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Antibiotic Inactivation with β-lactamase Therapy to Protect the Gut Microbiome

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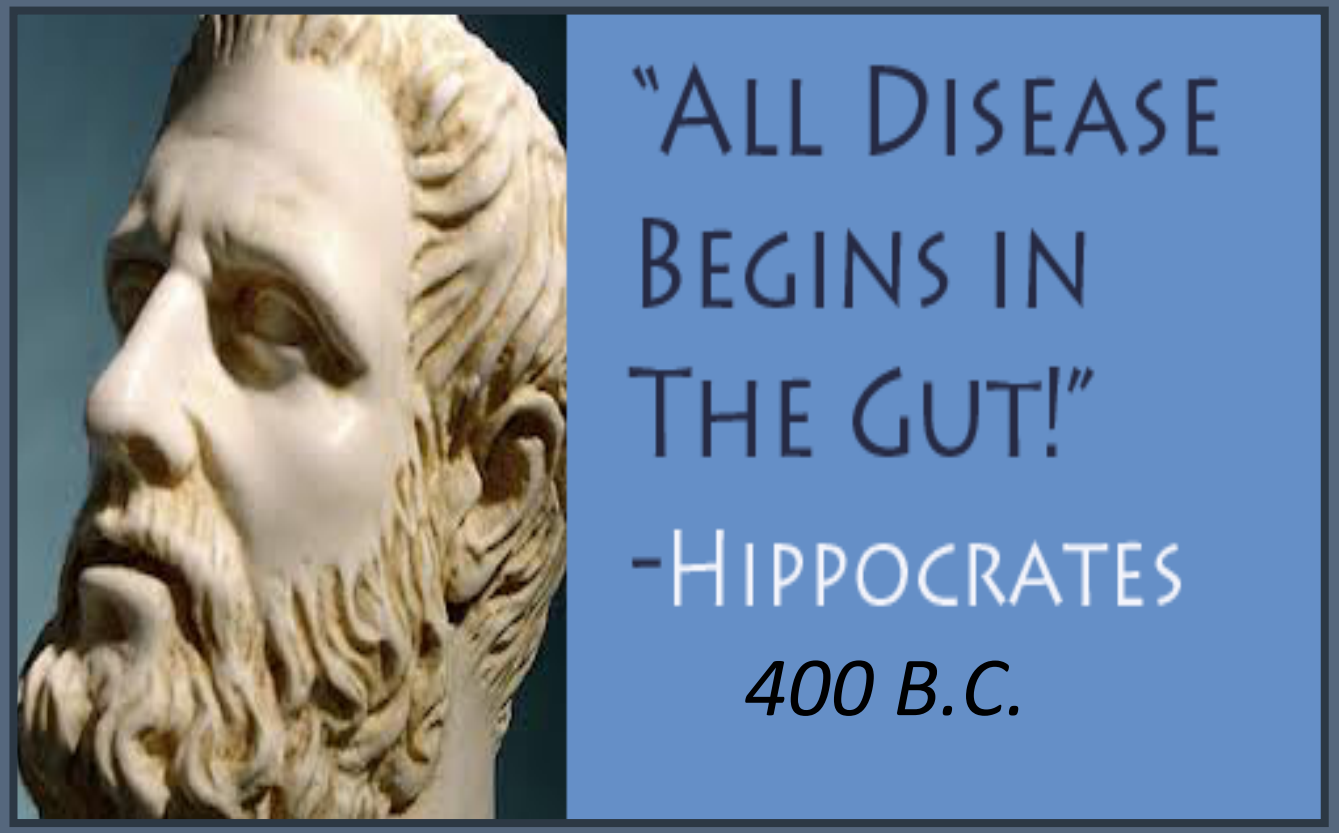
Effects of Antibiotics: The Gut Microbiome

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

1. Source: IMS August 2017

The Gut Microbiome Regulates Human Physiology



Gut Microbiome Involved in:

- Digestion
- Immune system
- Protection from pathogens
- Metabolic, cardiovascular, neurological diseases

Reservoir of antibiotic resistance

Disrupted by:

Antibiotics

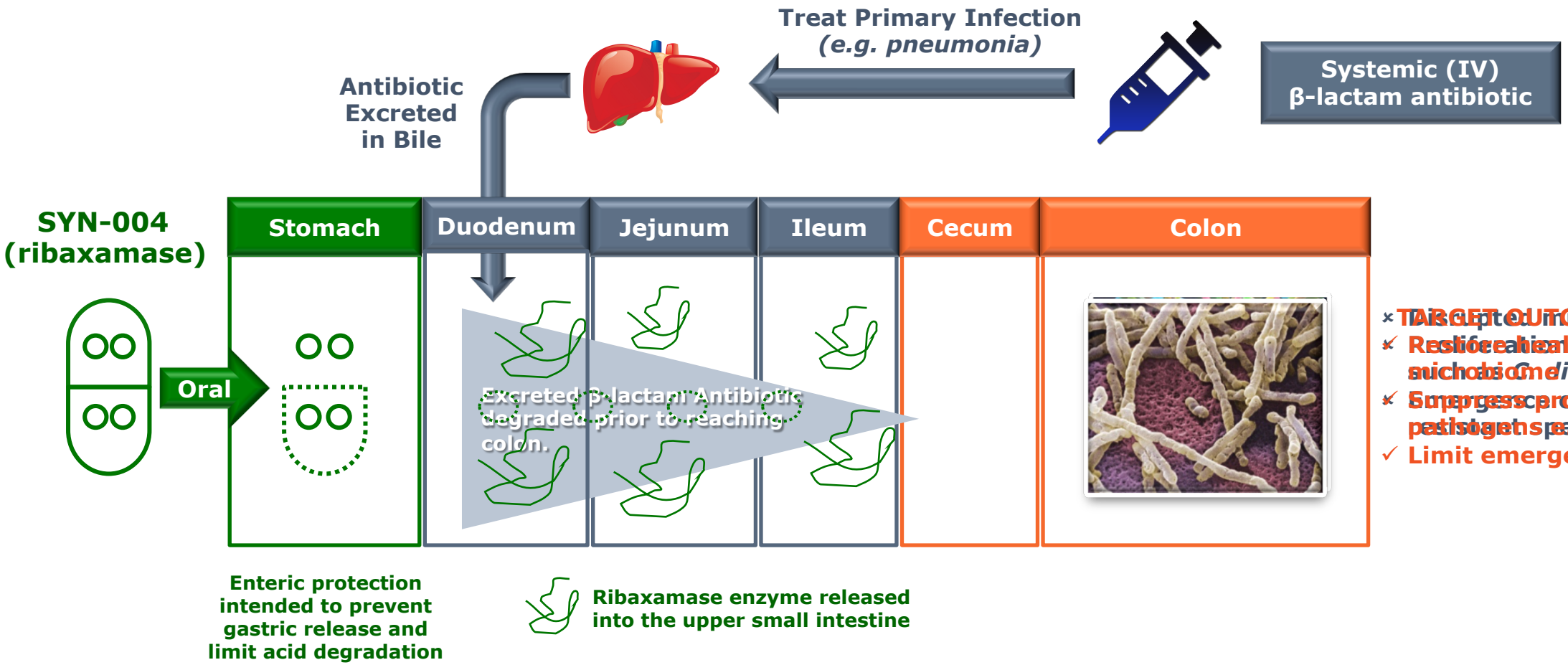
Opportunistic infections

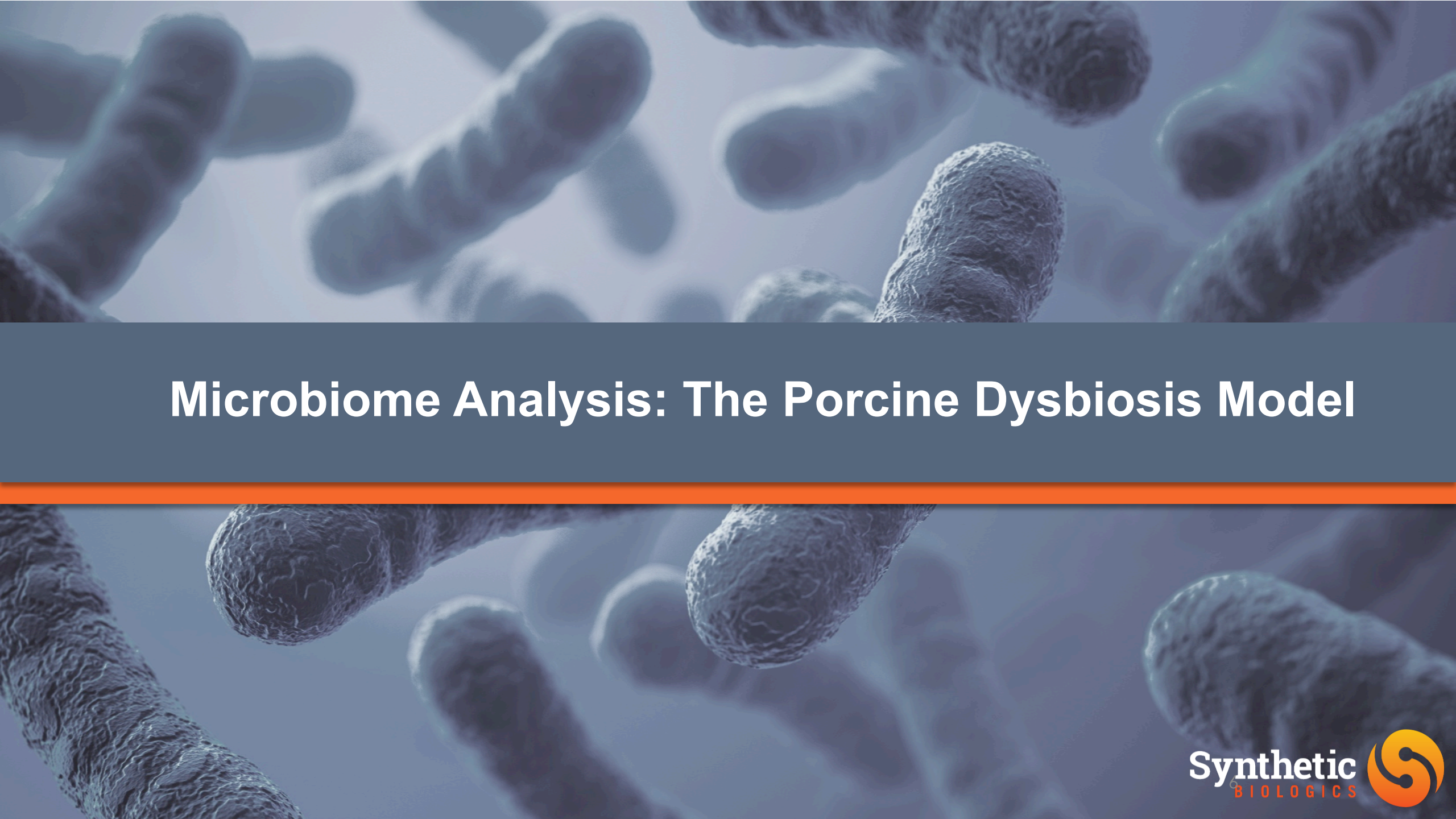
C. difficile
VRE
MDR

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





Microbiome Analysis: The Porcine Dysbiosis Model

