Regulatory Considerations for Microbiota Transplant (FMT)
Crohn’s & Colitis Congress
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Disclosures

I have no actual or potential conflict of interest in relation to this presentation.
The Human Microbiome Project

Discussion Of Current Status
And
International Plans To Explore
The Human Microbiome

Place:  Metro Toronto Convention Center
        (South Building), Room 714A, Toronto, Canada
Date:  May 24, 2007
Chair:  George Weinstock
        Baylor College of Medicine, Houston, TX

Agenda

<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>6:30 PM - 7:00 PM</td>
<td>Registration</td>
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<td>7:00 PM - 7:05 PM</td>
<td>Welcome</td>
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<tr>
<td>7:05 PM - 7:25 PM</td>
<td>Overview of the National Academy of Sciences report on metagenomics</td>
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<tr>
<td>7:25 PM - 7:45 PM</td>
<td>Lessons and challenges for metagenomic studies of the human microbiome</td>
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<td>7:45 PM - 8:05 PM</td>
<td>How will new sequencing technologies enable human microbiome research?</td>
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<td>8:05 PM - 8:25 PM</td>
<td>The NIH Roadmap human microbiome project workshop report</td>
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<tr>
<td>8:25 PM - 9:00 PM</td>
<td>Discussion - Q&amp;A</td>
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Working Group

– NIH-funded HMP researchers
– Clinicians
– Legal academics
– Food and drug law attorneys
– Government regulators
– Consumer/Patient advocates
– Bioethicists
– Industry representatives
Regulatory Framework for FMT: Factors to Consider

– ensure safety of the substance
– ensure effectiveness
– provide reliable information to patients/consumers
– ensure access for patients who need the procedure/product
– not unnecessarily discourage research on MTs
– support public health objectives, i.e., reducing the development of antibiotic resistant organisms
Drugs and INDs

• Drugs:
  – “Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”
  – Biological products are included within this definition

• Require Investigational New Drug application (IND) to administer
IND Application Requirements

• Application requires extensive information
  – Pharmacology and toxicology
  – Detailed protocols for pre-clinical studies (i.e. animal studies) as well as Phase I, II, III clinical trials on human subjects
  – Chemistry, Manufacturing and Control (CMC) Information to ensure the proper identity, strength, quality, and purity of the drug.
    • Physical, chemical or biological characteristics such as biological name and strain designations, original sources, clinical health of donor, summary of phenotype and genotype of product strains, and more
Challenges to regulating fecal material as a drug

• Transplanted material is not a “typical” drug
  – May not be appropriate for the drug regulatory pathway
• Material consists of a community of living organisms
  – “metabolically active and highly dynamic in response to multiple factors”
• Many organisms are challenging to culture in vitro
• Difficult to test effectiveness in animals
• Characterization requirements difficult to meet
  – Whole community genome sequencing to characterize all microbes scientifically challenging and prohibitively expensive
• Requirement for consistency in product composition
  – Stool differs from person to person
  – Chemical and biological components “vary from batch to batch”
DIY Equipment
Stool Banks
Regulatory and Research Milestones

Timeline

- **2010:** Physician requests to FDA as to whether IND needed for FMT research
- **2011:** Rebiotix founded
- **2012:** Openbiome founded and begins operation
- **2012:** Rebiotix meets with FDA
- **July 29, 2013:** FDA approves Rebiotix IND and starts Phase II clinical trials
May 2013: FDA announces classification of fecal matter as both IND and biologic
Regulatory and Research Milestones

Timeline

May 2013: FDA announces classification of fecal matter as both IND and biologic

July 18, 2013: FDA changes course – will keep classification but will exercise enforcement discretion

July 29, 2013: FDA approves Rebiotix IND and starts Phase II clinical trials
Regulatory and Research Milestones

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May 2013: FDA announces classification of fecal matter as both IND and biologic

