Protecting the Gut Microbiome from Antibiotics

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Digestive Disease Week

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The Gut Microbiome Regulates Human Physiology

Gut Microbiota Involved in

- Digestion
- Immune Regulation
- Protection from pathogens
- Metabolic, CV, Neuro, Immune, Inflammatory, and other diseases
- Reservoir of antibiotic resistance

Disrupted by

- Opportunistic infections
- Antibiotics
- C. difficile
- VRE
- MDR
Synthetic Biologics is developing therapies designed to protect the gut microbiome from antibiotic collateral damage.
Beta-Lactamases: From Enemies to Therapies

• SYN-004 (ribaxamase) is a beta-lactamase enzyme
• Formulated for oral delivery
• For use with selected IV beta-lactam antibiotics
• Released in the upper small intestine
• Intended to degrade antibiotics in the GI tract
• To protect gut microbiome
Ribaxamase is intended to degrade residual antibiotics in the GI tract without affecting antibiotic infection control efficacy

- Protect the gut microbiome
- Prevent opportunistic infections (*C. difficile*)
- Reduce antibiotic resistance
Ribaxamase Phase 2b Proof of Concept Clinical Study

Patients received IV ceftriaxone for a lower respiratory infection + ribaxamase or placebo

- Met primary endpoint: significant reduction in *C. difficile* disease
- Significantly reduced new colonization by VRE
- Protected the gut microbiome from antibiotic damage
- Reduced emergence of antibiotic resistance
- Did not compromise pulmonary infection control

Ribaxamase is intended for use with selected IV penicillins and cephalosporins.

**SYN-007: Delayed Release Formula for Use with Oral Beta-Lactams**

**SYN-007 → Canine Study**
- Oral amoxicillin or oral amox/clavulanate +/- SYN-007 TID, 16 doses
- Serum amox PK, after first and last dose
- Feces for metagenomic analyses collected before and after treatment

**SYN-007 → Use with oral antibiotics**
- Delayed-released formulation of ribaxamase
- Intended for release distal to site of oral antibiotic absorption
- Tested in canine model
SYN-007 Allows Oral Amoxicillin Absorption in Dogs

Amoxicillin Serum PK After 16 Doses

Kruskal-Wallis nonparametric ANOVA with Dunn’s multiple comparisons test

*Amoxicillin (ng/mL)

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<th>2</th>
<th>4</th>
<th>6</th>
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<td>30000</td>
<td>25000</td>
<td>20000</td>
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Area Under the Curve

Oral Amox
Oral Amox+SYN-007

p=0.40*

Oral Amox/Clav
Oral Amox/Clav+SYN-007

p>0.99*
Amoxicillin/Clavulanate Damages the Gut Microbiome More Than Amoxicillin Alone

**Pretreatment:**
- Amoxicillin
- Amoxicillin/Clavulanate

**Post-treatment:**
- Amoxicillin
- Amoxicillin/Clavulanate

**Principal Coordinate Analysis (Jaccard):**

**Shannon Alpha Diversity:**
- **Pre:**
  - Amoxicillin: 6.5 ± 0.5
  - Amoxicillin/Clavulanate: 5.5 ± 0.5
- **Post:**
  - Amoxicillin: 4.5 ± 0.5
  - Amoxicillin/Clavulanate: 4 ± 0.5

*P-values:* p=0.028, p=0.008
SYN-007 Protects Gut Microbiome from Amox and Amox/Clav in Dogs

Stack Bar Chart (Genus Level)

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<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
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<tr>
<td>Amoxicillin/Clav + SYN-007</td>
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Principal Coordinate Analysis (Jaccard)

Pretreatment: Amoxicillin/Clavulanate
Post-treatment: Amoxicillin/Clavulanate + SYN-007
SYN-007 Reduces Emergence of Antibiotic Resistance Genes in Dogs
Summary

**Ribaxamase** is intended for use with selected IV beta-lactam antibiotics

**SYN-007** is intended to expand microbiome protection to include selected oral beta-lactams

**SYN-007**
- Oral ribaxamase delayed release formulation
- Did not interfere with oral amoxicillin absorption in dogs
- Activity was not inhibited by clavulanate in the GI tract of dogs
- Protected the gut microbiome in dogs
- Reduced antibiotic resistance gene emergence in dogs

Ribaxamase and SYN-007 have the potential to protect the gut microbiome from antibiotic collateral damage and to mitigate emergence and spread of antibiotic resistance
Antibiotic inactivation represents a new treatment paradigm for preservation of the gut microbiome and reduction of antibiotic resistance.
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