A Clinical-Stage Oral β-Lactamase Therapy Prevents Antibiotic-Mediated Damage of the Gut Microbiome

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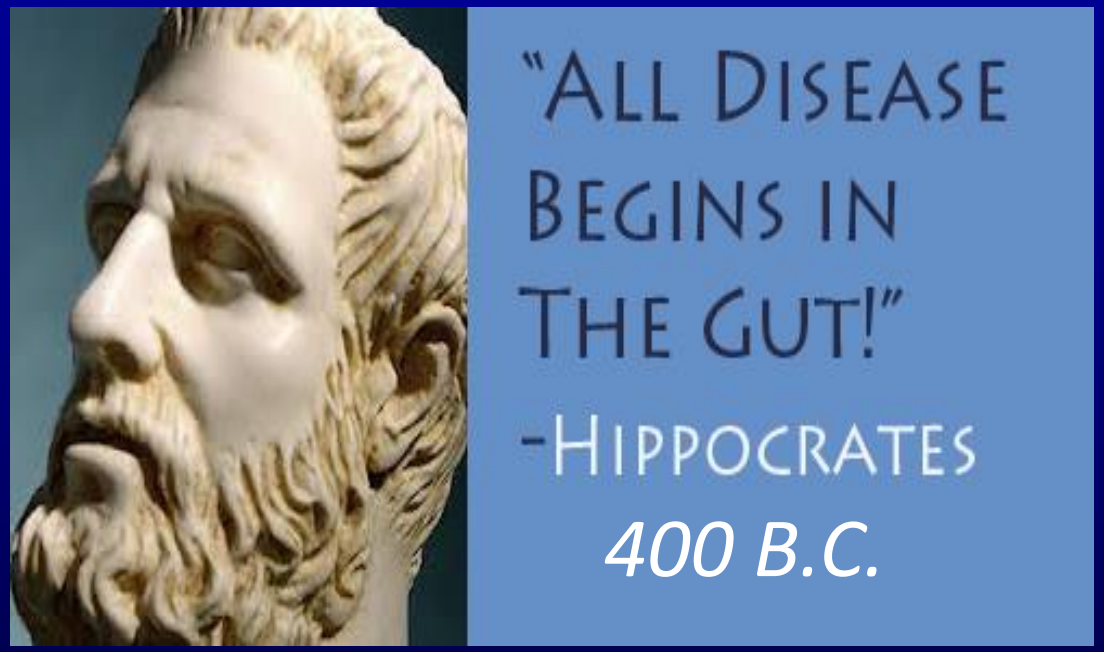
Importance of Intestinal Health Has Long Been Recognized



Gut Microbiome Involved in:

- Digestion
- Nutrient absorption
- Vitamin synthesis
- Bile salt metabolism
- Stimulation of immune system

