Interrogating the role of the gut microbiota in bortezomib-induced peripheral neuropathy through human-to-mouse faecal microbiota transfer

@SuppOncRG

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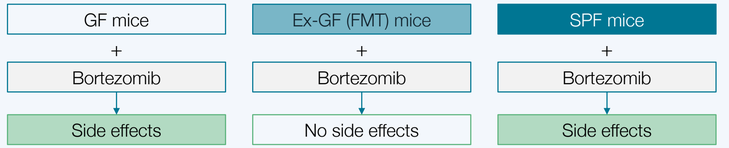
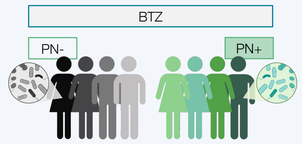
Introduction

- The gut microbiota is increasingly recognised to modulate side effects of cancer treatment, including peripheral neuropathy[1,2] and symptoms of gastrointestinal dysfunction[3]
- Faecal microbiota transfer (FMT) alters symptom profiles of bortezomib toxicity in germ-free (GF) mice[4], demonstrating a complex relationship between gut microbiota and bortezomib side effects

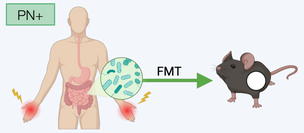


Aims

1. Do people with bortezomib-induced peripheral neuropathy have distinct microbial traits compared with those without symptoms?



2. Can peripheral neuropathy symptoms can be transferred from humans to mice via faecal microbiota transfer?



Clinical cohort study design

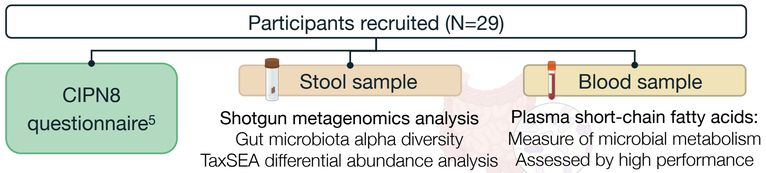


Table 1. Cohort demographics

Characteristic	N (%)	Characteristic	N (%)
Age, years		Months since diagnosis	
Mean [SD]	66.5 [11.3]	0-24	6 (20.7%)
Median	68.0	25-60	10 (34.5%)
Range (min, max)	37.0, 83.0	61-240	12 (41.4%)
Sex		Unknown	1 (3.4%)
Female	16 (55.2%)	Front-line regimen	
Male	13 (44.8%)	VCD	15 (51.7%)
Disease type		VRD	9 (31.0%)
MM + AL	7 (24.1%)	VDD/VPD	3 (10.3%)
MM only	22 (75.9%)	Unknown	2 (6.9%)

MM: Multiple myeloma; AL: Amyloidosis; VCD: Bortezomib, cyclophosphamide, dexamethasone; VRD: Bortezomib, lenalidomide, dexamethasone; VDD: Bortezomib, daratumumab, dexamethasone; VCD: Bortezomib, pomalidomide, dexamethasone

The gut microbiota of people with high-phenotypic bortezomib-induced peripheral neuropathy has reduced alpha diversity and functional capacity

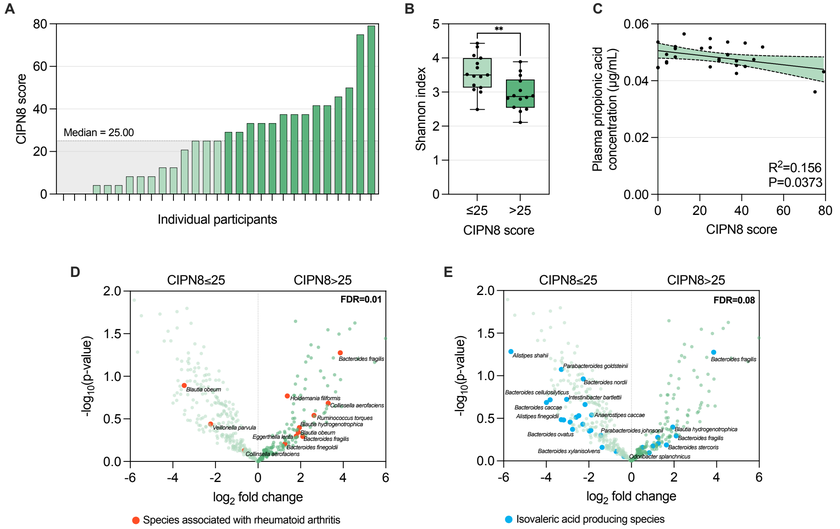
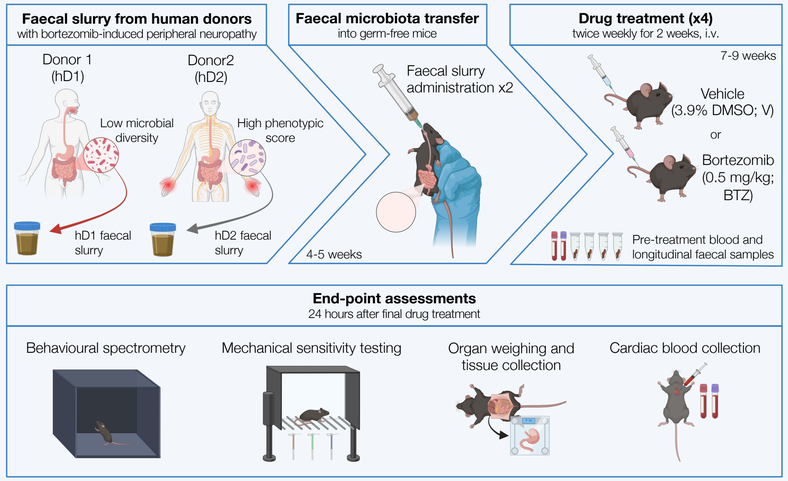


