Antibiotic Inactivation with $\beta$-lactamase Therapy to Protect the Gut Microbiome

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Effects of Antibiotics: The Gut Microbiome

Eradication, overgrowth, reduced diversity and impaired recovery

• In 2016, more than **75 billion** doses of all-forms of antibiotics were prescribed worldwide\(^1\)

• Antibiotics disrupt the natural balance of commensal gut microbial species (**dysbiosis**) and enable the overgrowth of opportunistic pathogens

• Antibiotic-mediated alterations to the natural balance of the gut microbiome are reflected by a loss of microbial **diversity** and are associated with disease such as **Clostridium difficile** infection (CDI)

• Antibiotic damage to the microbiome is not always completely reversed and the likelihood of recovery decreases with each additional course of antibiotics

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1. Source: IMS August 2017
The Gut Microbiome Regulates Human Physiology

“ALL DISEASE BEGINS IN THE GUT!”
-Hippocrates

400 B.C.

Gut Microbiome Involved in:
- Digestion
- Immune system
- Protection from pathogens
- Metabolic, cardiovascular, neurological diseases

Reservoir of antibiotic resistance

Disrupted by:
- Opportunistic infections
- C. difficile
- VRE
- MDR

Synthetic Biologics is developing therapies to protect the gut microbiome from antibiotic damage
**SYN-004 (ribaxamase): β-Lactamases: From Enemies to Therapies**

Degrading excess β-lactam antibiotic excreted into the GI tract

**TARGET OUTCOMES:**
- Restore healthy, diverse microbiome
- Suppress proliferation of pathogens e.g. *C. difficile*
- Limit emergence of AMR

**Enteric protection** intended to prevent gastric release and limit acid degradation

**Ribaxamase enzyme released into the upper small intestine**

**SYS-004 (ribaxamase):**

**Oral**

Antibiotic Excreted in Bile

Treat Primary Infection (e.g. pneumonia)

Systemic (IV) β-lactam antibiotic

**Stomach**

- **Duodenum**
- **Jejunum**
- **Ileum**
- **Cecum**
- **Colon**
Microbiome Analysis: The Porcine Dysbiosis Model
Pre-clinical Animal Model: Porcine Model of Antibiotic-Mediated Dysbiosis

2 month old 20 kg pigs N=5 per cohort

Days:
-7 -4 0 1 2 4 7 8 9

Feces collections

Blood collections

Oral SY-N-004 (ribaxamase) (75 mg QID)

Antibiotics: IV Ceftriaxone
IV Ertapenem
Oral Amoxicillin

Study End

Readouts:
- Fecal DNA whole genome shotgun sequencing analyses
- Antibiotic blood levels

Ribaxamase reduced antibiotic-mediated changes to the microbiome

Ribaxamase Protected the Microbiome in Pigs

Heatmap of bacterial strains displayed as the relative abundance

Ribaxamase reduced antibiotic-mediated changes to the microbiome

β-Lactam Antibiotics Caused Dysbiosis in Pigs

Antibiotic exposure significantly changed the composition of the fecal microbiomes.
A broad spectrum of antibiotic-resistance genes was propagated in response to ceftriaxone, not just those conferring resistance to beta-lactams.

Ribaxamase reduced emergence of antibiotic-resistance genes

Antibiotic Exposure Rapidly Results in Propagation of AR Genes

A broad spectrum of antibiotic-resistance genes were propagated in response to antibiotic exposure, not just those conferring resistance to β-lactams.
**SYN-004 (ribaxamase): Completed Clinical Trials**

**Pre-Clinical and Clinical Development Overview**

**• Pre-clinical Animal Models:** Demonstrated the tolerability and in vivo activity of ribaxamase
  - SYN-004 (ribaxamase) + IV ceftriaxone showed that SYN-004 (ribaxamase) degraded IV β-lactam antibiotics excreted into the animal intestine, based on analysis of chyme collection
  - SYN-004 (ribaxamase) administered up to 57mg/kg/day was well tolerated when administered with IV ceftriaxone, was not absorbed and did not change the plasma PK of the ceftriaxone

**• Clinical:**
  - **Phase 1** – 2 studies in normal, healthy volunteers
    - Well tolerated up to 750 mg single dose and 300 mg q.i.d. for 7 days, Not systemically absorbed and no anti-drug antibodies were detected
  - **Phase 2a** – 2 studies in subjects with functioning ileostomies, administered IV ceftriaxone ± oral ribaxamase
    - Ribaxamase: Degraded ceftriaxone to below the level of detection in the intestine, did not affect the plasma PK of the ceftriaxone, can be administered in the presence of proton pump inhibitors
  - **Proof of Concept (PoC) Study**
    - Demonstrated a significant relative risk reduction in CDI and showed a significant reduction in new colonization by vancomycin-resistant enterococci (VRE) in patients receiving SYN-004 (ribaxamase) with IV ceftriaxone for a lower respiratory tract infection
    - Through CDC funding, microbiome assessments are in progress to evaluate ribaxamase’s ability to reduce the emergence of antibiotic resistance
    - Dr. John Kokai-Kun will present: SYN-004 (ribaxamase), an Orally Administered β-Lactamase, Prevents *Clostridium difficile* Infection and Significantly Reduced New Colonization by Opportunistic Pathogens in a Phase 2b Clinical Study, Location: Poster section in the exhibition hall

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SYN-004 (ribaxamase) is intended as an orally-delivered β-lactamase to protect the gut microbiome from IV penicillins and cephalosporins to prevent *C. difficile* infection (CDI).

SYN-004 (ribaxamase) protected the gut microbiome from ceftriaxone-mediated dysbiosis in pigs.

SYN-004 (ribaxamase) reduced the emergence of antibiotic-resistance genes in pigs.

Clinical data from the proof-of-concept study, being presented by Dr. John Kokai-Kun at this meeting, demonstrated a statistically significant reduction in relative risk of CDI and new VRE colonization in patients that received ribaxamase with ceftriaxone compared to placebo.

Please stop by the poster to learn more and get your questions answered.

Goal of this antibiotic-inactivation strategy is to reduce exposure of the gut microbiome to antibiotics in order to protect the patient’s unique, normal gut flora.

- Protect from CDI and secondary infections with MDR organisms
- Reduce antibiotic resistance
- Diminish risks associated with beta-lactam antibiotics

**Conclusion**

SYN-004 (ribaxamase) has the potential to become the first prophylactic therapy designed to prevent antibiotic-mediated microbiome damage including *C. difficile* infection.
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