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March 2014: FDA publishes draft guidance that adds another qualification for use of FMT for C.diff
March 2014 Draft Guidance

- FMT product must be “obtained from a donor known to either the patient or to the licensed health care provider treating the patient”
- Stool donors and stool must be qualified by screening and testing
Regulatory and Research Milestones

Timeline

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March 2014: FDA publishes draft guidance that adds another qualification for use of FMT for C.diff

July 2013: FDA changes course – will keep classification but will exercise enforcement discretion

March 2016: FDA issues revised draft policy
“Centralized manufacturing in stool banks presents safety concerns related to the use of FMT from a limited number of donors administered to multiple patients. These safety concerns include transmission of infectious agents and potentially other unidentified risks related to changes in the microbiome.”
March 2016 Draft Guidance

• Stool banks need to submit an IND application and receive FDA approval before product can be used by physicians

• Health care providers who receive FMT product from stool bank can be sub-investigators
  – Must submit protocol to IRB
  – Must report adverse events to IRB and sponsor
Adverse Event Reporting Requirements

• Adverse event must be reported to IRB when:
  • Unexpected
  • Serious
  • Would have implications for the conduct of the study (e.g. requiring significant change to protocol such as revised inclusion/exclusion criteria, change to ICF, or investigator’s brochure)
<table>
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<tr>
<th>Project</th>
<th>Disease/Condition</th>
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<tr>
<td>SER-109</td>
<td>Recurrent <em>C. difficile</em></td>
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<tr>
<td>SER-287</td>
<td>Ulcerative colitis</td>
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<tr>
<td>SER-262</td>
<td>Primary <em>C. difficile</em></td>
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<tr>
<td>SER-301</td>
<td>Inflammatory Bowel Disease (IBD)</td>
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<tr>
<td>SER-401</td>
<td>Immuno-oncology – in combination with anti-PD-(L)1 therapy</td>
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<tr>
<td>SER-155</td>
<td>Prevention of infection and GVHD following hematopoietic stem cell or solid organ transplant</td>
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- Synthetically fermented
- Biologically sourced
- Infectious
- Inflammatory
METHODOLOGY

Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: ‘RePOOPulating’ the gut

Elaine O Petrof\(^{1,4}\), Gregory B Gloor\(^{2,4}\), Stephen J Vanner\(^1\), Scott J Weese\(^3\), David Carter\(^4\), Michelle C Daigneault\(^5\), Eric M Brown\(^5\), Kathleen Schroeter\(^5\) and Emma Allen-Vercoe\(^5\)

Abstract

**Background:** Fecal bacteriotherapy (stool transplant) can be effective in treating recurrent *Clostridium difficile* infection, but concerns of donor infection transmission and patient acceptance limit its use. Here we describe the use of a stool substitute preparation, made from purified intestinal bacterial cultures derived from a single healthy donor, to treat recurrent *C. difficile* infection that had failed repeated standard antibiotics. Thirty-three isolates were recovered from a healthy donor stool sample. Two patients who had failed at least three courses of metronidazole or vancomycin underwent colonoscopy and the mixture was infused throughout the right and mid colon. Pre-treatment and post-treatment stool samples were analyzed by 16 S rRNA gene sequencing using the Ion Torrent platform.

**Results:** Both patients were infected with the hyper virulent *C. difficile* strain, ribotype 078. Following stool substitute treatment, each patient reverted to their normal bowel pattern within 2 to 3 days and remained symptom-free at 6 months. The analysis demonstrated that rRNA sequences found in the stool substitute were rare in the pre-treatment stool samples but constituted over 25% of the sequences up to 6 months after treatment.

**Conclusion:** This proof-of-principle study demonstrates that a stool substitute mixture comprising a multi-species community of bacteria is capable of curing antibiotic-resistant *C. difficile* colitis. This benefit correlates with major changes in stool microbial profile and these changes reflect isolates from the synthetic mixture.

