SYN-004 (ribaxamase), a Beta-Lactamase, Protects the Gut Microbiome from IV Antibiotics and Reduces Propagation of Antibiotic-Resistance Genes in a Porcine Dysbiosis Model

S. Connelly1, J.A. Bristo1, S. Hubert1, C. Furlan Freguia1, P. Subramanian2, N.A. Hasan2, R.R. Colwell2, J. Silitman1, M. Kalexko1
1Synthetic Biologies, Inc., Rockville, MD; 2CosmosID, Inc., Rockville, MD USA

ABSTRACT

BACKGROUND: Disruption of the intestinal microbiome is a major, unintended consequence of antibiotic treatment that can lead to overgrowth of pathogenic organisms such as Clostridium difficile. SYN-004 (ribaxamase) is an orally delivered beta-lactamase for use with ceftriaxone (IV penicillins and cephalosporins) and is designed to degrade residual antibiotics in the GI tract, thereby protecting the microbiome. A phase 2b, proof-of-concept study demonstrated statistically significant reduction of C. difficile disease and new colonization with C. difficile in naive pigs. Here, a porcine model of antibiotic-mediated gut dysbiosis was established and used to assess the ability of ribaxamase to protect the gut microbiome from IV beta-lactam antibiotics and mitigate propagation of antibiotic resistance.

RESULTS: Ceftriaxone serum levels were similar in antibiotic alone and antibiotic-coated plates, indicating that ribaxamase did not alter the systemic antibiotic level. Ceftriaxone exposure caused significant changes to the gut microbiome while CRO+ribaxamase microbiomes were not significantly different from pre-treatment microbiota. Exposure to CRO resulted in greater abundance of resistance genes compared to treatment with CRO+ribaxamase. As expected, many of the resistance genes encoded extended spectrum beta-lactamases, conferring resistance to third generation cephalosporins, including CRO. However, other genes, such as those encoding 

Ceftriaxone

Ceftriaxone + Ribaxamase

Comparison of fecal microbiota in ceftriaxone (CRO)-treated pigs reveals depletion of some species (red boxes) and overgrowth of others (yellow boxes). Ribaxamase reduced the CRO-mediated microbiome changes.

Ribaxamase Reduces Propagation of Antibiotic-Resistance Genes

Heat maps of the fecal resistome, based on % gene frequency as a measure of relative abundance, were generated. Each square represents an antibiotic-resistance (AR) gene in individual animal microbiota. The genes are displayed horizontally and fecal collection day and animal are displayed vertically. The yellow, black, and white boxes display changes in AR gene abundance caused by antibiotic treatment.

DISCLOSURES

SC, JAB, SH, CFF, JS, and MK are employees of Synthetic Biologies, Inc. PS, NAH, and RRC are employees of CosmosID, Inc., a fee-for-service provider engaged by Synthetic Biologies, Inc.