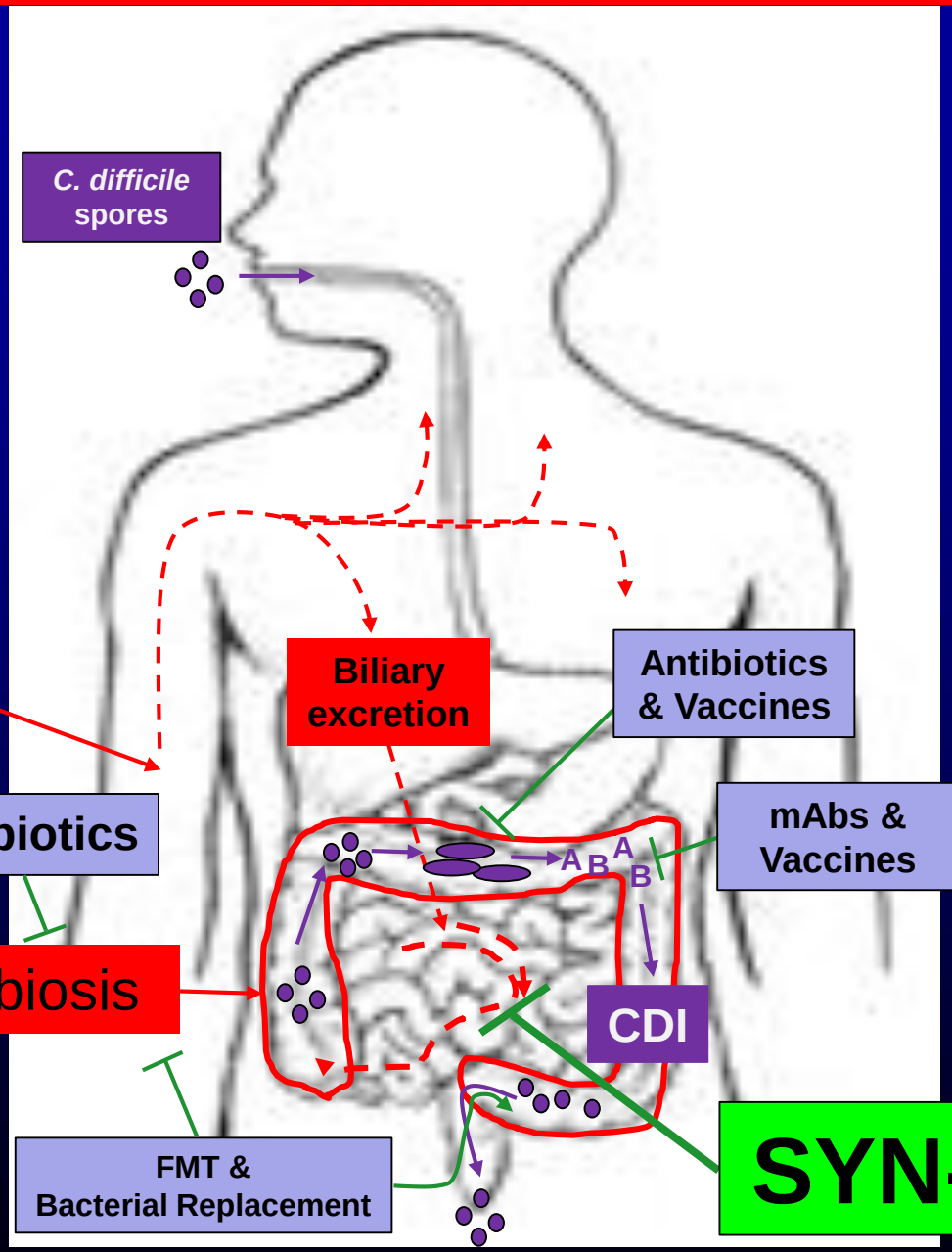
SYN-004, A NOVEL STRATEGY TO PROTECT THE GUT MICROBIOME FROM THE DELETERIOUS EFFECTS OF RESIDUAL IV β-LACTAM ANTIBIOTICS