**Trial registration:** Clinical trial registration number: ClinicalTrials.gov NCT01372943
A proposed definition of microbiota transplantation for regulatory purposes

Diane E. Hoffmann\textsuperscript{a}, Francis B. Palumbo\textsuperscript{b}, Jacques Ravel \textsuperscript{c}, Virginia Rowthorn\textsuperscript{a}, and Erik von Rosenvinge\textsuperscript{d}

\textsuperscript{a}School of Law, University of Maryland, Baltimore, MD, USA; \textsuperscript{b}Center for Drugs and Public Policy, University of Maryland School of Pharmacy, Baltimore, MD, USA; \textsuperscript{c}Institute for Genome Sciences, University of Maryland School of Medicine, Baltimore, MD, USA; \textsuperscript{d}Division of Gastroenterology & Hepatology, University of Maryland School of Medicine, VA Maryland Health Care System, Baltimore, MD, USA

ABSTRACT
The advent of fecal microbiota transplantation (FMT) and the prospect of other types of microbiota transplants (MT), e.g. vaginal, skin, oral and nasal, are challenging regulatory agencies. Although FDA is regulating FMT (as a biologic), there is currently no widely accepted or agreed upon scientific or legal definition of FMT or MT. The authors report on discussions regarding a definition of MT that took place among a working group of stakeholders convened under a National Institutes for Allergies and Infectious Diseases grant to address the regulation of MT. In arriving at a definition, the group considered the 1) nature of the material being transplanted; 2) degree of manipulation of the transferred materials prior to implantation; 3) ability to characterize the transplanted product using external techniques; and 4) origin of the stool product (single vs multiple donors).

ARTICLE HISTORY
Received 22 September 2016
Revised 24 January 2017
Accepted 6 February 2017

KEYWORDS
definition; fecal; microbiota transplantation; regulation

The advent of fecal microbiota transplantation (FMT) and the prospect of other types of microbiota transplants (MT), e.g. vaginal, skin, oral and nasal, are challenging regulatory agencies. In the US, the FDA has modified its position on regulating FMT several times and has asked for comments on its most recent draft industry guidance.\textsuperscript{1,3} While FDA has, at least for now, A number of authors have commented on the difference between MT and more traditional drugs. For example, Petrof and Khoruts argue that “[a]lthough the FDA considers the fecal microbiota to be a drug, like any agent used to treat, mitigate, or prevent disease, it is certainly not like any other drug. It is incredibly complex, comprising hundreds of species of
Essential Elements of FMT

• Transplanted material:
  – Is a group of micro-organisms in a biological matrix
  – Designed to change an entire ecosystem
  – Includes non-microbial components
  – Is “minimally manipulated”
Range of Fecal Material Manipulation for CDI Treatment
Public Comments on March 2016 FDA Draft Guidance

From patients/consumers: (n=55)

– fear lack of access to life-saving therapy
– may not meet eligibility criteria for clinical trial
– if selected, may receive a placebo
Public Comments on March 2016 FDA Draft Guidance

From physicians: (n=41)

– Stool banks provide a safe, rigorously tested product in a timely manner
– Hospital and local labs, especially in rural areas, do not have facilities or training to conduct same type of screening as stool banks and unable to screen donors quickly
– Screening is expensive, not reimbursed by all payers, and hardest on poor patients
What will FDA do next?

• Will they be responsive to comments or continue stance that stool banks must obtain an IND?
• If stool banks require an IND, can stool meet consistency requirements and be approved as a new drug?
• If modified stool product is approved as a drug, will FDA allow stool banks to remain open?
Acknowledgements

- Frank Palumbo, JD, PhD, University of Maryland School of Pharmacy
- Jacques Ravel, PhD, University of Maryland School of Medicine
- Mary-Claire Roghmann, MD, University of Maryland School of Medicine
- Virginia Rowthorn, JD, University of Maryland School of Law
- Eric von Rosenvinge, MD, University of Maryland School of Medicine