Significantly reducing *C. difficile* infection in patients treated with IV ceftriaxone and demonstrated protection of the gut microbiome with reduced emergence of antibiotic resistance. Ribaxamase is intended for use with IV penicillins and cephalosporins, but does not degrade carbapenems. β-lactamase-mediated microbiome protection was expanded to include oral and carbapenem antibiotics.

**Methods.** For use with oral β-lactams, a ribaxamase formulation, SYN-007, was engineered for release in the lower small intestine, distal to the site of antibiotic absorption. For use with IV carbapenems, SYN-006, a novel metallo-β-lactamase, was formulated for oral delivery. SYN-007 (10 mg, PO, TID) was evaluated in dogs treated with oral amoxicillin (20 mg/kg, PO, TID) for 5 days. SYN-006 (50 mg, PO, QID) was evaluated in pigs treated with ertapenem (30 mg/kg, IV, SID) for 4 days. Serum antibiotic levels were measured and fecal DNA whole-genome shotgun sequence analyses were performed.

**Results.** In dogs and pigs, systemic antibiotic levels were not significantly different (SYN-006, n=6; SYN-007, n=5). Fecal DNA metagenomics analysis showed that oral amoxicillin and IV ertapenem resulted in significant changes to the gut microbiome. SYN-007 and SYN-006 attenuated microbiome damage and reduced emergence of antibiotic resistance.

**Conclusion.** Ribaxamase, SYN-007, and SYN-006 have the potential to protect the normal colon microbiota from antibiotic-mediated collateral damage and to mitigate emergence and spread of antibiotic resistance, thereby broadening the utility of this prophylactic approach to include all classes of β-lactam antibiotics, delivered both systemically and orally. Antibiotic inactivation represents a new paradigm for preservation of the gut microbiome and reduction of antibiotic resistance.

**Disclosures.** S. Connelly, Synthetic Biologics, Inc.: Employee and Shareholder, Salary. C. Furlan-Freguia, Synthetic Biologics, Inc.: Employee and Shareholder, Salary. B. Fanelli, CosmodID, Inc.: Employee, Salary; N. A. Hasan, CosmodID, Inc.: Employee, Salary. R. R. Colwell, CosmodID, Inc.: Employee and Shareholder, Salary. M. Kaleo, Synthetic Biologics, Inc.: Employee and Shareholder, Salary.

**620. Oral β-Lactam Therapies Prevent Microbiome Damage and Attenuate Antibiotic Resistance From IV and Oral Antibiotics in Large Animal Models of Antibiotic-Mediated Gut Dysbiosis**

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**Session:** 64. Microbiome and Beyond

**Thursday, October 4, 2018: 12:30 PM**

**Background.** Antibiotics can damage the gut microbiome leading to overgrowth of pathogens and provide selective pressure for emergence of antibiotic resistance. SYN-004 (ribaxamase) is a clinical-stage β-lactamase formulated for oral delivery intended to degrade certain β-lactam antibiotics in the GI tract to preserve the gut microbiome. Ribaxamase was evaluated in a phase 2b clinical study that met its primary endpoint of successfully reducing *C. difficile* infection in patients treated with IV ceftriaxone and demonstrated protection of the gut microbiome with reduced emergence of antibiotic resistance. Ribaxamase is intended for use with IV penicillins and cephalosporins, but does not degrade carbapenems. β-lactamase-mediated microbiome protection was expanded to include oral and carbapenem antibiotics.

**Methods.** For use with oral β-lactams, a ribaxamase formulation, SYN-007, was engineered for release in the lower small intestine, distal to the site of antibiotic absorption. For use with IV carbapenems, SYN-006, a novel metallo-β-lactamase, was formulated for oral delivery. SYN-007 (10 mg, PO, TID) was evaluated in dogs treated with oral amoxicillin (20 mg/kg, PO, TID) for 5 days. SYN-006 (50 mg, PO, QID) was evaluated in pigs treated with ertapenem (30 mg/kg, IV, SID) for 4 days. Serum antibiotic levels were measured and fecal DNA whole-genome shotgun sequence analyses were performed.

**Results.** In dogs and pigs, systemic antibiotic levels were not significantly different (SYN-006, n=6; SYN-007, n=5). Fecal DNA metagenomics analysis showed that oral amoxicillin and IV ertapenem resulted in significant changes to the gut microbiome. SYN-007 and SYN-006 attenuated microbiome damage and reduced emergence of antibiotic resistance.

**Conclusion.** Ribaxamase, SYN-007, and SYN-006 have the potential to protect the normal colon microbiota from antibiotic-mediated collateral damage and to mitigate emergence and spread of antibiotic resistance, thereby broadening the utility of this prophylactic approach to include all classes of β-lactam antibiotics, delivered both systemically and orally. Antibiotic inactivation represents a new paradigm for preservation of the gut microbiome and reduction of antibiotic resistance.

**Disclosures.** All authors: No reported disclosures.