Engineering the Human Microbiome: Current practices to future therapies

1/9/2017
Whitehead Institute
Mark Smith, PhD
Agenda

1. Enabling safe access to FMT

2. Creating a generalizable toolkit for engineering the human microbiome

3. Discovering and scaling microbial therapies
C. difficile is a major public health threat

- 450,000 cases per year
- 29,000 deaths per year
- $3B in hospitalization & treatment costs
- 5-10% of healthy adults are colonized

C. difficile is a spore-forming clostridium
CDI causes severe diarrhea
Active disease strongly associated with antibiotic use
Standard of care is antibiotic therapy and colectomy

Source: CDC National Center for Health Statistics 2012, Lessa, 2015
The natural history of CDI

Healthy microbiome

Antibiotics

More antibiotics

Antibiotic-perturbed microbiome

C. difficile infection

C. difficile microbiome

FMT

Natural exposure
FMT is a highly effective treatment for rCDI

FMT: A long time coming

“It is suggested that this simple yet rational therapeutic method should be given more extensive clinical evaluation.”

-Ben Eiseman, 1958
Developing OpenBiome

OpenBiome Mission
To expand safe access to FMT and to catalyze research into the human microbiome

Operational Objectives
- Rigorous donor screening (11,000+ applicants, 2.8% pass rate)
- Single interface for FDA (registered biologics master file)
- Standardized processing (audited quality systems)
- Pareto improvement (safety, convenience, cost, patient experience)
Donor screening at OpenBiome

- **Pre-Screen Survey**: 1,387
- **Clinical Assessment**: 477
- **Laboratory Investigations**: 74

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<thead>
<tr>
<th>Stage</th>
<th>Excluded</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>910 (66%)</td>
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<tr>
<td>Stage 2</td>
<td>403 (84%)</td>
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<tr>
<td>Stage 3</td>
<td>35 (47%)</td>
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- **Eligible Donor Demographics**
  - Sex: Female 36%, Male 64%
  - Age (years): Mean 28, Median 27, SD 6
  - BMI (kg/m²): Mean 23.7, Median 23.1, SD 2.9
  - Female Waist Circumference (inches): Mean 30.3, Median 30.5, SD 2.2
  - Male Waist Circumference (inches): Mean 34.0, Median 35.0, SD 2.0

- **Eligible Donor**: 39 (2.8%)
# Three years at OpenBiome

<table>
<thead>
<tr>
<th>Year</th>
<th>Vision</th>
<th>Reality</th>
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<tbody>
<tr>
<td>2013</td>
<td>1(^{st}) Patient Treated</td>
<td>6 Patients treated</td>
</tr>
<tr>
<td>2014</td>
<td>1000 Patients Treated</td>
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<tr>
<td>2015</td>
<td>10% of rCDI</td>
<td>20% of rCDI</td>
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OpenBiome today

Treatments Provided by Quarter

The New York Times
BBC News
Nature
The Boston Globe
Wire
USA Today
Disease discovery is the frontier of FMT research

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<td>Find the next disease to transform</td>
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Agenda

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3. Developing defined microbial therapeutics
The microbiome is associated with many diseases

Cell Host & Microbe
The Treatment-Naive Microbiome in New-Onset Crohn’s Disease

nature
A metagenome–wide association study of gut microbiota in type 2 diabetes

Genome Research
Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma

Science
Anticancer immunotherapy by CTLA–4 blockade relies on the gut microbiota

PLOS ONE
Reduced Incidence of *Prevotella* and Other Fermenters in Intestinal Microflora of Autistic Children
Discovering therapeutic applications may require new tools

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PMAseq is a culture-independent tool for measuring viability
PMAnseq is a culture-independent tool for measuring viability
The microbiome engineering toolkit

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Short-term dosing may not be sufficient for treatment of chronic disease

The microbiome engineering toolkit

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FMT delivered via multiple modalities is effective for rCDI
New tools will enable targeted delivery
## The microbiome engineering toolkit

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<td><strong>Targeted delivery</strong></td>
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The response to FMT may be donor dependent outside of CDI

## The microbiome engineering toolkit

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**Current standards**

- **Oxygen exposure**: Aerobic processing
- **Dosing**: Single dose
- **Delivery targeting**: None needed
- **Donor selection**: None needed
- **Pre-treatment**: None needed

**New Directions**

- **Oxygen exposure**: Anaerobic
- **Dosing**: Maintainance
- **Delivery targeting**: Targeted delivery
- **Donor selection**: Disease specific
Evaluating the impacts of pre-treatment antibiotics on microbial engraftment

<table>
<thead>
<tr>
<th>IBS Patients</th>
<th>Intervention</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>1.</td>
<td>Prep + Placebo</td>
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<tr>
<td>2.</td>
<td>Prep + FMT</td>
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</tr>
<tr>
<td>3.</td>
<td>Prep + Rifaximin + FMT</td>
<td>Microbial Engraftment</td>
</tr>
<tr>
<td>4.</td>
<td>Prep + Cipro + Flagyl + FMT</td>
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# The microbiome engineering toolkit

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A grand challenge for public health
Clinical Research Pipeline

**Pre-clinical**
- Autism
- CDI detection
- Nutrition
- Parkinson’s
- Rotavirus assay development
- Sleep deprivation
- VRE

**CDI**
- CDI in solid organ transplant recipients
- Geriatric CDI prophylaxis
- Primary CDI
- Severe-complicated CDI

**Non-CDI**
- Ankylosing spondylitis
- Autoimmune hepatitis
- Bowel-associated dermatosis-arthritis syndrome
- MDROs
- Multiple sclerosis
- Nonalcoholic steatohepatitis
- Obesity
- Peanut allergies
- Pediatric Crohn’s disease
- Primary Sclerosing Cholangitis
- Rheumatoid arthritis
- VRE

**Planning & Design**

**Active Studies**
- Adult Ulcerative Colitis
- Capsule dose finding study
- Crohn’s Disease
- Diarrheal predominant irritable bowel syndrome
- Hepatic encephalopathy
- HIV-associated diarrhea
- Longitudinal safety study of FMT (STOOL study)
- Pediatric Ulcerative Colitis
- Post-operative Crohn’s Disease
- Pouchitis
Defined therapies will facilitate translation and scale

Challenges with scaling FMT

1. **Regulatory** – BLA required outside of rCDI

2. **Mechanistic** – inconsistent efficacy and need for consistent potency

3. **Scale** – if maintenance therapy required, FMT becomes costly
Leveraging FMT data to develop defined microbial therapies

**Dorea longicatena**

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<tr>
<th>Pre-FMT</th>
<th>Donor</th>
<th>Post-FMT</th>
</tr>
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<tbody>
<tr>
<td>Patient 1</td>
<td><img src="image1" alt="Pie chart" /></td>
<td><img src="image2" alt="Pie chart" /></td>
</tr>
<tr>
<td>Patient 2</td>
<td><img src="image3" alt="Pie chart" /></td>
<td><img src="image4" alt="Pie chart" /></td>
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- Each color represents a unique strain.
- In this example, two patients received an FMT from the same donor.
- The resulting communities are highly divergent, yet we can predict these results accurately.

**Bacterial phylogeny illustrating clade-specific engraftment efficiencies**

**FINCH THERAPEUTICS**

**OPENBIOME**
Acknowledgements

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