The gut microbiome enhances anti-PD-1 efficacy in a tumor-agnostic manner: results from a phase II trial of fecal microbiota transplantation and anti-PD-1 re-induction in MSI-H refractory cancers

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BACKGROUND

The gut microbiome has been associated with response to anti-PD-1 therapy in melanoma, lung cancer, and kidney cancer. Small clinical trials combining gut microbiome modulation via fecal microbiota transplantation (FMT) and anti-PD-1 therapy showed promising results. However, the mechanisms driving the gut microbiome effect on anti-tumoral immunity remain elusive.

FMT TRIAL

We conducted a single-center, phase II clinical trial enrolling 15 patients with metastatic, anti-PD-1 refractory microsatellite instability-high (MSI-H) cancers, regardless of their primary cancer type (NCT04729322). Responders were defined as CR, PR, or SD ≥4 months per RECIST criteria.

- Ten patients underwent antibiotic preconditioning prior to FMT via colonoscopy, followed by maintenance FMT via capsules.
- Five patients underwent FMT via colonoscopy only, without antibiotic preconditioning or capsules.

Patients

- 15 metastatic, MSI-H, anti-PD-1 refractory patients with CRC (10), Small bowel adenocarcinomas (2), pancreatic adenocarcinoma (1), endometrial adenocarcinoma (1), and pineal brain tumor (1).
- Previous treatments: median: 3, max:14

TRANSLATIONAL STUDIES

Melanoma and CRC-bearing germ-free and specific-pathogen free mice were treated with anti-PD-1 and either FMT from the trial's CR donor (Superdonor), FMT from a metastatic melanoma patient who did not respond to anti-PD-1 therapy, or a bacterial consortium derived from the trial's CR donor.

RESULTS

FMT and anti-PD1 re-induction enhanced efficacy in patients anti-PD-1 refractory MSI-H cancers

Treatment Outcomes

- Disease Control Rate was observed in 27% (4/15) of patients.
- 2 small bowel adenocarcinoma patients, CR > 2 years, SD of 16 months, respectively. 2 CRC, SD of 5 months. All responders had a primary anti-PD-1 failure.
- One grade 3/4 immune-related adverse event occurred. Grade 3 hepatitis in a patient with a history of immunotherapy-related colitis.

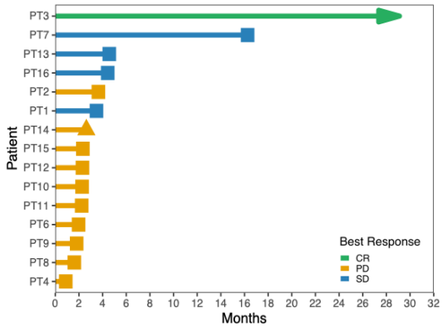

Fig. 1. Time to response amongst the 15 patients treated with FMT and reinduction of anti-PD-1. Objective radiological response by RECIST criteria as CR, PR, SD ≥4 months.

CONCLUSIONS

FMT enabled response to re-introduced anti-PD-1 in patients with IO refractory MSI-H cancers. Our results suggest that the gut microbiome affects anti-tumoral immunity in a tumor-agnostic manner. Molecular profiling of clinical and pre-clinical samples is ongoing to unveil the mechanisms driving this effect.

A SYNTHETIC MICROBIAL CONSORTIUM AS AN EFFECTIVE ALTERNATIVE TO FMT

In collaboration with Kanvas Biosciences, we developed a synthetic bacterial consortium based on a CR-donor from the MSI-H FMT trial (Superdonor) and tested it in germ-free and specific-pathogen-free preclinical models of melanoma and colorectal cancer.

Taxonomic and Functional Equivalence Between Source and Synthetic Consortium

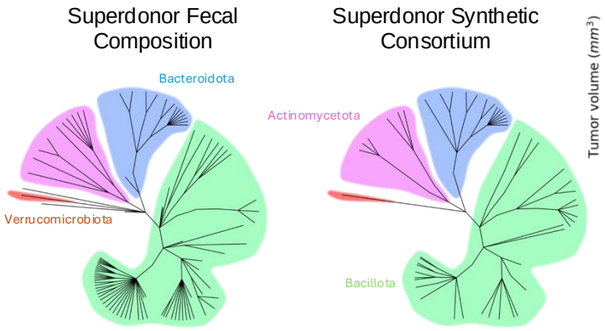

Fig. 2. Comparison between Superdonor Fecal Composition (left, >0.1% abundance, 3 separate donations) and a synthetic bacterial consortium (right). Colors represent key phyla, as labeled.