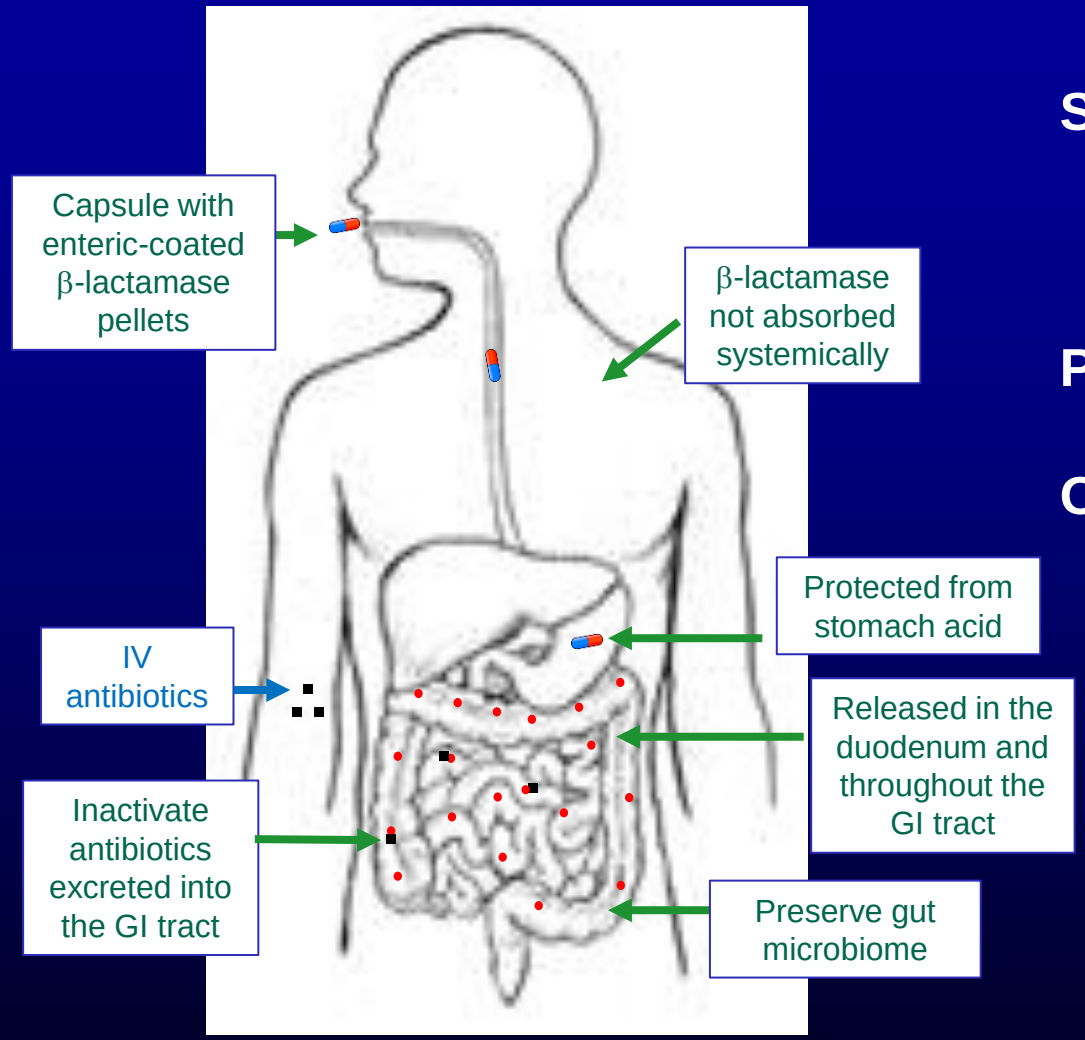
Disrupted by:

- Disease
- Antibiotics

Synthetic Biologics is developing therapies to protect the gut microbiome from the damage caused by antibiotics

SYNTHETIC BIOLOGICS

β-Lactamases: From Enemies to Therapies



Strategy: β-lactamase enzyme is intended to degrade residual antibiotics in the GI tract to protect the microbiome

Product: Capsule with enteric-coated enzyme

Outcome: Prevention of *Clostridium difficile* infection and antibiotic-associated diarrhea

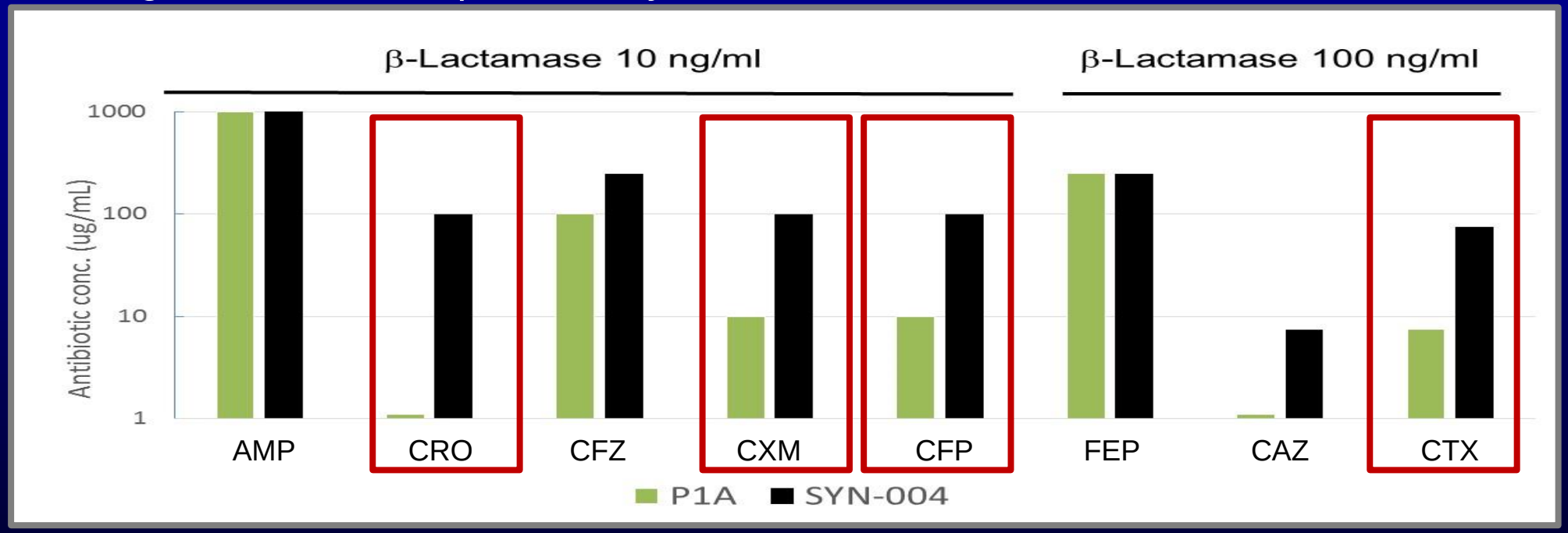
Orally-delivered β–lactamases intended to degrade residual antibiotics in the GI tract to protect the gut microbiome without affecting antibiotic efficacy