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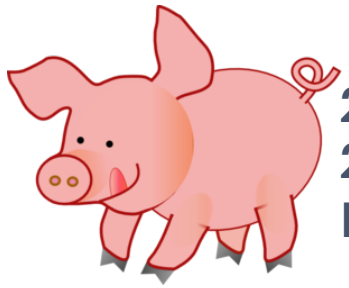
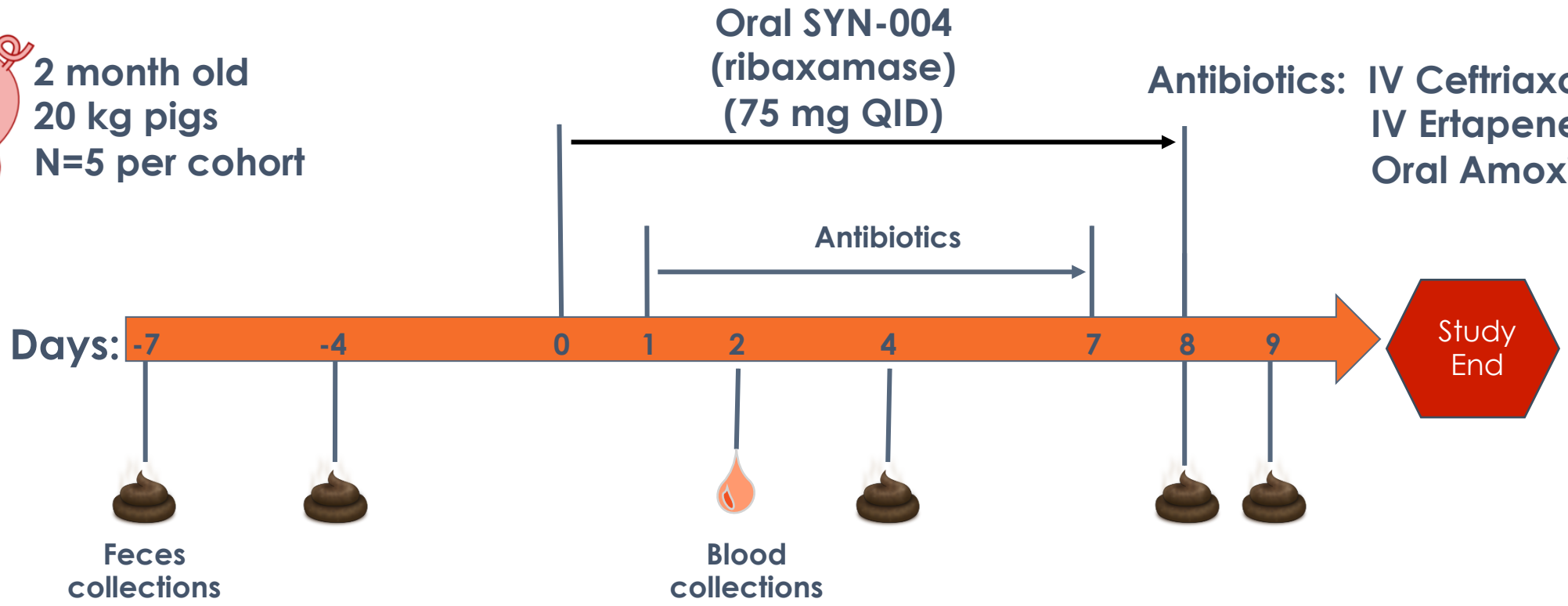
Pre-clinical Animal Model:
Porcine Model of Antibiotic-Mediated Dysbiosis



2 month old
20 kg pigs
N=5 per cohort



Readouts:

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

Connelly et al. 2017. Journal of Applied Microbiology, Open Access, 2016/2575.

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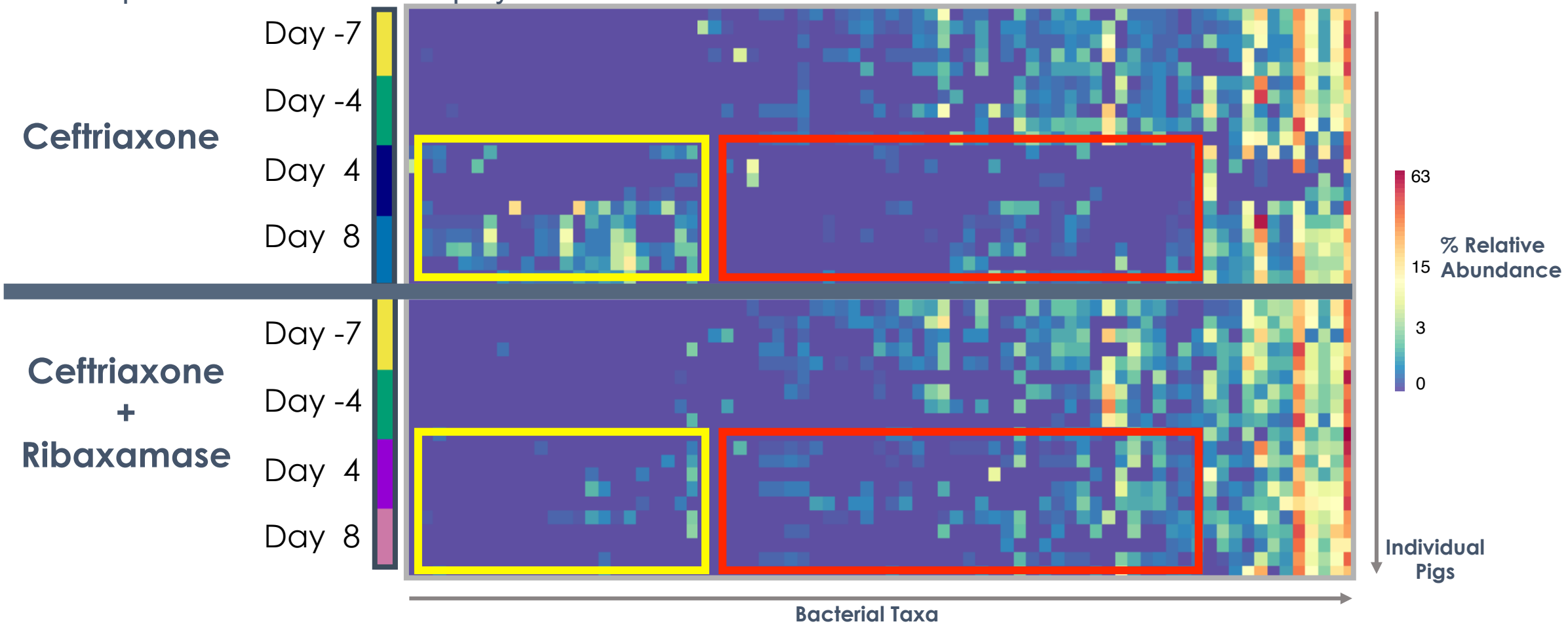
Ribaxamase Protected the Microbiome in Pigs

