FMT – based discovery: From platform to product

Microbiome R&D and Business Collaboration Forum: Europe Rotterdam
23 May 2019
Topics

• Fecal Microbiota Transplants – background

• FMT as discovery tool

• FMT as intervention

• Innovations in FMT

• Regulatory environment

• Q&A
Fecal transplantation

In a fecal transplant, stool from a healthy donor is used to replace a patient’s gut microbial flora. Exact preparations vary, but usually the stool is blended with saline and put through a strainer. It can be frozen before use. In the future, scientists hope to replace fecal transplants with an odorless mix of bacterial strains derived from human stool, grown in the lab. It could be applied using existing methods or in capsules.

The stool can be applied into the small intestine via a tube through the nose or mouth (a) or deep into the colon, using a colonoscopy (b). Enemas are popular for at-home treatments, but they only reach the lower end of the colon (c).
Power of FMT: Double-blind randomised controlled studies

Satokari et al
CRP 2014
Rossen et al
Gastro 2015
Konig et al
submitted 2018
Van Nood et al
NEJM 2013

Kootte et al Cell Met 2017
Fatlose 2

Fatlose 1
Vrieze et al Gastro 2012
Udayappan et al B&M 2016
Li et al Science 2016

Published

S Fuentes & WM de Vos 2015

Ongoing

Cure Patients - Cause–Effect Relation of the Microbiome – Reverse Engineering
FMT in Clostridium difficile – groundbreaking results

- Clostridium difficile infection
- Increasing numbers
- Lack of efficacy of antibiotics
- High rate of recurrence

- FMT study at AMC – Amsterdam\(^1\)
  - Effective treatment
  - No adverse events
  - Low rate of recurrence

- Subsequent development of consortia
  - Seres Therapeutics and others

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Strategies for developing Microbial therapies

Can we avoid large cohorts and confounders?

Fecal microbiota transplantation – start with causality

Less subjects are needed as the studies have more power and underpin causality
Oral route for later solutions
Duodenal FMT as a discovery tool

- Success of FMT Indicates Causality of Microbiome
- Autologous (Placebo) Transplantation Provides Baseline Situation
- Samples Before and After FMT– Reduces Impact of Personalized Microbiome

...Reverse Engineering: Identify the Causal Microbes....

- FMT Allows Upper Intestinal Tract Sampling – More Relevant Than Fecal Sampling
- Analysis Microbiota and Host Gene Expression
- Duodenal Delivery Resembles Oral Route
- Single Strains – Multiple Strains – Synthetic Communities
Lead discovery program

FMT-studies in Key Areas – AMC Transfers leads to Caelus:

- Metabolic Syndrome (MetS)
- Liver disorders NAFLD / NASH
- Type I Diabetes Mellitus (T1DM)
- Underweight subjects (Oncology)
FMT in Metabolic Syndrome – two successful clinical trials

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals with Metabolic Syndrome

Successful Allogenic = Healthy Donor Transplantation

Plasma LPS Binding Protein (LBP) Significantly Decreased After Allogenic FMT

Baseline Fecal Microbiota Predicts Responders

Serum Metabolite Analysis Shows Allogenic FMT Reduces Oxidative Stress
Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome, Vrieze et al, Gastroenterology 2012
Beneficial changes in small intestinal *E. hallii* after fecal transplant

Remarkably high correlation of beneficial gene expression was linked to the abundance of relatives of *E. hallii*

The abundance of relatives of *E. coli* was linked to damaging gene expression

Demonstration of colonisation resistance versus new species

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome, Vrieze et al, Gastroenterology 2012
Lessons from strain level metagenomics

Durable coexistence of donor and recipient microbiota strains after fecal microbiota transplantation

- Donor-recipient match determine colonization success
- Colonization resistance to new species
- Long-term co-existence of donor & recipient strains
- One stool does not fit all … role of phages is being studied
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FMT as intervention in AML and Graft versus Host disease

- **Odyssee trial** by MaaT Pharma
  - Phase 1b/2a study
  - 25 Acute Myeloid Leukemia patients
  - Microbiome Restoration Biotherapeutic
    - Fecal microbiota of patient
    - Processed and frozen (GMP-certified)
    - 2 doses of collected microbiota administered as enema
  - Restored functional microbiome

