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# POSTER ABSTRACTS

## 722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

### Rational Modification of Human Gut Microbiome and Metabolites By Dietary Resistant Starch in Allogeneic Hematopoietic Stem Cell Transplantation: A Feasibility Study

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Allogeneic hematopoietic stem cell transplantation (allo-HCT) is limited by acute graft versus host disease (GVHD). GVHD is the principal cause of non-relapse mortality (NRM) and a major cause of morbidity after allo-HCT. Recent published experimental data demonstrated that altering the microbiome-metabolite axis regulates acute GVHD severity. Specifically, short chain fatty acid (SCFA) butyrate was significantly decreased in the intestinal epithelial cells (IECs) of mice experiencing GVHD, while restoring butyrate levels by increasing intestinal butyrate-producing bacteria, reduced experimental acute GI GVHD severity and mortality. Prebiotics usually refer to indigestible carbohydrates that are metabolized by the intestinal microbiota to produce microbial metabolites, such as SCFAs, that serve as nutrients for IECs. Administration of defined quantities of resistant potato starch (RPS), as a prebiotic, to normal healthy human volunteers promoted increase in butyrogenic bacteria and increased intestinal levels of SCFA butyrate to a greater extent than other commercially available resistant starch preparations tested. These data form the rationale for this study and led to prospectively study the clinical feasibility and impact of the administration of RPS as a prebiotic dietary intervention on the intestinal microbiota and its dependent metabolites in allo-HCT recipients.

Adults undergoing human leukocyte antigen-matched, related-donor myeloablative allo-HCT were recruited and received RPS orally daily from day -7 to day 100 after allo-HCT. Stool samples were collected in the OMNIgene-Gut® (DNA Genotek) collection kit. Fecal samples were subjected to 16S rRNA gene sequencing to determine microbiota composition and quantification of fecal SCFAs was performed by liquid chromatography. Blood specimens were collected using standardized protocols. The effect of RPS on plasma SCFAs and > 200 other metabolites was longitudinally assessed using targeted and global metabolomic analyses. Mass spectrometry was utilized for quantification of plasma metabolites. The primary objective was to assess the feasibilty and test the effect of RPS on the structure of the patients' intestinal microbiome. Metrics for the feasibility of this dietary intervention were prespecified by setting a target for $\geq$ 60 % of patients to adhere to $\geq$ 70% of scheduled doses. We hypothesized that RPS would be feasible and increase stool butyrate levels as a byproduct of microbial metabolism. Key secondary objectives were to longitudinally evaluate plasma metabolites in recipients of RPS compared to historical controls as well as assess tolerability of RPS in allo-HCT recipients.

Ten subjects were enrolled. The primary endpoint was met. Feasibility exceeded the preset goal of $\geq$ 70% adherence to scheduled dosages in $\geq$ 60 % of patients as 8 of the 10 patients (80%) received $\geq$ 70 % of scheduled doses. Intestinal butyrate levels were significantly higher while participants were on RPS as compared to when they were not on RPS ($p < 0.0001$) (fig. 1A). We observed longitudinal changes in plasma metabolites post allo-HCT compared to baseline independent of whether allo-HCT recipients received RPS ($p < 0.0001$) (fig. 1B). In RPS recipients, the dominant plasma metabolites were, however, much more stable across timepoints when compared to historic controls suggesting a greater equilibrium in their production and consumption (fig. 1C). The median age of participants was 57 years (range 52-62 years). All subjects received standard GVHD prophylaxis with tacrolimus and methotrexate as well as standard antibiotic prophylaxis with levaquin, and standard neutropenic fever treatment with IV cefepime (90%) or IV vancomycin, No adverse effects/toxicities attributed to RPS were observed and longitudinal specimens were collected successfully (table 1).

This study showed that a dietary intervention using RPS in allo-HCT recipients is feasible, and was able to rationally alter the salutary intestinal microbial metabolite SCFA butyrate, despite the utilization of several HCT related medications, includ-

ing antibiotics. These data demonstrate translation of fundamental discoveries in mouse allo-HCT studies, to testing RPS in healthy humans, to showing that RPS is a feasible microbiome-modifying intervention in allo-HCT recipients, and that a prebiotic strategy can now be applied and tested to mitigate acute GVHD in allo-HCT.

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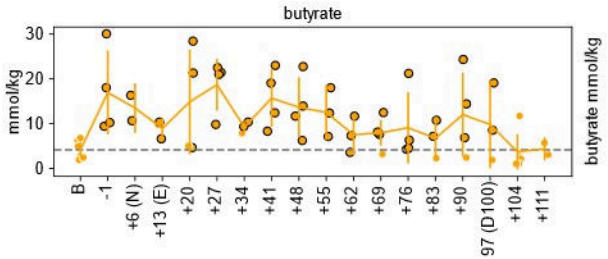
Figure 1A



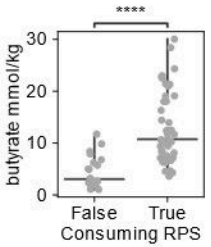




Figure 1C

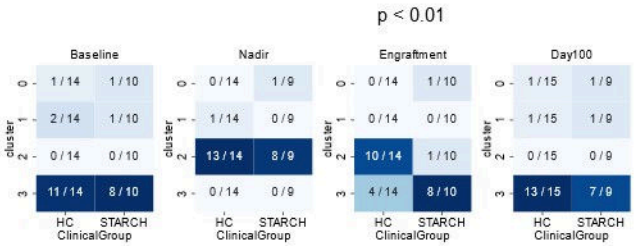



Figure 1B

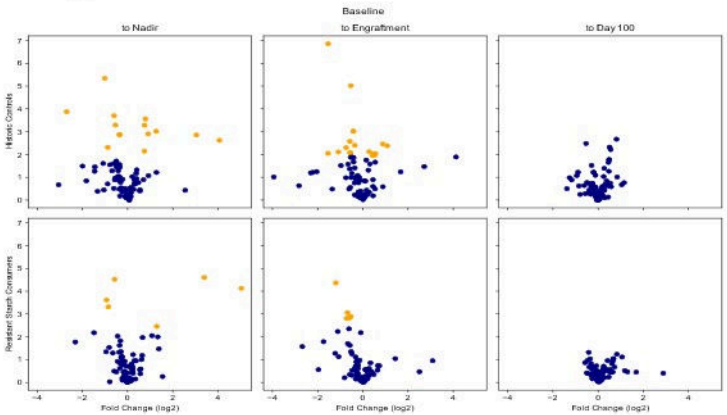



Table 1

| Patient #: | 1 | 2 | 3 | 4* | 5 | 6 | 7* | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| % doses taken: | 78 | 99 | 97 | 33 | 88 | 79 | 31 | 74 | 92 | 97 |
| % specimens collected: | 93 | 93 | 87 | 40 | 100 | 100 | 27 | 73 | 100 | 93 |

- Median % doses taken adherence rate: **84%**
- Median % biospecimens collected: **93%**
- No adverse events related to RPS administration in any patient

** Patient 4 relapsed and came off study early. Patient 7 came off study early due to personal preference, not due to any study-related adverse events.*

**Figure 1**