Disclosures
Advisory boards (Janssen, Lilly)
Potential Interventions

• Nomenclature of environmental challenge
• Antibiotics
• Beneficial bacteria
• Microbial products
  – Beneficial
  – Undesirable
Potential Interventions

- Nomenclature of environmental challenge
- Antibiotics
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Nomenclature of environmental challenge
Potential Interventions

• Nomenclature of environmental challenge
• Antibiotics
• Beneficial bacteria
• Microbial products
  – Beneficial
  – Undesirable
Different microbiomes in health and IBD

- Shared differences in many with either UC or CD
- IBD can have “normal” or “altered” microbiome
- Healthies can have “altered” phenotype
## Antibiotics and Probiotics

### Probable
- Ulcerative Colitis
- Pouchitis

### Unlikely
- Crohn’s disease

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<table>
<thead>
<tr>
<th>Situation</th>
<th>Product</th>
<th>Control</th>
<th>n</th>
<th>Duration, weeks</th>
<th>Effect</th>
<th>Product, %</th>
<th>Control, %</th>
<th>p</th>
<th>Ref.</th>
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<tr>
<td>CD</td>
<td>Clarithromycin + rifabutin + doxazosine</td>
<td>Placebo</td>
<td>213</td>
<td>16 (100/156)</td>
<td>Remission at week 16: 66</td>
<td>50</td>
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<td>Rifaximin</td>
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<td><em>Saccharomyces boulardii</em></td>
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<td>24/24</td>
<td>Relapse at week 24: 49</td>
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<td>UC</td>
<td>Amoxicillin + tetracycline + metronidazole</td>
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<td>2/52-60</td>
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<td>Response at week 52: 49.5</td>
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<td>Placebo</td>
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<td>24/52</td>
<td>Response at week 24: 79</td>
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<td>UC-PR</td>
<td><em>E. coli</em> Nissle 1917</td>
<td>5-ASA</td>
<td>120</td>
<td>52/52</td>
<td>Relapse: 67</td>
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<td>UC-PR</td>
<td><em>E. coli</em> Nissle 1917</td>
<td>5-ASA</td>
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<td>Relapse: 36.4</td>
<td>33.9</td>
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<td>CD fistulas</td>
<td>Infliximab + ciprofloxacin</td>
<td>Infliximab</td>
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<td>Fistula response at week 18: 73</td>
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<td>Fistula response at week 18: 71</td>
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<td>[69]</td>
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</tbody>
</table>

*Product administration/total study duration. *Statistically equivalent, p < 0.05.

Bejaoui, Dig Dis 2015;33(suppl 1):105–112
Crohn’s disease (ECCO guidelines 2010)

– Antibiotics cannot be recommended in mildly active localized ileocecal CD (EL1b, RG A).
– However, they can be added if septic complications are suspected (temperature or focal tenderness or imaging indication of an abscess) (EL5, RG D).
– Adding ciprofloxacin and metronidazole to budesonide has shown no advantage over budesonide alone in active CD.
– At present, antibiotics are only considered appropriate for septic complications, symptoms attributable to bacterial overgrowth or perineal disease.
– Anti-mycobacterial therapy cannot be recommended on the evidence from controlled trials.
– \textit{E. coli Nissle} is an effective alternative to 5-ASA for maintenance (EL1b, RG A).

Ulcerative colitis (ECCO guidelines 2012)

– Antibiotic therapy may induce remission in active UC, but the diverse number of antibiotics tested means the data are difficult to interpret.
– Data are regarded as insufficient by the consensus to recommend antibiotics for maintenance of remission in UC.
– There is insufficient evidence for the use of T. suis ova, Saccharomyces boulardii or bifidobacteria in the treatment of UC (EL5, RG D).
Pouchitis (ECCO guidelines 2008)

– The majority of patients respond to metronidazole or ciprofloxacin, although the optimum modality of treatment is not clearly defined (EL1b, RG B).
– In chronic pouchitis, combined antibiotic treatment is effective (EL1b, RG B).
– VSL#3 has shown efficacy for maintaining antibiotic-induced remission (EL1b, RG B).
– VSL#3 has shown efficacy for preventing pouchitis (EL2b, RG C).
Potential Interventions