SYNTHETIC BIOLOGICS

SYN-004 Degrades Cephalosporins

- SYN-004 was engineered from P1A
- P1A is a clinical isolate from *Bacillus licheniformis*

E. coli growth microtiter plate assay



Amp: ampicillin
CRO: ceftriaxone
CFZ: cefozolin
CXM: cefuroxime
CFP: cefoperazone
FEP: cefepime
CAZ: ceftazidime
CTX: cefotaxime

SYN-004 efficiently degrades cephalosporins, including ceftriaxone, cefuroxime, cefoperazone, ceftazidime, and cefotaxime

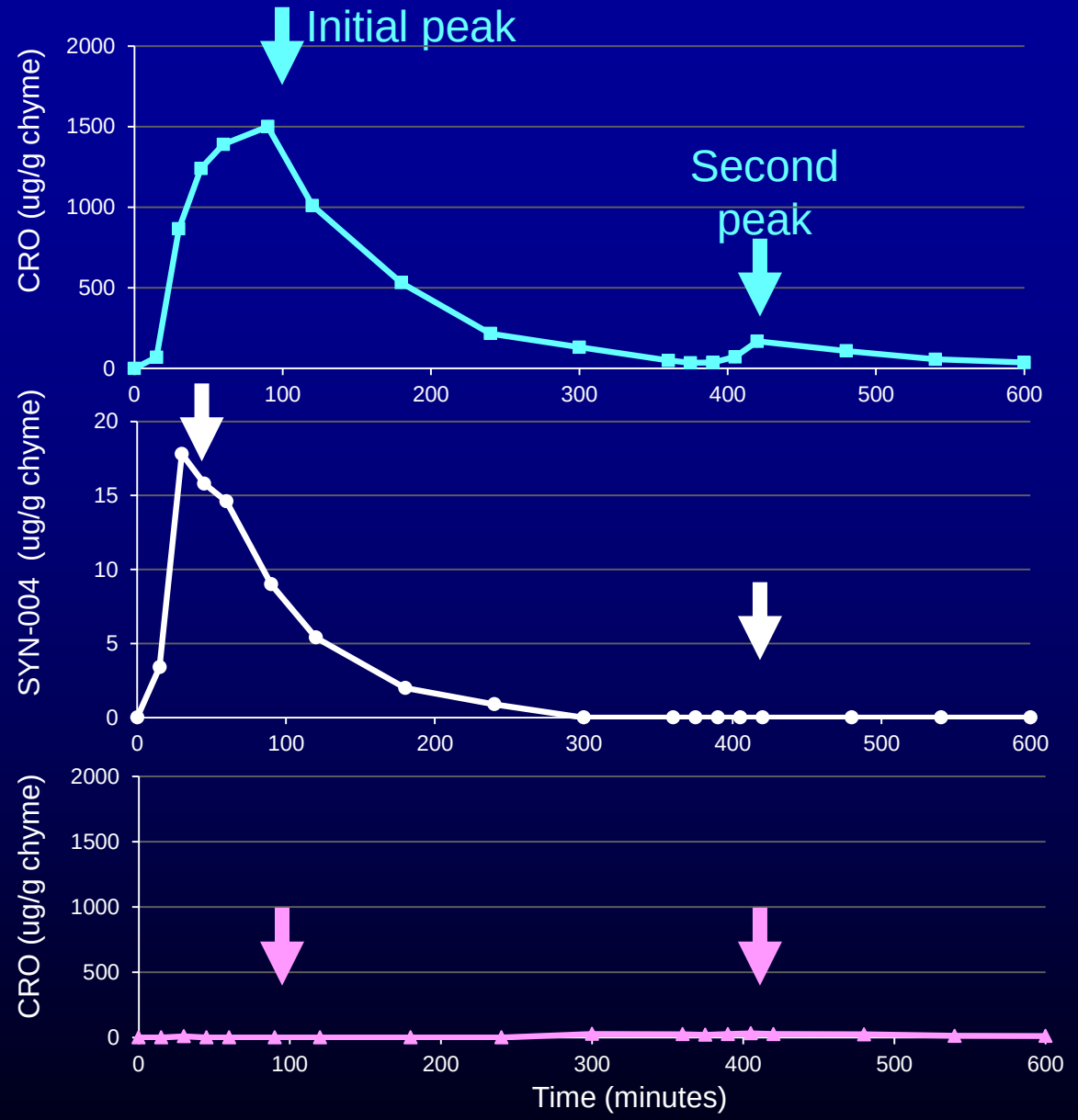
SYNTHETIC BIOLOGICS

SYN-004 Degraded Ceftriaxone (CRO) in Dog GI Tract

Pretreatment
CRO Alone

Treatment
SYN-004 + CRO

Treatment
SYN-004 + CRO



CRO in Chyme

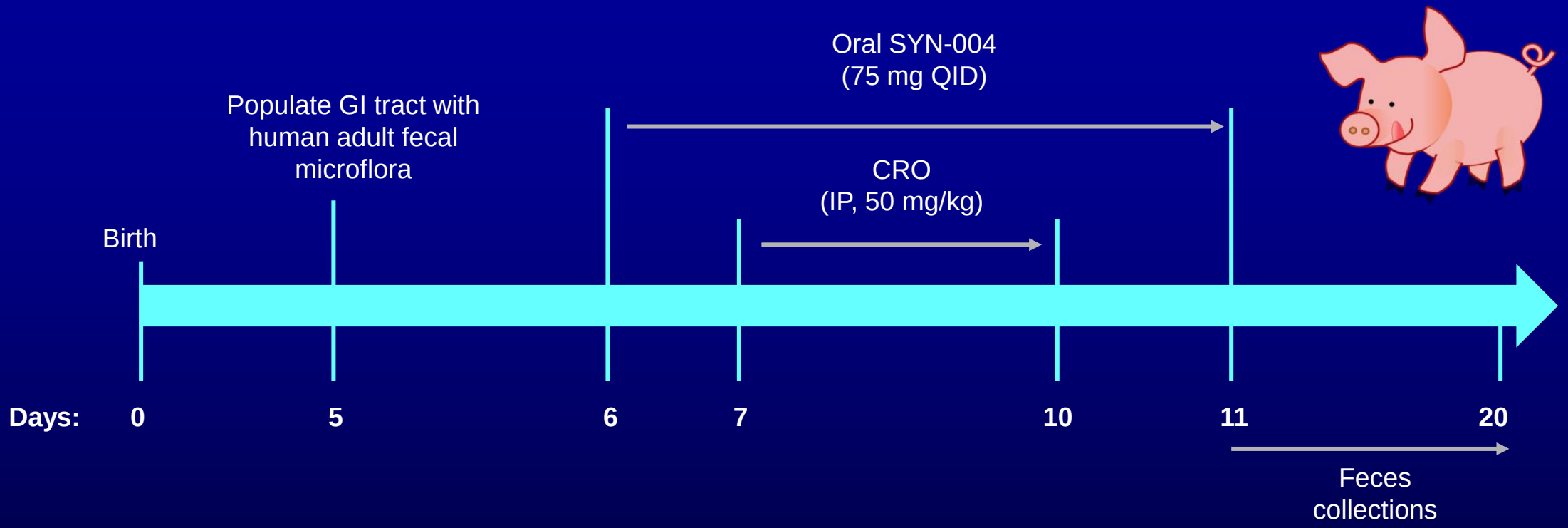
SYN-004 in Chyme

CRO in Chyme

In the presence of SYN-004 no CRO was detected in chyme

SYNTHETIC BIOLOGICS

Neonatal Pigs with Human Gut Microflora



Readouts:

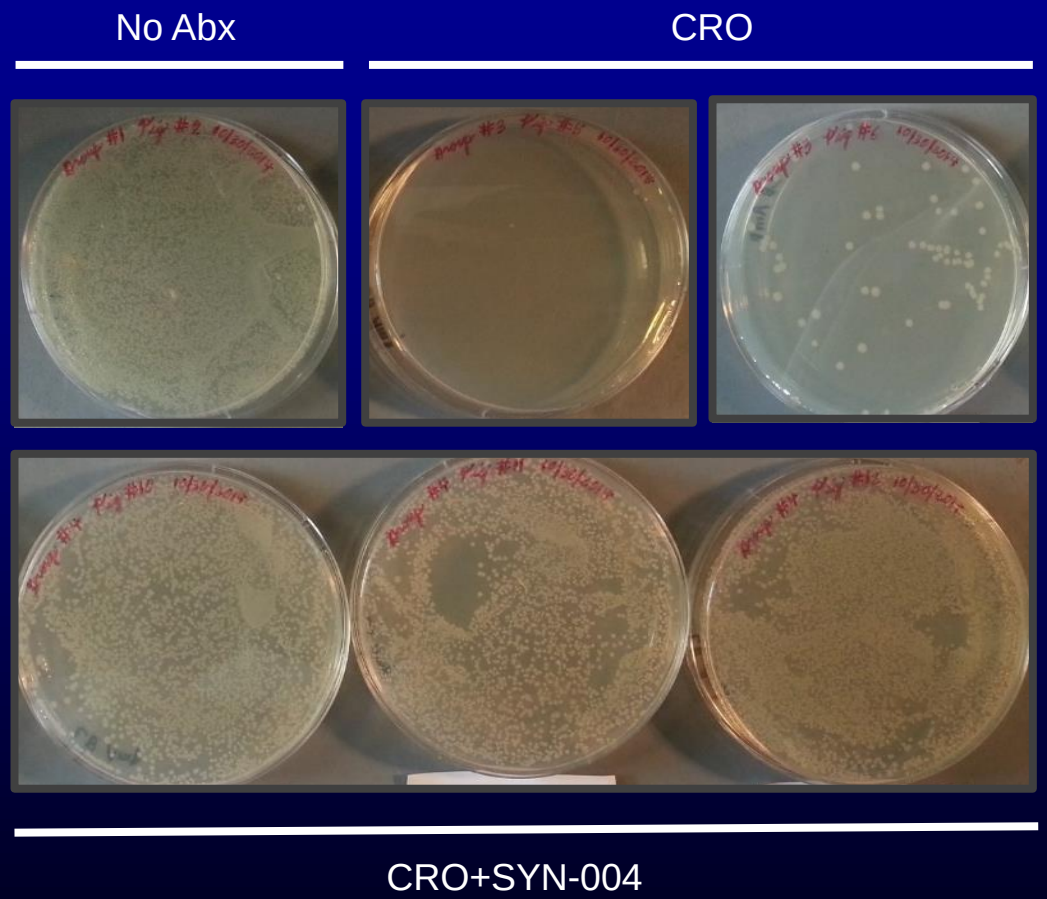
- Direct measure of CRO-sensitive bacterial population
- Fecal DNA 16S rRNA V6 region sequence analyses
- Shotgun deep sequencing analyses