Experimental Design Using Tumor-Bearing Pre-Clinical Models

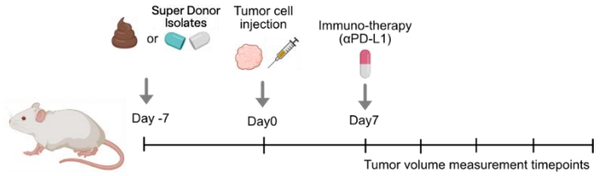

Fig. 3. Experimental design of studies in germ-free (GF) and specific-pathogen free (SPF) mice that received FMT from a complete responder (CR) donor, a non-responder (NR), or Superdonor consortium before tumor injection [2.5 × 105 to 8 × 105 BRAFV600E/PTEN−/− (BP) tumor cells or MC38 cells] and treatment with anti–PD-L1.

Synthetic Consortium Replicates FMT's Anti-Tumor Effects

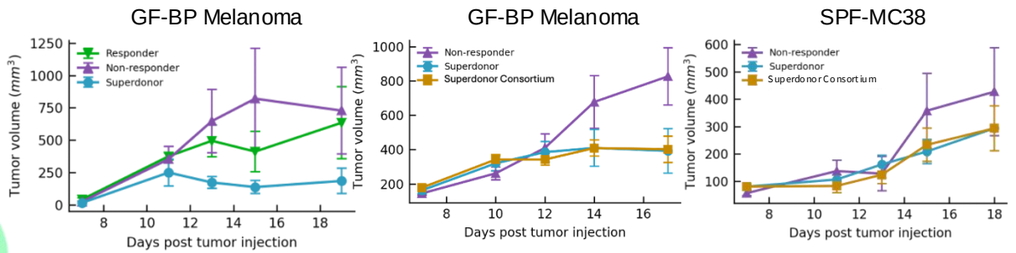

Fig. 4. Independent mouse tumor growth experiments comparing volume of tumors in mice who received FMT from a melanoma-CR (responder), melanoma-NR (non-responder), CRC-CR (superdonor), or CRC-CR superdonor consortium before tumor cell injection and treatment with anti–PD-L1.

Synthetic Consortium Engrafts in Clinical FMT Recipients and in Pre-Clinical Mouse Models

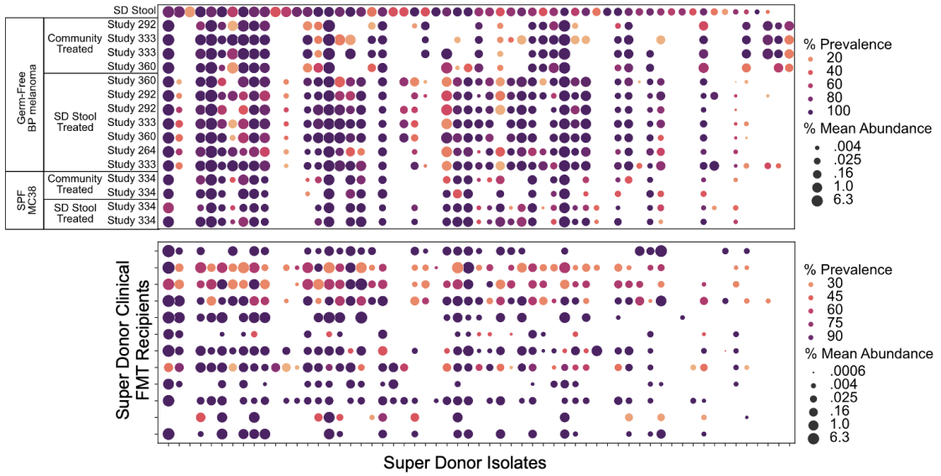

Fig. 5. Engraftment dynamics of Superdonor derived isolates in preclinical models and FMT recipients

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