Figure 1. Distribution of CIPN8 scores (A). Alpha diversity of gut microbiota (B). Plasma propionic acid vs CIPN8 score (C). Volcano plots of differential taxon sets between phenotypic groups (D, E). **P<0.01.

Human to mouse study design



Evidence of human to mouse transfer of symptoms associated with reduced animal well-being consistent with bortezomib effects

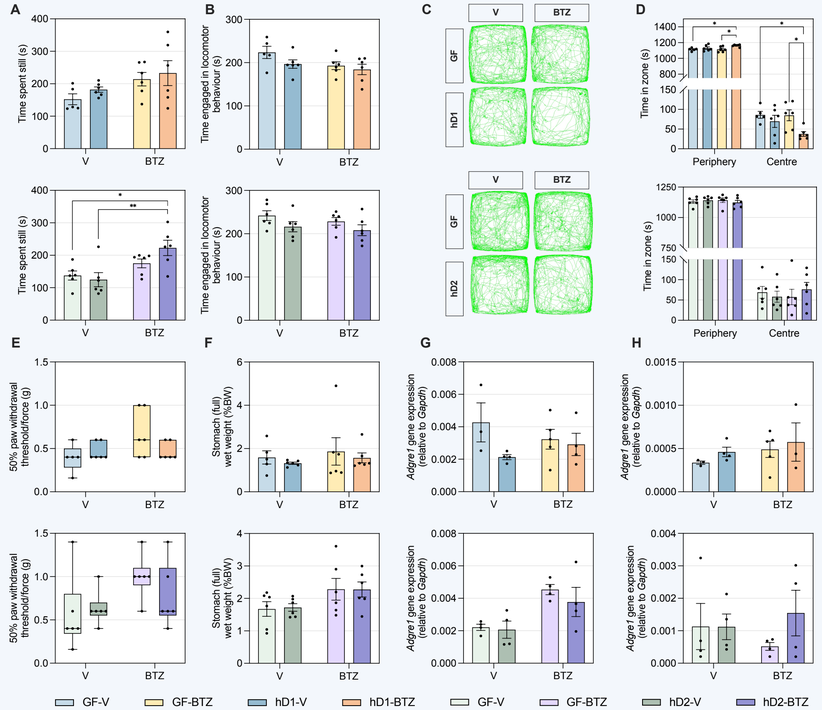


Figure 2. Time engaged in still (A) and locomotor behaviour (B), and representative track maps of total distance travelled over 20 minutes (C). Time spent in periphery and centre zones (D). Hind paw sensitivity to mechanical stimulus (E). Full stomach weight as percent body weight (F). Expression of *Adgre1* (gene encoding macrophage marker F4/80) in dorsal root ganglia (G) and nodose ganglia (H). **P<0.01, *P<0.05.

Conclusions

- People with high-phenotypic bortezomib-induced peripheral neuropathy have distinct gut microbial traits compared with low-phenotypic individuals
- Preliminary findings from human to mouse transfer provide some evidence for gut microbiota causality in bortezomib side effects
- Higher powered studies are required to determine whether these effects are statistically- and clinically-meaningful

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References: [1]Ramakrishna et al., 2019. Sci Rep 9(1), 20324. [2]Shen et al., 2017. Nat Neurosci 20(9), 1213-16. [3]Mafe & Busselberg, 2025. Biomedicines 13(2), 422. [4]2024. Supp Care Cancer 32(1), 434. [5]Li et al., 2023. J Natl Compr Cancer Netw 21(2), 125-132.