SYNTHETIC BIOLOGICS

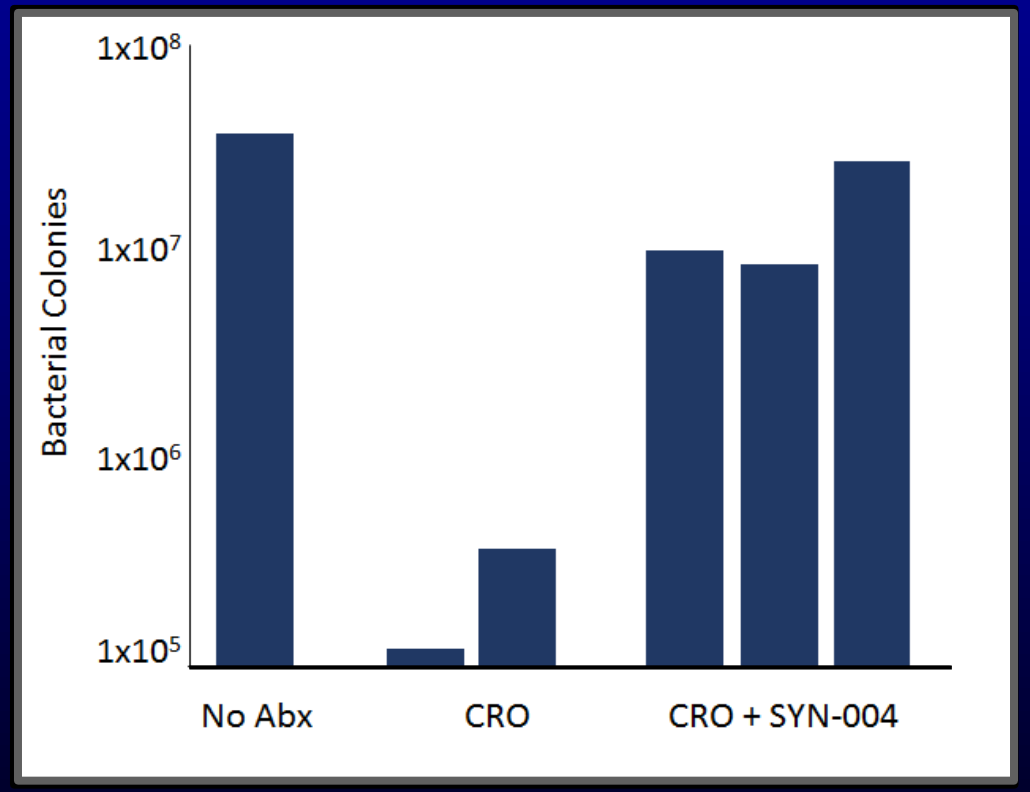
SYN-004 Protected the Gut Microflora in Pigs

- Monitored CRO-sensitive bacterial population, Amp^R aerobes

Bacterial Growth on LB+Amp Plates



Bacterial Colonies



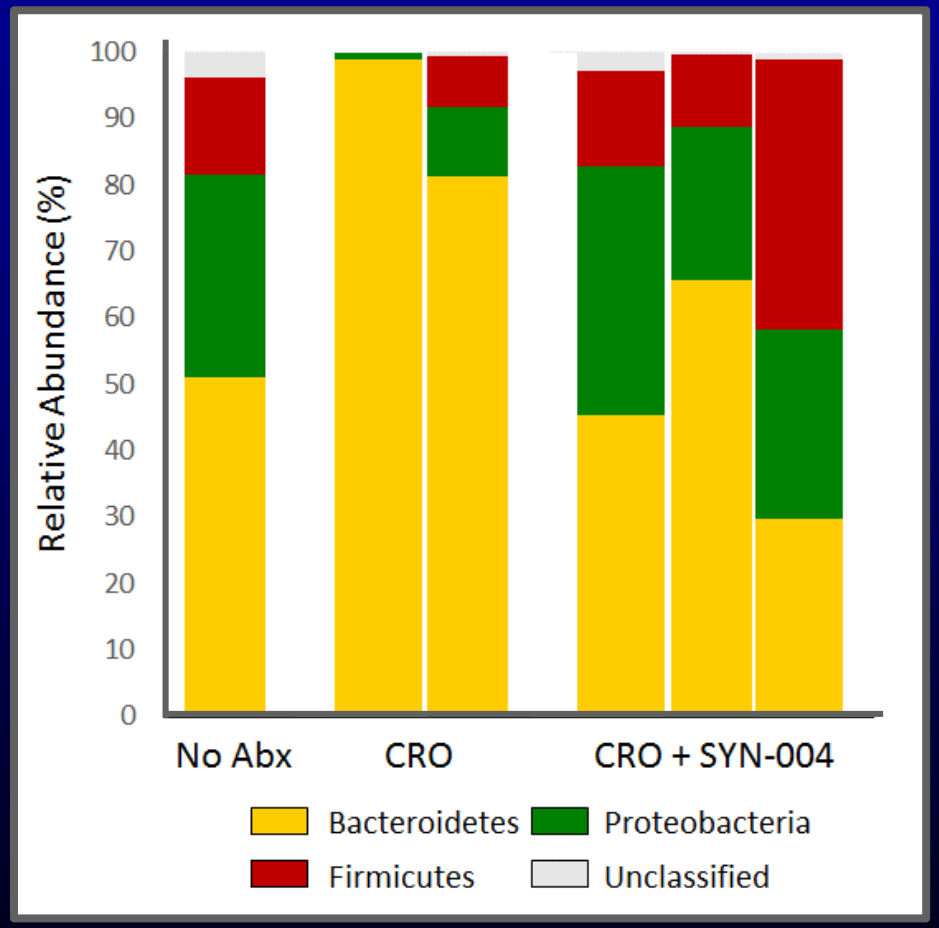
SYN-004 protected the CRO-sensitive fecal bacterial population