• Nomenclature of environmental challenge
• Antibiotics
• **Beneficial bacteria**
• Microbial products
  − Beneficial
  − Undesirable
Donor microbiota and response to FMT

• Adult
  - Meta-analysis of 9 cohort studies, 8 case studies, 1 RCT
  - 122 IBD patients
  - Remission rate of 45% during follow-up
  - Better result in CD than in UC

• Pediatric
  - Open-label study
  - 78% remission rate at 2 weeks (7 of 9)

Donor microbiota and response to FMT

• Fourteen refractory patients (8 ulcerative colitis and 6 Crohn's disease)
• Fecal microbiota transplantation through naso-jejunal (n=9) or rectal tube (n=5).
• Efficacy was assessed by endoscopic healing at week 8, clinical activity scores and C-reactive protein measurement.
• Fecal microbiota transplantation led to endoscopic and long-term (> 2 years) remission in 2 out of 8 ulcerative colitis patients.
• Higher donor richness was associated with successful transplant.

Vermeire S, J Crohns Colitis. 2015
Effects of intervention on microbial composition

Stressor-specific responses of ecosystem
FMT, the way ahead

- Defining optimal microbial features(s)
- Source (donor, synthetic)
- Matching to recipient genetics and microbiota

Vermeire S, J Crohns Colitis. 2015
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T_{reg} induction by a rationally selected mixture of Clostridia strains from the human microbiota

Koji Atarashi\textsuperscript{1,2,3*}, Takeshi Tanoue\textsuperscript{1,2*}, Kenshiro Oshima\textsuperscript{4,5*}, Wataru Suda\textsuperscript{5}, Yuji Nagano\textsuperscript{1,2}, Hiroyoshi Nishikawa\textsuperscript{6}, Shinji Fukuda\textsuperscript{1,7}, Takuro Saito\textsuperscript{6}, Seiko Narushima\textsuperscript{1}, Koji Hase\textsuperscript{1,2,3}, Sangwan Kim\textsuperscript{3}, Joëlle V. Fritz\textsuperscript{3}, Paul Wilm\textsuperscript{5}, Satoshi Ueha\textsuperscript{9}, Kouji Matsushima\textsuperscript{8}, Hiroshi Ohno\textsuperscript{3}, Bernat Olle\textsuperscript{10}, Shimon Sakaguchi\textsuperscript{6}, Tadatsugu Taniguchi\textsuperscript{2}, Hidetoshi Morita\textsuperscript{4,11}, Masahira Hattori\textsuperscript{5} & Kenya Honda\textsuperscript{1,2,4}
Clostridium consortium
Short chain fatty acid production

**Acetyl-CoA**
- 10 \( \rightarrow \) K01057 acetyl-CoA hydrolase [EC:3.1.2.1]
- 24 \( \rightarrow \) K01026 propionate CoA-transferase [EC:2.8.3.1]
- 6 \( \rightarrow \) K01905 acetyl-CoA synthetase (ADP-forming) [EC:6.2.1.13]

**Acetate**

**Acetyl-CoA**
- 15 \( \rightarrow \) K0132 acetaldehyde dehydrogenase (acetylating) [EC:1.2.1.10]

**Acetoaldehyde**
- 22 \( \rightarrow \) K00128 aldehyde dehydrogenase (NAD+) [EC:1.2.1.3]

**Butyrate**

**Acetyl-CoA**
- 27 \( \rightarrow \) K00626 acetyl-CoA C-acetyltransferase [EC:2.3.1.9]

**Acetoacetyl-CoA**
- 27 \( \rightarrow \) K00074 3-hydroxybutyryl-CoA dehydrogenase [EC:1.1.1.157]

**Butyryl-CoA**
- 10 \( \rightarrow \) K1692 enoyl-CoA hydratase [EC:4.2.1.17]

**Crotonoyl-CoA**
- 33 \( \rightarrow \) K00248 butyryl-CoA dehydrogenase [EC:1.3.99.2]

**Butanoyl-CoA**
- 8 \( \rightarrow \) K00634 phosphate butyryltransferase [EC:2.3.1.19]

**Butanoyl-P**
- 20 \( \rightarrow \) K00929 butyrate kinase [EC:2.7.2.7]

**SCFA concentration (mM)**

- Butyrate
- Acetate
- Hexanoic acid
- Varelic acid
- Iso-butyrate
- Propionate

**Medium**

**Sl. 1 to Sl. 30**
Clostridium consortium

Other properties

![Table and Diagram](image.png)

