microarray (HITChip) analysis of 16s ribosomal RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moayyedi et al.\textsuperscript{37}</td>
<td></td>
<td>Change in microbiota closer to donor profile Lachnospiraceae, Ruminococcus</td>
<td></td>
</tr>
<tr>
<td>16s ribosomal RNA sequencing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paramsothy et al.\textsuperscript{39}</td>
<td></td>
<td>Clostridium cluster IV, XVIII, Ruminococcus, Barnesiella spp, Blautia spp, Dorea spp, Parabacteroides spp</td>
<td>Fusobacterium spp and Sutterella spp</td>
</tr>
<tr>
<td>16s ribosomal RNA sequencing</td>
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Lancet 2017; 389: 1218-28
Most responders received FMT from donor B.
Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

Niv Zmora,1,2,11 Gili Zilberman-Schapia,1,11 Jotham Suez,1,11 Uria Mor,1,11 Mally Dori-Bachash,1 Stavros Bashiarides,1 Eran Kotler,3,4 Maya Zur,1 Dana Regev-Lehavi,1 Rotem Ben-Zeev Brik,1 Sara Federici,1 Yotam Cohen,1 Raquel Linevisky,1 Daphna Rothschild,3,4,11 Andreas E. Moor,3 Shani Ben-Moshe,3 Alon Harmelin,3 Shalev Itzkovitz,3 Nitsan Mahershak,3,7,11 Oren Shibolet,3,6,8 Hagit Shapiro,1 Meirav Pevsner-Fischer,1 Itai Sharon,9,10 Zamir Halpern,6,7,8,12,13 Eran Segal,3,4,12,13 and Eran Elinav1,12,13,17
Probiotics spp detected in stool samples of all human participants

Probiotics spp detected only in colonic mucosa of permissive humans

<table>
<thead>
<tr>
<th>Probiotics species</th>
<th>Probiotics</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>During</td>
<td>After</td>
</tr>
<tr>
<td>BBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBR</td>
<td>*</td>
<td></td>
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<tr>
<td>BIN</td>
<td></td>
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<tr>
<td>BLO</td>
<td></td>
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<tr>
<td>LAC</td>
<td>*</td>
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<tr>
<td>LCA</td>
<td>*</td>
<td></td>
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<tr>
<td>LLA</td>
<td>*</td>
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<tr>
<td>LPA</td>
<td>*</td>
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<tr>
<td>LPL</td>
<td>*</td>
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<tr>
<td>LRH</td>
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<td></td>
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<tr>
<td>STH</td>
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Cell 174, 1388–1405, September 6, 2018 © 2018 Elsevier Inc.
Differential host gene transcriptome
Effective fecal microbiota transplantation for recurrent *Clostridioides difficile* infection in humans is associated with increased signalling in the bile acid-farnesoid X receptor-fibroblast growth factor pathway

Tanya Monaghan**, Benjamin H Mullish ^b^*, Jordan Patterson^c^, Gane KS Wong ^c,d,h^, Julian R Marchesi ^b,e^, Huiping Xu^i^, Tahseen Jilani ^g^, and Dina Kao ^h,j^
Moving forward….

- Recognize fecal and mucosal microbiome differ
  - Fecal microbial composition analysis not an ideal surrogate marker
- Colonization resistance exerted by resident microbiome
  - Highly individualized engraftment pattern
- Unique host gut transcriptome
- Systemic host response
- Rationale design of microbiome based therapy will need to take these factors into consideration
3. Using microbial signatures towards personalized medicine
8 groups of microorganisms discriminate CD vs UC and healthy controls

- **Faecalibacterium**
- **Peptostreptococcaceae;g__**
- **Anaerostipes**
- **Christensenellaceae;g__**
- **Collinsella**
- **Methanobrevibacter**
- **Fusobacterium**
- **Escherichia**

Validation of microbial biomarker to distinguish CD from UC, IBS and healthy controls

