Protecting the Gut Microbiome from Antibiotics

Sheila Connelly
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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
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Disrupted by

- Opportunistic infections
- Antibiotics
- C. difficile
- VRE
- MDR
The Gut Microbiome Regulates Human Physiology

Synthetic Biologics is developing therapies to protect the gut microbiome from antibiotic collateral damage.
• 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
Beta-Lactamases: From Enemies to Therapies

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 Clinical Trials

Completed two Phase 1, two Phase 2a, and Phase 2b trials

- **Well-tolerated** alone and in combination with IV ceftriaxone
- **Negligible absorption** of ribaxamase at doses up to 5x those used in Phase 2b
- **Degraded** ceftriaxone in chyme
- Was effective with proton pump inhibitors
- **Did not alter PK** of IV ceftriaxone

Phase 2b Proof of Concept Study

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

- **Met primary endpoint** of significant reduction in *C. difficile* disease
- **Significantly reduced** new colonization by vancomycin-resistant enterococci
- **Protected the gut microbiome** from antibiotic damage
- Reduced emergence of antibiotic resistance
Ribaxamase Pipeline Products

Ribaxamase is intended for use with selected IV penicillins and cephalosporins
Ribaxamase Pipeline Products

Ribaxamase is intended for use with selected IV penicillins and cephalosporins

Use with oral antibiotics → SYN-007

- Delayed-released formulation of ribaxamase
- Intended for release distal to site of oral antibiotic absorption
- Tested in canine model
Ribaxamase Pipeline Products

Ribaxamase is intended for use with selected IV penicillins and cephalosporins

Use with oral antibiotics → SYN-007

- Delayed-released formulation of ribaxamase
- Intended for release distal to site of oral antibiotic absorption
- Tested in canine model

Use with carbapenems → SYN-006

- Novel metallo-beta-lactamase with broad antibiotic degradation activity
- Formulated for oral delivery (enteric coating)
- Potential to protect gut microbiome from all classes of beta-lactams
- Tested in pig model
SYN-007 Allows Oral Amoxicillin Absorption in Dogs

Oral amoxicillin +/- SYN-007 TID, 16 doses
Serum amoxicillin PK, after first and last dose
Feces for metagenomic analyses collected before and after treatment

*p=0.10 Area Under the Curve*

Amoxicillin Serum PK After 16 Doses

*Student T-test, 2 tailed, unpaired, unequal variance*
SYN-007 Preserves Dog Gut Microbiome Diversity

Shannon Alpha Diversity

*p=0.0007*

*p=0.1555*

Alpha diversity compared to pretreatment:

- Significantly different with oral amoxicillin alone
- NOT significantly different with SYN-007

*One way ANOVA-Kruskal-Wallis test, multiple comparisons
SYN-007 Reduces Emergence of Antibiotic Resistance Genes

Resistome analysis of fecal DNA whole genome sequencing data
Heatmap of beta-lactamase gene frequency
SYN-007 Reduces Emergence of Antibiotic Resistance Genes

Resistome analysis of fecal DNA whole genome sequencing data
Heatmap of beta-lactamase gene frequency

Increased frequency of beta-lactamase genes with amoxicillin alone
Emergence of beta-lactamase genes attenuated with SYN-007
SYN-007 Protects Gut Microbiome from Amoxicillin/Clavulanate

Amoxicillin Serum PK (Day 6)

Oral amoxicillin/clavulanate +/- SYN-007 TID, 16 doses

Serum amoxicillin PK, after first and last dose

Feces for metagenomic analyses collected before and after treatment

*A Student T-test, unpaired, 2 tailed, non-parametric, Mann Whitney test
SYN-007 Protects Gut Microbiome from Amoxicillin/Clavulanate

Amoxicillin Serum PK (Day 6)

Principal Coordinate Analysis (Jaccard)

*Student T-test, unpaired, 2 tailed, non-parametric, Mann Whitney test
SYN-007 Protects Gut Microbiome from Amoxicillin/Clavulanate

Amoxicillin Serum PK (Day 6)

Amoxicillin Serum PK (Day 6) after pretreatment and post-treatment with Amoxicillin/Clavulanate and Amoxicillin/Clavulanate + SYN-007. The AUC is p=0.8413.

Principal Coordinate Analysis (Jaccard)

Principal Coordinate Analysis (Jaccard) showing the difference in microbiome before and after treatment with Amoxicillin/Clavulanate and Amoxicillin/Clavulanate + SYN-007.

*Student T-test, unpaired, 2 tailed, non-parametric, Mann Whitney test
SYN-007 Protects Gut Microbiome from Amoxicillin/Clavulanate

Amoxicillin Serum PK (Day 6)

- **Amox/Clav**
- **Amox/Clav+SYN-007**

**Principal Coordinate Analysis (Jaccard)**

- Pretreatment: Amoxicillin/Clavulanate
- Amoxicillin/Clavulanate + SYN-007
- Post-treatment: Amoxicillin/Clavulanate
- Amoxicillin/Clavulanate + SYN-007

_AUC: p=0.8413*

*Student T-test, unpaired, 2 tailed, non-parametric, Mann Whitney test*
SYN-007 Protects Gut Microbiome from Amoxicillin/Clavulanate

**Amoxicillin Serum PK (Day 6)**

- **Amox/Clav Amox/Clav+SYN-007**
- AUC: p=0.8413

**Principal Coordinate Analysis (Jaccard)**

**Pretreatment:** Amoxicillin/Clavulanate

**Post-treatment:** Amoxicillin/Clavulanate + SYN-007

*Student T-test, unpaired, 2 tailed, non-parametric, Mann Whitney test*
SYN-006 Does Not Affect Ertapenem Serum PK in Pigs

SYN-006 is a carbapenemase formulated for oral delivery

IV ertapenem SID +/- oral SYN-006 TID for 4 days

Serum ertapenem PK, day 3

Feces for metagenomics analyses collected before and after treatment

*Student T-test, 2 tailed, unpaired, unequal variance
SYN-006 Preserves Pig Gut Microbiome Diversity

**Shannon Alpha Diversity**

Post/Pretreatment ratios significantly different with ertapenem alone and ertapenem + SYN-006

*Student T-test, 2 tailed, unpaired, unequal variance*
SYN-006 Reduces Propagation of Antibiotic Resistance Genes

Resistome analysis of fecal DNA whole genome sequencing data
Heatmap of antibiotic resistance gene frequency
SYN-006 Reduces Propagation of Antibiotic Resistance Genes

Resistome analysis of fecal DNA whole genome sequencing data
Heatmap of antibiotic resistance gene frequency

SYN-006 attenuated ertapenem-induced increased frequency of aminoglycoside, macrolide, tet, and efflux pump AR genes
Antibiotic inactivation represents a new treatment paradigm for preservation of the gut microbiome and reduction of antibiotic resistance.
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