SYNTHETIC BIOLOGICS

SYN-004 Prevented CRO-Induced Dysbiosis

- 16S rRNA V6 region sequence analyses

Phylum-Level Taxonomic Classification

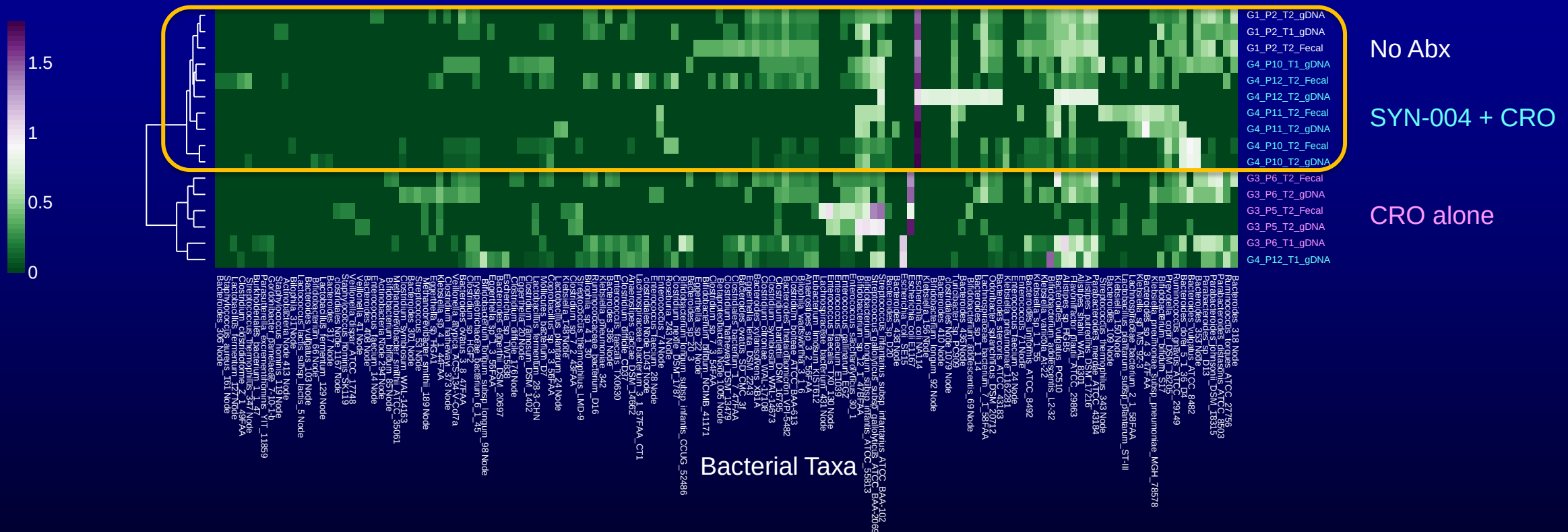


SYN-004 protected the
Proteobacteria and Firmicutes
and
prevented overgrowth of
Bacteroidetes in the presence of CRO

SYNTHETIC BIOLOGICS

SYN-004 Protected the Pig Microbiome

- Whole genome shotgun sequencing and taxonomic profiling
- Heatmap of bacterial strains based on compositional similarity and relative abundance
- Dendrogram clustering samples with similar compositions

