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Title: A Clinical Stage Oral Beta-Lactamase Therapy Prevents Antibiotic-Mediated Damage of the Gut Microbiome

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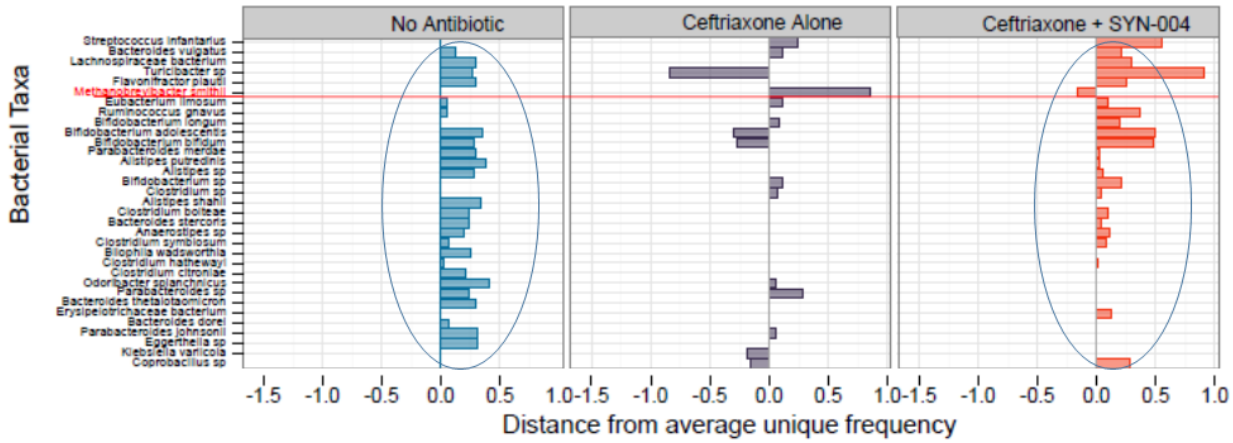
Background: Antibiotic (abx)-mediated disruption of intestinal flora is a risk factor for *C. difficile* infection (CDI). SYN-004 is designed to degrade IV abx in the GI tract to preserve the microbiome and prevent CDI and antibiotic-associated diarrhea (AAD). Phase 1 clinical studies demonstrated safety and tolerability at all doses. Phase 2 studies are in progress to assess intestinal ceftriaxone (CRO) degradation in ileostomy subjects.

Methods: SYN-004, a beta-lactamase engineered to degrade cephalosporins such as CRO, was manufactured in *E. coli* and formulated into enteric-coated pellets that release enzyme at pH >5.5. Efficacy studies were performed in dogs and humanized pigs.

Results: Jejunal-fistulated dogs (n=6) were treated with CRO (IV, 30 mg/kg) and/or SYN-004. Abx alone resulted in high intestinal CRO levels (C_{max} of 1500 ug/g). In the presence of SYN-004 ($\leq$5ug/g), gut CRO was completely eliminated. Neonatal pigs populated with human fecal microflora received CRO (IP, 50 mg/kg), and/or SYN-004. Whole genome sequence analyses of fecal DNA revealed SYN-004 protection of species abundance and prevention of the CRO-induced increase in methanogenic archaea, *M. smithii*, a species associated with constipation, IBS, and obesity (Figure 1). Additional pig studies are in progress.

Conclusions: Orally-delivered SYN-004 completely eliminated CRO from the GI tract of dogs and protected the gut microflora from abx-mediated damage in humanized pigs. These data demonstrate that SYN-004 has the potential to become the first prophylactic therapy designed to prevent abx-mediated microbiome damage, including CDI and AAD.

Figure 1: Centroid classification of fecal bacterial species



Centroid classification (pamr R package) compared the average frequency (absolute abundance) of each bacterial species with the deviation of the centroid from each group to the overall centroid of all groups. The ovals indicate that the No Antibiotic control and the ceftriaxone+SYN-004 groups display less severe distortion of species abundance than the ceftriaxone alone group. The red line indicates an over abundance of the methanogenic archaea, *M. smithii,* in the ceftriaxone alone group. *M. smithii* has been implicated in constipation, irritable bowel syndrome, and obesity.