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Fecal microbiota transplantation reverses antibiotic and chemotherapy induced gut dysbiosis in mice

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Background:

Fecal microbiota transplantation (FMT) is applied with clinical success in relapsing Clostridium difficile infection, but has had less study in the restoration of microbiome diversity and composition following antibiotics or chemotherapy, both known to cause major disruption to the gut microbiota.

Objective:

- **Assess the efficacy of FMT in a mouse model to restore antibiotic and chemotherapy induced gut dysbiosis and to identify bacterial species associated with the restoration of the dysbiosis.**

Method:

- C57BL/6J mice treated with 1 week ampicillin
- 1 day after antibiotic discontinuation : one intraperitoneal injection of 150 mg/kg 5-Fluorouracil
- Feces from untreated mice were resuspended in PBS and given by oral gavage during 3 days, starting one day after the chemotherapy administration.
- shotgun metagenomics with MiSeq Illumina sequencing platform

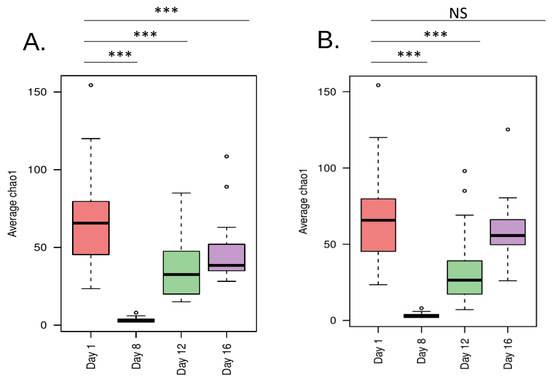

Fig 1. Alpha diversity is decreased in mice that received ampicillin and chemotherapy (A) and restored by FMT (B).

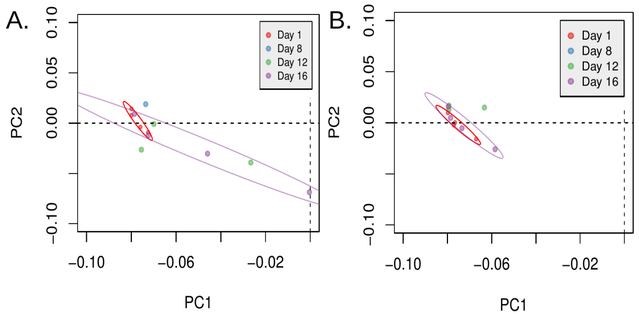

Fig 2. Species beta diversity is decreased in mice exposed to chemotherapy and ampicillin (A) and is restored by FMT (B). Principal coordinate analysis (PCoA) of Bray Curtis distances.

Main results:

FMT restores richness and diversity

- Ampicillin caused an immediate decrease in richness and diversity that persist one week after treatments discontinuation.
- Disruption of the intestinal microbiota was restored immediately after FMT. [Fig 1,2]

Taxonomic profile is modified by antibiotics and chemotherapy [Fig 3] **:**

- Decreased species including *Clostridium scindens* and *Faecalibacterium prausnitzii*
- Incerased species uncluding *Enterococcus saccharolyticus, Enterococcus faecalis* and *Enterobacter cloacae*.

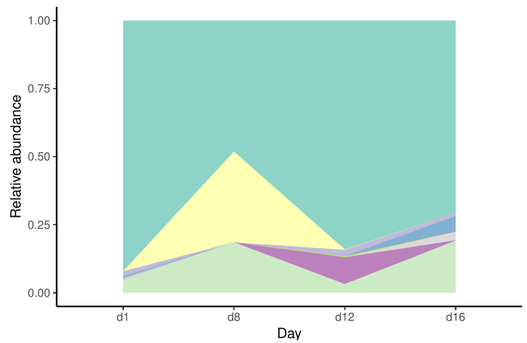

Fig 3. Longitudinal follow up of 10 most abundant genii in a mouse exposed to antibiotic treatment from day 1 to day 7 and chemotherapy on day 8.

Taxonomic imbalance was restored by FMT :

- *Barnesiella, Clostridium leptum* and *Clostridium butyricum,* known to exhibit anti-inflammatory properties were significantly increased after FMT and *Faecalibacterium prausnitzii* levels were restored immediately after FMT.

Functional profile is modified by antibiotics and chemotherapy and restored by FMT:

- Increased functional modules including cobalamin biosynthesis and riboflavin biosynthesis, reported increased in acute intestinal inflammation models.
- Decreased in secondary bile acid biosynthesis, known to inhibit the growth of *Clostridium difficile*
- After FMT, *Lactobacillus johnsonii* was positively correlated with conjugated bile acid biosynthesis and modules linked to the pentose phosphate pathway, known to protect against oxidative stress.

Conclusions:

- Antibiotic and chemotherapy lead to a critical decrease in key ‘health-promoting’ species and to an altered functional profile.
- After FMT, we observed a rapid restoration of *Clostridium scindens*, which has been shown to inhibit the growth of *Clostridium difficile* through bile acid homeostasis and conversion of primary bile acids, and *Clostridium butyricum* known to resolve acute experimental colitis.
- Our results should help to customize and design consortium of bacteria for transplantation of microbiome-targeted therapeutics.