John F. Kokai-Kun

Disruption of the Gut Microbiome Can Lead to *Clostridium difficile* Infection



IV Antibiotics

Probiotics

Dysbiosis

SYN-004

SYNTHETIC BIOLOGICS

SYN-004

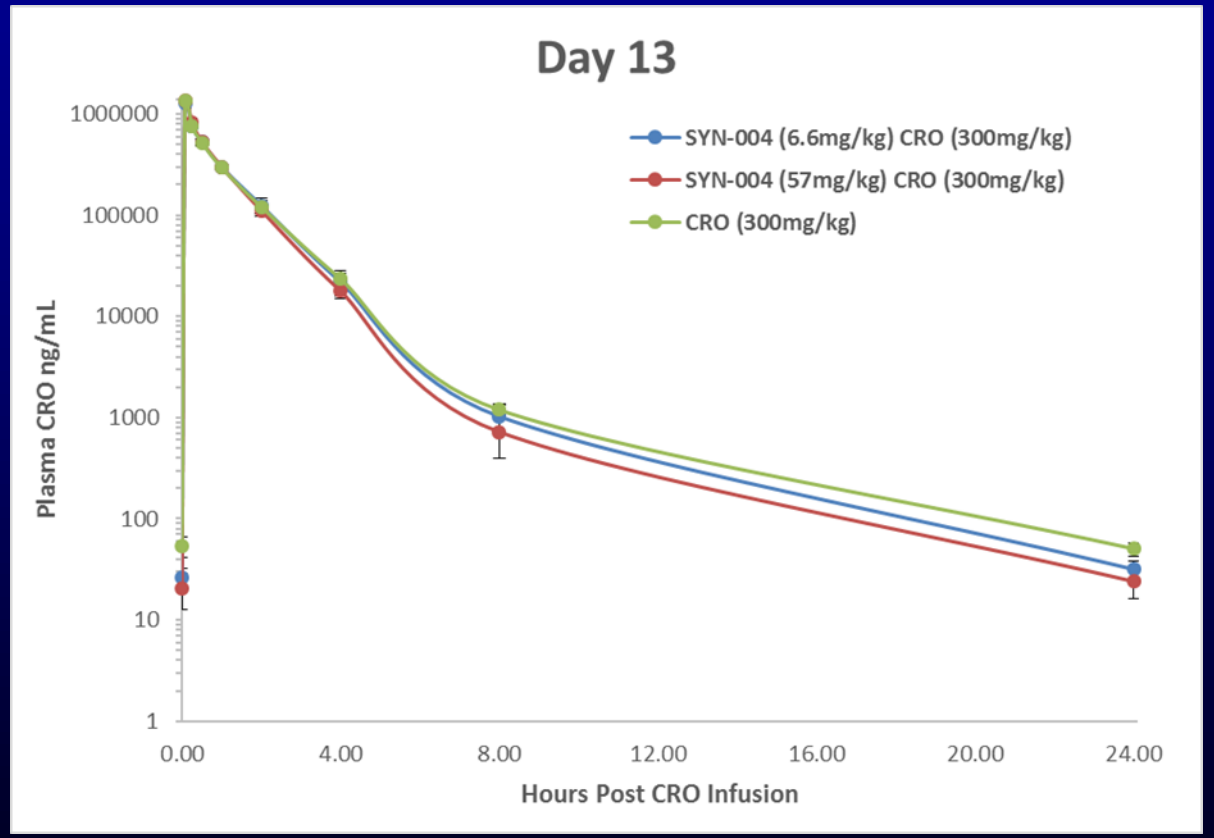
- Orally administered, β-lactamase enzyme that degrades penicillins and cephalosporins, formulated for release at pH ≥ 5.5 (proximal small intestine)
- To be given during and after administration of intravenous (IV) β-lactam-containing antibiotics like ceftriaxone
- Degrade the excess antibiotics that are excreted into the small intestine via the bile
- Prevent disruption of the gut microbiome and thus protect from opportunistic GI pathogens like *C. difficile*

SYNTHETIC BIOLOGICS

SYN-004 Non-clinical Studies

- Oral SYN-004 degrades IV ceftriaxone excreted into the dog small intestine
- Safe when dosed up to 57 mg/kg/day (19 mg/dose, t.i.d.) for 28 days in dogs
- Minimal and sporadic systemic absorption of SYN-004
- Safe when dosed up to 57 mg/kg/day with 300 mg/kg/day of IV ceftriaxone for 14 days in dogs

Ceftriaxone Plasma PK



SYNTHETIC BIOLOGICS

Clinical Trials with SYN-004

- **Phase 1**-two studies in normal healthy volunteers
- Single ascending oral dose up to 750 mg
- Multiple ascending oral doses up to 300 mg q.i.d. for 7 days
- SYN-004 was safe and well tolerated with no systemic bioavailability of SYN-004 and no anti-drug antibodies
- Adverse events were mild and self-limiting

SYNTHETIC BIOLOGICS

Clinical Trials with SYN-004

- **Phase 2a** - two studies in subjects with functioning ileostomies to obtain intestinal chyme samples-on going
- Administering IV ceftriaxone with or without oral SYN-004, measuring chyme concentrations and plasma PK of ceftriaxone and SYN-004
- Administering IV ceftriaxone plus SYN-004 in the presence or absence of proton pump inhibitors, measuring chyme concentration and plasma PK of ceftriaxone and SYN-004

SYNTHETIC BIOLOGICS

Clinical Trials with SYN-004

- **Phase 2b**: A Phase 2B, Parallel-Group, Double Blind, Placebo-Controlled, Multicenter Study of SYN-004 Compared to Placebo for the Prevention of *Clostridium difficile* Associated Diarrhea in Patients with a Diagnosis of a Lower Respiratory Tract Infection
- ~370 patients to be treated with IV ceftriaxone for lower respiratory tract infections will receive SYN-004 or PBO
- Will compare the incidence of CDI and AAD
- Will also look at changes in the gut microbiome
- Study has been initiated, ~75 global sites when fully active

SYNTHETIC BIOLOGICS

SYN-004 Conclusions

- SYN-004 degrades IV penecillins and cephalosporins *in vitro* and *in vivo* in the small intestine in dogs when antibiotics are excreted via the bile
- Oral SYN-004 is safe and well tolerated in GLP toxicity studies in dogs and does not affect the plasma PK of IV ceftriaxone
- Oral SYN-004 is safe and well tolerated in normal human volunteers with no systemic bioavailability or immunogenicity
- Clinical studies to confirm the mechanism of action of oral SYN-004 and to examine its capacity to prevent dysbiosis and CDI are ongoing

SYNTHETIC BIOLOGICS

Acknowledgements

Synthetic Biologics, Inc.

Clinical
Joe Sliman
Klaus Gottlieb
Heidi Whalen
Tracey Roberts
Heather McFall

Project Management
Olivia Coughlin

Manufacturing
J. Andrew Bristol
Steve Hubert

Regulatory
Amy Sloan
Scott Shapot

Research
Sheila Connelly
Michael Kaleko

Consultants
Mike Schlosser
Carol Reed
Ralph Stevenson
Jim Longstreth