

Logbook - Science Fair 2021

Various project ideas: January 23, 2021

1. **Organ Transplant Awareness:**

Recent changes have made organ transplant opt-out instead of an opt-in approach.

2. **Colorectal Cancer and Novel Treatments**

3. **Ulcerative colitis and IBS**

My mom has UC for more than 10 years on medications and still gets very sick and IBD got my attention. She is on probiotics so looking into the role of probiotics and - gave me insight into the gut microbiome.

How FMT is different than probiotics and pre-biotics and why FMT is better than probiotics and pre-biotics and how effective is FMT treatment.

January 30, 2021

Title of my final project:

Effect of Short-Term Diet Modulation of Donor on the Efficacy of Fecal Microbial Transplant (FMT)

Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. inflammation results in damage to the GI tract.

There is no evidence that IBD results from an overgrowth of one specific pathogen. The disease is likely brought on by complex interactions involving the host's genetics, immune system, and gut microbiota

Both Crohn's disease and ulcerative colitis are broadly characterized by reduced diversity of the gut microbiota with lower relative abundances of the Bacteroidetes and Firmicutes phyla and higher proportions of Proteobacteria

Research:

What is FMT- Fecal Microbiota Transplant is a medical procedure that takes stool from a healthy donor and implants it in the gut of a sick individual. A successful FMT microbiome of a patient and treat the associated illness.

The goal of FMT is to provide healthy and diverse bacteria to the gut microbiome of a patient who is lacking healthy diversity in their microbiome.

How FMT works: By engrafting those with weakened microbiomes with more bacteria, that bacteria will be able to help reinvigorate their gut microbiome. By treating the microbiome, the hope is that the symptoms associated with the microbiome-related illness will be gone.

Feb, 2. 2021

The gut microbiome is the densest of our microbiomes. There are trillions of bacteria living in our gut.

The overall composition of the gut microbiota and the presence or absence of specific species is important for homeostasis and tolerance of the immune system

The first FMT for IBD was successful in 1989. FMT is not yet approved in Canada as a clinical therapy. It is accessible only through ongoing clinical trials. More than 100 trials have been done globally very recently as FMT looks promising.

FMT Success rate

Disease	Success Rate
<i>Clostridium Difficile</i>	90%
Ulcerative Colitis	44%
Crohn's Disease	61%
Autism	60%

FMT has been reported to be 90% effective in CDI, in IBD however, FMT was effective at inducing clinical remission to 52 % in Crohn's disease (CD) patients and 32 % in ulcerative colitis (UC)

Feb, 3. 2021

Disease burden - Currently 270,000 Canadians are living with IBD requiring lifelong medication and often significant morbidity. While multiple treatment options exist for IBD, many patients will either fail to respond or lose response to therapy.

Crohn's affects 1.3 million Americans and its prevalence is rising globally. It is a disease with no cure; at the moment, treatment only exists to decrease Crohn's Disease symptoms.

FMT studies conducted on IBD patients have identified differential recipient responses associated with variability in the donor stool.

IBD does not result from an overgrowth of one specific pathogen. Rather, the disease is likely brought on by complex interactions involving the host's genetics, immune system, and gut microbiota

It was found that recipient microbial diversity at baseline predicted response to FMT, that microbial diversity increased with FMT, and that this persisted for 8 weeks following FMT.

One of the biggest factors is donor gut microbiome diversity which is why it's important to identify microbiome characteristics of donor stool which can increase much-needed FMT efficacy. In other words, to model donor microbiome leading to FMT success

This my project idea and I **choose donor stool microbiome as a variable for my project.**

My project research focus

To understand **if** high diversity of the gut microbiota, particularly in the donor, appears to best predict an IBD patient's response to FMT and if Short-term changes in dietary patterns can have some influences on gut microbiota composition.

Feb, 4. 2021

Hypothesis:

Pre-donation short-term diet modulation of the stool donor "by introducing exclusive vegetarian diet and eliminating meat diet" can lead to the diverse microbiome in IBD recipients and increased FMT efficacy.

Procedure and Methods:

Identify the difference in gut microbiome diversity of healthy subjects and IBD patient

Utilize FMT as a treatment to populate/transplant the recipient microbiome

Examine different parameters affecting FMT treatment response

Understand the role of donor selection in FMT success and find out if FMT success was donor-dependent

Study changes in recipient's microbiome after transplant

Find the difference in microbiome diversity of responders and non-responders by review of microbiological data and explain the variation in recipient responses.