- Next: randomized trial with off-the-shelf capsule formulation MaaT033

1. MaaT Press Release – December 1, 2018
FMT as intervention in recurrent Clostridium difficile and Ulcerative colitis

• Microbiota Restoration Therapy (MRT)\textsuperscript{1}
• Drug platform
  • Focus on C. diff, IBD and Multi-Drug Resistant Organisms (MDRO)
  • Lead product RBX 2660
    • Enema for treatment of rec C. diff
  • Oral formulation for prevention of recurrent C. diff in Development
• Acquired by Ferring on 5 April 2018\textsuperscript{2}

1. Rebiotix website: www.rebiotix.com
2. Ferring/Rebiotix press release
FMT in IBD – innovation in formulation

• Established MHRA-GMP certified facility
• ISO-accredited donation facility
• Rowett Institute for Nutrition and Health
• Based in Aberdeen, Scotland

• Initial focus on C. diff. and IBD
• Developing oral formulations and enriched or depleted formulations
• Individual banking of samples for later use
• Developing innovative microbiota treatments
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Innovations in FMT

- Formulation development
  - Enema formulation
  - Encapsulation of freeze dried powder

- Enrichment of FMT
  - Enrich with specific microbiota
  - Enrich with specific metabolites
    
    *Publication by Paramsothy et al, Gastroenterology, 2018*

- Antibiotic pretreatment -> Enhanced colonization ("engraftment")
  
  *Publication by Segal et al, Cell 2018*

- Proprietary systems
  - Collection and Processing of fecal matter
Innovations in FMT – relevance of diet/nutrients

• Food intake
  • Crucial factor influencing the microbiome
  • Relevant for patients and FMT-donors
  • Unbalanced diet – disturbed microbiome
  • Specific nutrients may change microbiome

• Glycans as tool to influence microbiome and enhance health
  • Glycans – library of proprietary compounds
  • Microbiome Metabolic Therapies (MMTs)
  • Leveraging the Microbiome organ ...
  • Targeting ammonia, MDR, SCFAs, more
Innovations in FMT – relevance of donors

Ref. Wilson et al, 2019, Frontiers in Cellular and Infection Microbiology
Innovations in FMT – relevance of donors

Super donors?
• Recent publication Jan 2019 by Wilson et al (Auckland/MIT-Broad)
• Dependence on microbial diversity and composition of donor stool?
• Key stone species as predictors of FMT success?
• Effect of host-genetics and diet on FMT engraftment?

Donor selection
• Inclusion criteria
  • Males and females, Age 18-65 yrs, BMI 18-25 kg/m², more
• Exclusion criteria
  • Medication use, Antibiotic use (< 3 months), Smoking, more
• Additional consideration
  • Stratification of donors; microbiota specific; indication specific
Interaction gut microbiota - host

Impact of metabolites – derived from microbiota
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Regulatory environment

• US-FDA
  • Guidance LBPs
  • CMC requirements
  • Issued Feb 2012
  • Updates June 2016

• Draft Guidance FMT
• IND requirements
• FMT to treat C. diff infection - not responsive to standard therapies

• Much more clarity vs EU
How do we operate?

European Parliament

Pieces of Legislation Proposal

Votes on Legislation Proposal

European Medicines Agency

Scientific & Technical Guidelines

Pharmabiotic Research Institute
An LBP, [...] is a biological product that:
1) contains live organisms, such as bacteria;
2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and
3) is not a vaccine.

FMTs are not LBPs but they are drug products because they are excreted.

Live Biotherapeutic products (LBPs) are
1) Medicinal products containing live microorganisms (bacteria or yeasts) for human use.
2) Administered orally and vaginally and are available in different pharmaceutical forms
3) May contain multiple microbial strains from the same or different species of microorganisms

FMT and products intended as gene therapy agents are excluded from this monograph
=> FMTs are not LBPs => regulatory status still under discussion
Ininnitiatives for harmonisation, standardisation, education and regulation

• USA: Microbiome Therapeutics Innovation Group (MTIG)
  • Founding members:
    • Seres Therapeutics
    • Vedanta Biosciences
    • Rebiotix

• EU: PRI - Working group on FMT: IMM-ETG
  • Founding members:
    • Caelus Health
    • Enterobiotix
    • Ferring / Rebiotix
    • MaaT Pharma
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