SYN-006, a Novel Carbenapenem, Intended to Protect the Gut Microbiome from Antibiotic-Mediated Damage, May Also Reduce Propagation of Carbenapenem-Resistant Pathogens

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ABSTRACT

Background: Beta-lactam antibiotics that are excoriated in bile can damage the gut microbiota, leading to antibiotic resistance, inflammation, and predisposing to antibiotic resistance. SYN-006 (ribamase) is a beta-lactamase intended for oral use with certain beta-lactam antibiotics to protect the GI tract to protect the microbiome. Ribamase was evaluated in a phase 2b clinical study and its primary endpoint of significance of carbapenem or SYN-006, C. constellatus, is added to control. The graph displays the highest antibiotic concentration at which bacterial growth was completely inhibited, indicating antibiotic resistance.

RESULTS

Antibiotic Degradation Profile

Purified SYN-006 is capable of degrading antibiotic compounds from beta-lactam antibiotics, including being resistant to meropenem, and was treated with enrofloxacin (10 mg/kg, IV). Blood and intestinal samples were collected at two post-antimicrobial time points (Time 1 to 4), and during treatment (Day 4) and after antibiotics were stopped (Days 8 and 9). Heatmap analysis was used for whole-genome shotgun sequence analyses.

Conclusions: SYN-006 efficiently degrades all classes of beta-lactam antibiotics including carbapenems in vitro, and mesopenems within the dog GI tract. The pig model of carbenapenem-mediated microbiome disruption is intended to be used to evaluate the ability of SYN-006 to protect the gut microbiome and attenuate antibiotic resistance. SYN-006 has the potential to protect the gut microbiome from all classes of beta-lactam antibiotics and to reduce the emergence of antibiotic-resistant pathogens.

BACKGROUND

Many IV beta-lactam antibiotics are associated with the gut into the intestine where they can disrupt the normal microbiota and potentially lead to the emergence of resistance. SYN-006, a beta-lactamase enzyme therapy for use with IV beta-lactam antibiotics to preserve the gut microbiome by degrading antibiotic activity in the intestine. A phase 2b study met its primary endpoint of significance of C.-difficile resistant to meropenem in patients treated with SYN-006. SYN-006 is a broad-spectrum antibiotic that does not inactivate carbapenems (1). To expand this prophylactic approach to all classes of beta-lactam, we are developing SYN-006, a broad-spectrum bacterial preparative antimicrobial.

SYN-006 is manufactured in C. constellatus and purified using a chromatographic step. Resistance to degrading beta-lactam antibiotics is a key attribute for orally-delivered enzymes. SYN-006 displays stable biological activity for at least 2 weeks after lyophilization to maintain oral activity.

Oral delivery formulations of SYN-006, engineered to protect SYN-006 from low stomach pH and allow enzyme release in the upper small intestine, are currently being developed.

SYN-006 is designed and developed as the oral arm of post treatment (Day 4) to treat the MIC of microbiota in patients treated with SYN-006, was delivered to determined the extent of degradation of SYN-006, C. constellatus, was added to control. The graph displays the highest antibiotic concentration at which bacterial growth was completely inhibited, indicating antibiotic resistance.

Emergence of Antibiotic Resistance (AR) Genes after Ertapenem Exposure

Pecal resistances were analyzed based on the % gene coverage as a measure of all gene relative abundance. Antibiotic resistance of selected genes was graphically represented for each animal.

SYN-006 has the potential to protect the gut microbiome from certain IV beta-lactam antibiotics including carbenapenems and to reduce emergence of antibiotic resistance.

REFERENCES

3. Synthetic BioLogics Inc. SYN-006 is a broad-spectrum antibiotic that does not inactivate carbapenems (1). To expand this prophylactic approach to all classes of beta-lactam, we are developing SYN-006, a broad-spectrum bacterial preparative antimicrobial.

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