Establish donor microbiome effect on recipient gut microbiome diversity

Establish the similarity between donor and recipient microbiome profile after transplant and the ability of the donor to transfer high levels of specific species to recipients

Establish the factors that can enhance donor gut microbiome diversity

Review the influence of dietary changes on donor's gut microbiome

Evaluate Meat Vs Plant-Based Diet Effect On Intestinal Bacteria

Assess the difference in microbiological composition of healthy subjects exclusive on in vegetarian diet and subjects on animal diet and meat diet

Examine if Short-term dietary changes can have some influences on intestinal microbiota composition

Tomorrow:

Find different parameters affecting FMT

Find what is the difference between clinical response and Endoscopic remission as some trials did not include colonoscopy to assess disease remission.

Initially, my hypothesis was to look into the effect of short-term diet modulation but during my research, I found out diet can alter the gut microbiome in 24 hours, so this gave me two more questions to look into my project.

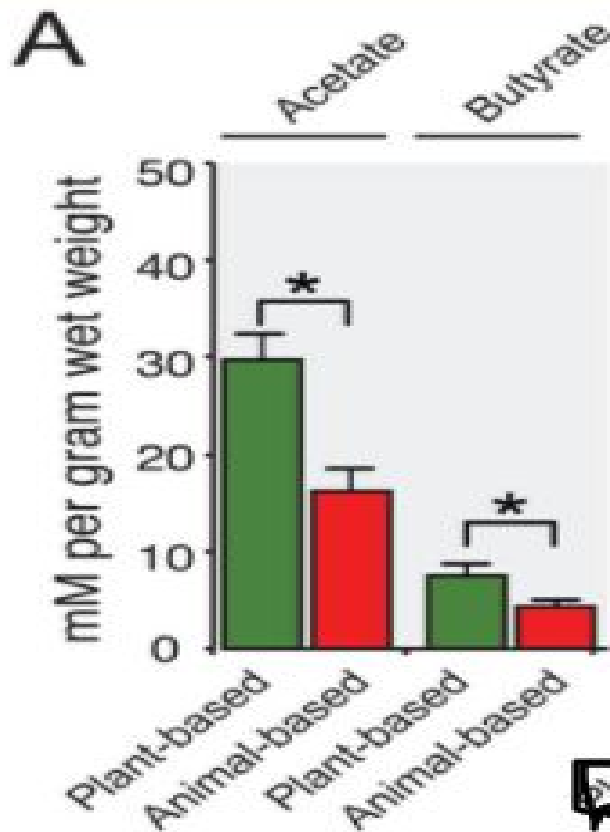
Identify how rapidly the diet can alter the gut microbiome and optimal duration of diet modulation.

Feb, 6. 2021

Findings:

- 1) FMT success is donor-dependent (in a randomized control trial investigating the efficacy of FMT). 75 patients with ulcerative colitis were given weekly enemas containing either fecal material or placebo for a period of 6 weeks. FMT was superior to the placebo, resulting in higher rates of endoscopic and clinical remission (24 vs. 5%, respectively). Out of the nine patients who achieved remission, seven had received FMT from the same donor. Thus, it was established that FMT success is donor-dependent
- 2) FMT success lies in the ability of the donor to transfer high levels of particular species to recipients -For IBD transfer of butyrate-producing is important for therapeutic restoration.
- 3) Microbial and metabolic profiling data on donors and recipients before and after FMT shows the microbial diversity of the stool donor to be one of the most significant factors influencing FMT outcome.
- 4) FMT recipients experience a significant increase in intestinal microbiota diversity, typically shifting in composition toward the profile of their respective stool donor
- 5) Responders (those who achieve a clinical response to FMT treatment) typically exhibit a higher microbial diversity and significantly higher bacterial richness than non-responders
- 6) 6) A specific microbial and metabolic signature
- 7) The gut microbiota composition of vegetarians and omnivores using qPCR analysis and showed the abundance of Firmicutes and Bacteroidetes in the vegetarian group and Proteobacteria being higher in the omnivore group. For IBD, transfer of butyrate-producing taxa is important for

8) therapeutic restoration



Findings on diet and gut microbiome - Meat Vs Plant-Based Diet Effect on Gut:

- Animal diet alters the gut microbiome significantly and immediately. One type of bacterium that flourishes in a meat-laden diet is *Bilophila*
- Diets rich in complex carbohydrates show fewer pathogenic species of bad bacteria such as Enterobacteriaceae than diets higher in fat or protein.
- Modifying the diet can lead to rapid changes in microbiota within the first day
- A study reported human gut microbiome changes after only 24 hours after shifting between plant and animal protein-based diets
- Microbial restoration can lead to alterations in metabolic outputs, which may be responsible for resetting the gut homeostasis in dysbiotic IBD and increase the efficacy of transplant.
- Specific genera within the *Clostridium* clusters *IV* and *XIVa* (e.g., *Roseburia*, *Oscillibacter*) have been shown to increase in relative abundance in responders following FMT. Likewise, stool donors that are rich in specific members

of *Clostridium* clusters *IV* and *XIVa* have been found to be predictive of sustained FMT response in IBD patients.

- Increased production of butyrate by key members within *Clostridium* clusters *IV* and *XIVa* has been associated with prolonged clinical remission in IBD in response to FMT therapy

Findings on the optimal duration of diet modulation:

- A study used 16S rDNA pyrosequencing to look into the effects of short-term diet on the microbiota of six healthy American volunteers over five consecutive days after being administered two different diets: an animal-based diet and a plant-based diet
- Animal diet led to a decrease in the levels of Firmicutes, in particular Roseburia spp, while the vegetarian diet led to the abundance of bile-tolerant microorganisms
- In one other study, nine volunteers were put on two extreme diets (vegetarian and meat) for five days each to find out whether fibre (or lack of it) could alter gut bacteria more rapidly
- The relative abundance of various bacteria species shifted within a day after the food reached the gut and after the volunteers had spent about three days on each diet, the bacteria in the gut even started to change their behaviour

Feb, 12. 2021

Analysis:

- FMT recipients experience a significant increase in gut microbiota diversity, typically shifting in composition toward the profile of their respective stool donor so we propose to alter the donor microbiome by diet modulation.
- Increased production of butyrate by members within *Clostridium* clusters *IV* and *XIVa* has been associated with prolonged clinical remission in IBD in response to FMT therapy
- Animal-based diet led to a decrease in the levels of Firmicutes, in particular, Roseburia and an increase in Proteobacteria

- vegetarian diet increase levels of clostridium clusters IV and XIVa which In turn result in increased butyrate production in as less as 2 days and shows microbiome alteration in 5 days
- A meat diet alters the gut microbiome significantly and immediately with in 24hrs
- In current FMT clinical trials, there are no significant studies reporting alteration of donor diet prior to stool donation

Conclusion:

- My research project recommends and shows novel approach of altering donor diet 5 days prior to stool donation by not only introducing vegetarian diet to increase butyrates but strictly eliminating meat diet to enrich donor microbiome with specific bacterial strains bacteria .
- This intervention can lead to enrich microbiome in recipient with specific strains which are missing in IBD patients geared to induces remission in patients.
- My hypothesis is correct!

For Reference From Literature

Microbiological Analysis:

“Microbiota analysis was performed in 17/41 UC, 4/11 CD, and 3/4 pouchitis studies [Table A7, available as Supplementary data at *ECCO-JCC* online]. Most studies assessed luminal [faecal] samples with only a limited number analysing mucosal [biopsy] samples.^{33,63,66,67} A range of studies commented on recipient microbiota changes after FMT, with increased α -diversity or richness^{9,11,38,42,48,50,61,66} and a shift towards the donor profile, which in some cases was associated with colonisation by donor-derived taxa, though this was reported in patients both with clinical benefit^{10,26,32,35,57,60,65} and without improvement.^{33,36} Some studies did report that the increase in recipient microbial diversity after FMT was greater in responders relative to non-responders.^{11,42,61,66} In particular, the study by Paramsothy *et al.*^{11, 66} found that recipient microbial diversity at baseline predicted response to FMT, that microbial diversity increased with FMT, and that this persisted for 8 weeks following FMT. In this study, the multi-donor FMT batches used for the FMT infusions had substantially greater microbial diversity relative to the individual donors. A correlation between increased donor microbial diversity and therapeutic success of FMT in UC has been identified in some studies^{42,68} but not others.⁵¹ In the RCT by Moayeddi *et al.*,⁹ there was a trend towards a difference in recipient outcomes based on particular donor, with improved outcomes noted in patients receiving infusions **derived from donor B [p = 0.06]**. A variety of taxa were reported to be associated with both FMT in IBD in general, and more specifically with therapeutic outcomes in IBD patients, across the identified studies.”