*Source: Narushima, Gut Microbes 2015*
On the search for other beneficial bacteria

- Shared differences in many with either UC or CD
- IBD can have “normal” or “altered” microbiome
- Healthies can have “altered” phenotype
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• **Microbial products**
  - Beneficial
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Functional diversity within a single genus (Solanales)
Three week yogurt ingestion

• No effect on microbial composition
• Striking effect on energy sourcing of entire microbiome
Multi-omics approach to characterizing the intestinal microbiome

**Microbes**
- Metagenomics
- Metatranscriptomics
- Metaproteomics
- Metabolomics

**Host**
- Genomics
- Transcriptomics
- Metaproteomics
- Metabolomics

Functional specialization of microbiota in Crohn’s disease and ulcerative colitis
The Microbiome Stuff (metabolites) made by microbiome

**The Microbiome**

**IBD**

**Healthy**

**Oxidative Stress**

**sulfur amino acid metabolism**
- methionine → homocysteine → cysteine

**redox homeostasis**
- glutathione = GSH
- Riboflavin
- NADPH
- NADP+
- GSSG

**glutathione biosynthesis**
- cysteine + glutamine → glutathione

**short chain fatty acid production**
- acetate
- fiber → butyrate
- propionate → CO₂
- H₂

**mucin biosynthesis/degradation**
- mucin → cysteine sulfate + N-acetyl galactosamine

**NAG transport**

**LPS production, virulence factor production**

**Clade IV and XIVa Clostridia**

**Tissue destruction**

**Auxotrophic specialists**

**purine and pyrimidine biosynthesis**

**lysine and histidine biosynthesis**

**Inflammation**

Morgan X, Genome Biol 2012
Each metabotype has a distinct metabolite signature

Spectral features mainly associate with metabotypes, not CD (multivariate modeling)
Microbe/metabolite interaction network

- **Amino acid related**
  - Phenethylamine
  - [Ruminococcus] gnavus
  - Lachnospiraceae
- **Bile acid related**
  - 3-Oxotetradecanoic acid
  - 3-Sulfodeoxycholic acid
- **Steroid related**
  - 7,10,13,16-Docosatetraenoic acid
  - 3-Oxo-4,6-choladienoic acid

**Metabolite**
- Increased
- Decreased

**Microbe**
- Correlation
  - Positive
  - Negative
Variant basal microbial ecosystems

Pre-disease variant ecosystems

**Basal variant ecosystems**
- Defined by microbial and metabolite features
- ? Formed by differential habitat due to diet, genetics

**Inflammatory ecosystem**
- Post-inflammation selection
- Neutral bystanders
- Augmenters of tissue damage
Potential implication:
Ecosystem detection and monitoring by absorbed metabolite biomarkers

- Basal ecosystems
  - Defined by enterotype/metabotypes
  - Diet, genetics

- Inflammatory ecosystem

- Disease Penetration

- Blood, Urine, Saliva
- Biopsy, Stool

Absorbed metabolites

~250 metabolites
Potential implication: metabolite targeted treatment

Organism-targeted treatment concepts
- FMT
- Elimination or modified diets to change ecosystem composition
- Probiotics to change ecosystem function

Metabolite-targeted treatment concepts
- Restore critical metabolites
- Enzymatically block production of undesired metabolites
Braun lab, UCLA
Jonathan Jacobs
Jonathan Braun
Maomeng Tong
Ian McHardy
Miro Asadourian
Allyson Ayson

Georgetown University
Maryam Goudarzi
Albert Fornace

Mount Sinai Hospital
Marla Dubinsky

Cedars-Sinai Medical Center
Namita Singh
Dermot McGovern

UC Riverside
Paul Ruegger
James Borneman

Broad Institute
Hailiang Huang