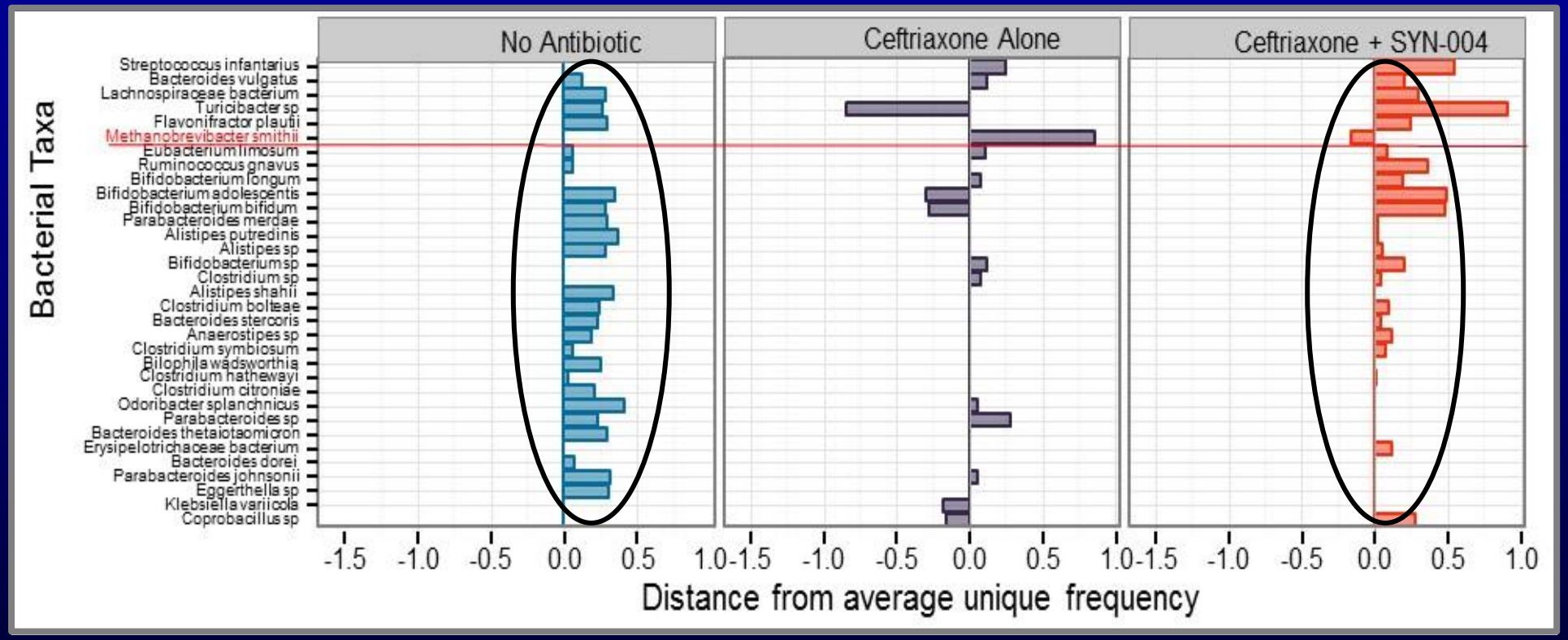


The SYN-004-treated animals clustered with the controls demonstrating that SYN-004 protected the GI microflora from the effects of CRO

SYNTHETIC BIOLOGICS

SYN-004 Prevented Overgrowth of *M. smithii*

- Whole genome shotgun sequencing and analyses
- Nearest shrunken centroid classification of fecal bacterial species



The SYN-004-treated animals were more similar to the no antibiotic controls demonstrating that SYN-004 protected the GI microflora from the effects of CRO

SYN-004 is in Phase 2 Clinical Trials

Preclinical Results

- Safe in two GLP toxicity studies in dogs
- Well tolerated with a NOAEL of 57 mg/kg/day, highest dose tested
- Not detected systemically
- Did not affect ceftriaxone blood levels

Clinical Results

- Phase 1 clinical studies demonstrated SYN-004 safety and tolerability with a single dose of up to 750 mg and multiple doses of 300 mg 4X a day for 7 days
- SYN-004 was not systemically bioavailable
- SYN-004 was not immunogenic
- Phase 2a studies are in progress
- Phase 2b study to initiate 3Q 2015

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Conclusions

- SYN-004 degraded ceftriaxone in the dog GI tract
- SYN-004 protected the intestinal microbiome from ceftriaxone in pigs
- SYN-004 prevented the overgrowth of *M. smithii* in antibiotic-treated pigs
- *M. smithii* was reported to be associated with constipation, IBS, and obesity
- SYN-004 is progressing though Phase 2 clinical trials

SYN-004 has the potential to become the first prophylactic therapy designed to prevent antibiotic-mediated microbiome damage including *C. difficile* infection and antibiotic-induced diarrhea

SYNTHETIC BIOLOGICS

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