Fecal Microbiota in Pediatric Inflammatory Bowel Disease and Its Relation to Inflammation

Kaija-Leena Kolho, MD, PhD\(^1\), Katri Korpela, MSc\(^2\,5\), Tytti Jaakkola, MD\(^1\), Madharasi V.A. Pichai, MSc\(^3\), Erwin G. Zoetendal, PhD\(^4\), Anne Salonen, PhD\(^5\) and Willem M. de Vos, PhD\(^2\,4\,5\)

Fecal calprotectin

-responders
-non responders

*Am J Gastroenterol 2015; 110:921–930; doi:10.1038/aig.2015.149; published online 19 May 2015*
Six groups of fecal bacteria at baseline predicted favorable response to infliximab

Figure 4. Baseline differences between the non-responders (N, N=5) and responders (R, N=6) to anti-tumor necrosis factor-α (anti-TNF-α) treatment. P values are based on the analysis of variance.
Gut Microbiota Offers Universal Biomarkers across Ethnicity in Inflammatory Bowel Disease Diagnosis and Infliximab Response Prediction

Youliang Zhou, a, c Zhenjiang Zech Xu, d, k, l Yan He, b, j Yunsheng Yang, e Le Liu, a Qianyun Lin, a Yuqiang Nie, c Mingsong Li, a Fachao Zhi, a Side Liu, a Amnon Amir, d Antonio González, d Anupriya Tripathi, d Minhu Chen, f Gary D. Wu, g Rob Knight, d, h, i Hongwei Zhou, l Ye Chen a

Gut Microbiome Function Predicts Response to Anti-integrin Biologic Therapy in Inflammatory Bowel Diseases

Ashwin N. Ananthakrishnan, 1, 2, 5 Chengwei Luo, 3, 5 Vijay Yajnik, 1, 2 Hamed Khalili, 1, 2 John J. Garber, 1 Betsy W. Stevens, 2 Thomas Cieladl, 1 and Ramnik J. Xavier 1, 2, 3, 4, 5, 6, *

1 Division of Gastroenterology, Massachusetts General Hospital, Boston, MA 02114, USA
2 Harvard Medical School, Boston, MA 02115, USA
3 Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
4 Center for Microbiome Informatics and Therapeutics, Massachusetts Institute of Technology, Cambridge, MA 02142, USA

Cell Host & Microbe 21, 603–610, May 10, 2017
Fecal Microbiota Signatures Are Associated with Response to Ustekinumab Therapy among Crohn’s Disease Patients


**A** Induction randomization

- Placebo IV
- Ustekinumab IV

**Week 6 Response Status**

- In clinical response
- Not in clinical response

**Week 8**

- Placebo SC
- Ustekinumab 270 mg SC → 90 mg SC

**B**

- Week 0
- IV
- Week 4
- SC
- Week 6
- 16
- SC
- Week 8
- RR
- Week 22
- Major secondary endpoints, maintenance phase

*X = Fecal sample collected*
Responders had increased microbial diversity
Predicting response using baseline stool microbial signature

A

B

Week 0 OTUs: AUC=0.838
Week 0 Clinical Data: AUC=0.616
Combined: AUC=0.844

Clostridium IV (OTU162)
Ruminococcus (OTU35)
Escherichia/Shigella (OTU1)
Prevotella (OTU491)
Porphyromonadaceae (OTU542)
Clostridiales (OTU155)
Lachnospiraceae (OTU265)
Coprococcus (OTU189)
Faecalibacterium (OTU7)
Clostridiales (OTU330)

Week 0 Relative Abundance (%)
2 taxa can differentiate responders vs non responders
Conclusion

• IBD microbiome is characterized by intestinal dysbiosis with disrupted metabolic pathways and functions

• Manipulating microbiome through FMT appears to be a promising therapy for IBD
  • Many unanswered questions
  • Need to move towards refined therapy

• Microbial biomarkers are promising tools in personalized medicine in IBD
  • Diagnosis
  • Predicting therapeutic response