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Myeloma drug, bortezomib, causes dysregulated gastric and intestinal motility in mice

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Introduction

- **Bortezomib** is a highly effective, frontline myeloma therapy
- Its clinical use is limited by symptoms of **gastrointestinal (GI) dysfunction**, which occur in up to **84% of patients**
- Unlike chemotherapy, bortezomib does not cause mucosal changes in the gastrointestinal tract (Fig 1), despite similar GI symptom profiles

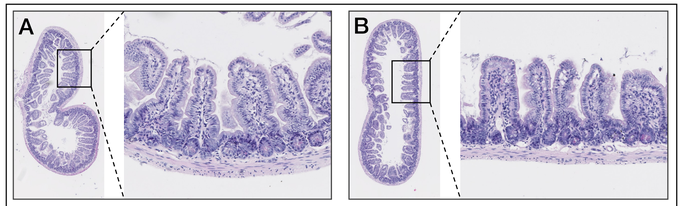

Figure 1. Mucosal architecture in ileum of **(A)** vehicle-treated (3.904% DMSO, i.v.) and **(B)** bortezomib-treated (1 mg/kg, i.v.) mice.

? Mechanisms driving bortezomib-induced gastrointestinal dysfunction remain unknown

Aim: To characterise changes in the gastrointestinal microenvironment induced by bortezomib in a preclinical setting

Methods

Treatment

C57BL/6 mice treated twice weekly for two weeks with
i) Bortezomib (1 mg/kg, i.v.), or
ii) Vehicle control (3.904% DMSO, i.v.)

48 h after final treatment

Outcome measures

- Organ toxicity: Organ wet weights
- Total gastrointestinal transit time: Evans blue test
- Intestinal permeability: 4kDa FITC-dextran assay
- Microbiome composition: 16S rRNA gene sequencing of pre- and post-bortezomib faecal samples

Results

1. Bortezomib causes gastroparesis and increased intestinal motility in mice

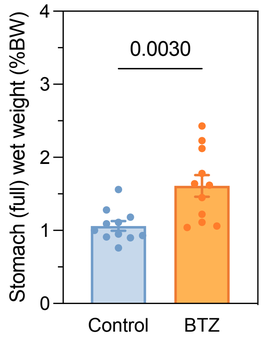

Figure 2. Bortezomib caused a profound increase in (full) stomach weight in mice, compared to vehicle-treated controls (P=0.0030, unpaired t-test).

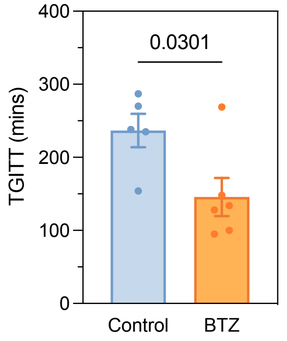

Figure 3. Total gastrointestinal transit time (TGITT) was measured as time taken from intragastric gavage of Evans blue solution until the presentation of the first blue faecal pellet. TGITT was decreased in bortezomib-treated mice compared to vehicle controls (P=0.0301, unpaired t-test).

2. Bortezomib causes increased intestinal permeability

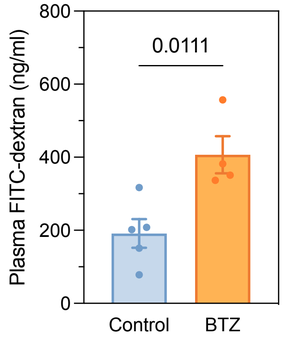

Figure 4. 4kDa FITC-dextran was administered via oral gavage 2 hours prior to termination and post-gavage fluorescence levels measured in blood to determine intestinal permeability. Bortezomib significantly increased intestinal permeability compared to controls (P=0.0111, unpaired t-test).

3. Bortezomib causes differences in the β-diversity of the gut microbiome

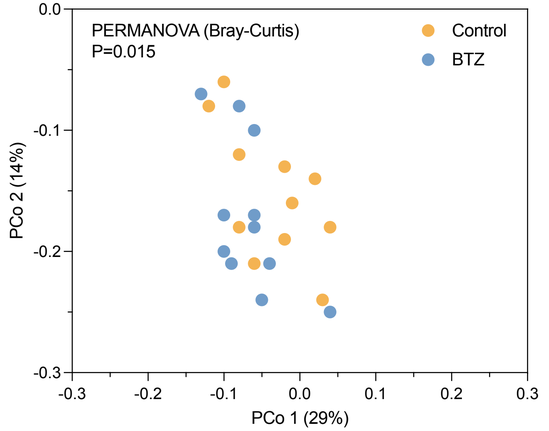

Figure 5. Pre- and post-bortezomib faecal samples were collected and 16S rRNA gene sequencing used to determine gut microbiome composition. PERMANOVA analysis identified differences in the β-diversity of the gut microbiome in bortezomib-treated mice, after four treatments, compared to vehicle controls (P=0.015).

Conclusions and future directions

- ✓ Bortezomib induces changes in the gastrointestinal microenvironment
- Findings highlight possible mechanisms driving bortezomib-related gastrointestinal symptoms, e.g. gastroparesis, increased motility and permeability, altered microbial composition
- ⇢ Future investigations should explore gut microbiota-enteric nervous system interactions as potential causative mechanism