Heatmap of bacterial strains displayed as the relative abundance



Ribaxamase reduced antibiotic-mediated changes to the microbiome

Connelly et al. 2017. Journal of Applied Microbiology, Open Access, 2016/2575.

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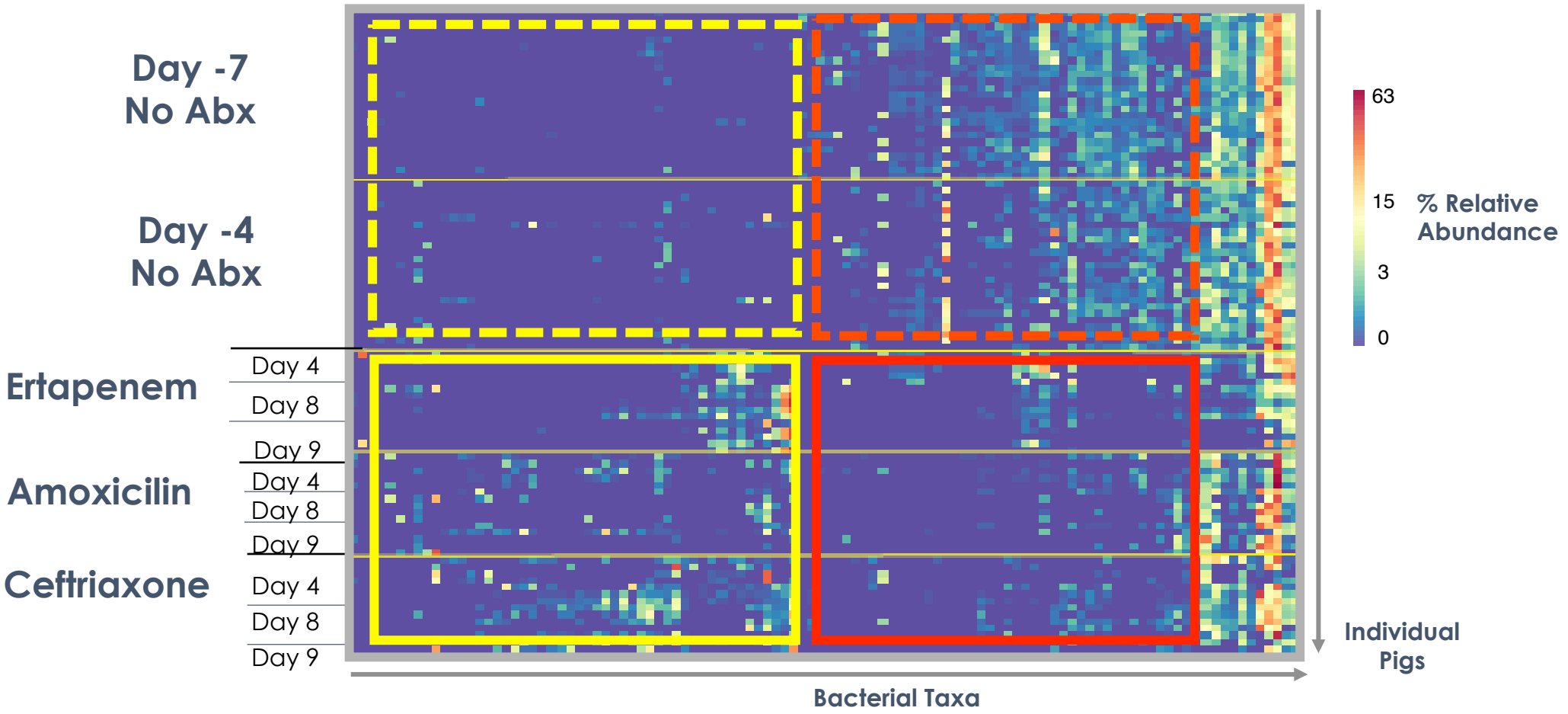
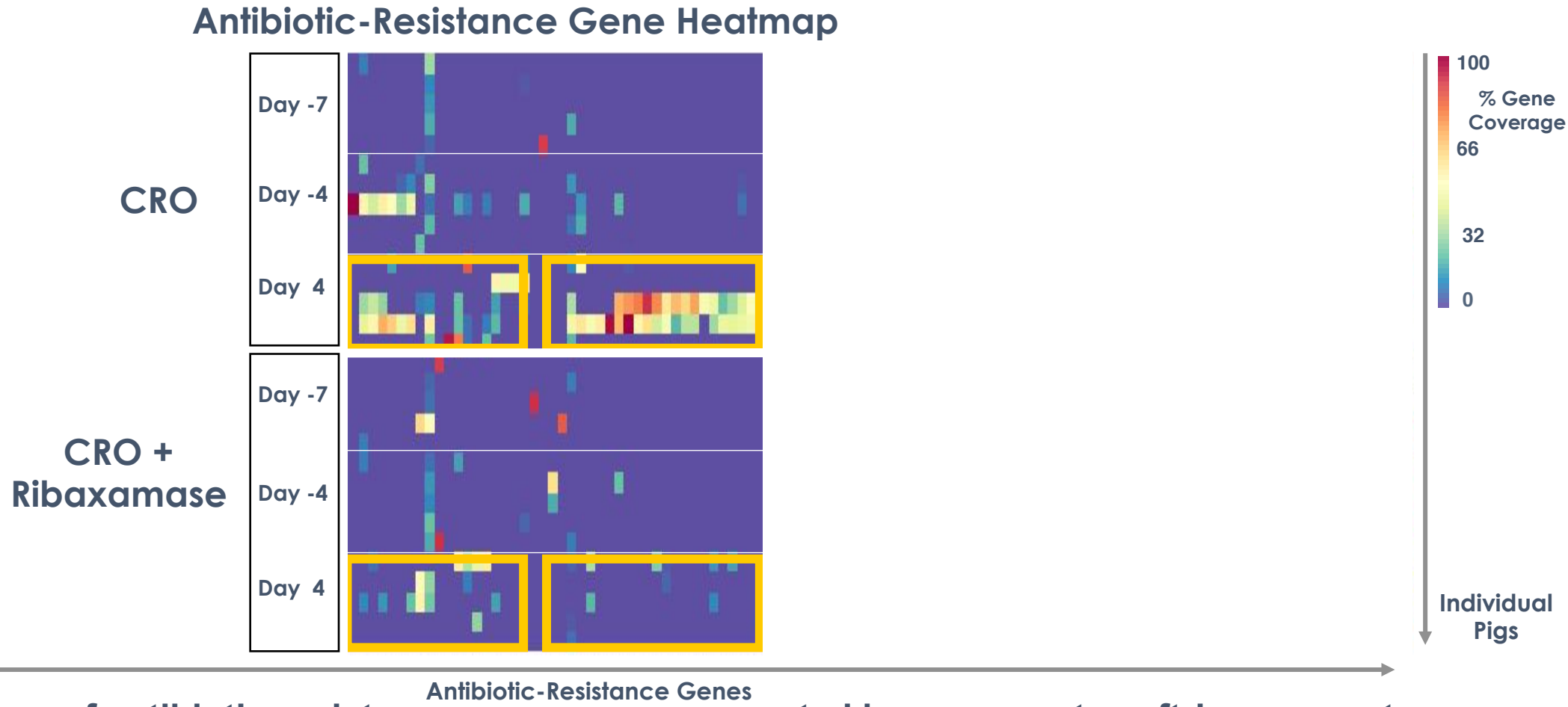
β-Lactam Antibiotics Caused Dysbiosis in Pigs

Heatmap of bacterial strains displayed as the relative abundance



Antibiotic exposure significantly changed the composition of the fecal microbiomes

Ribaxamase Reduced Propagation of Antibiotic-Resistance Genes in Pigs



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

Connelly et al. 2017. Journal of Applied Microbiology, Open Access, 2016/2575.

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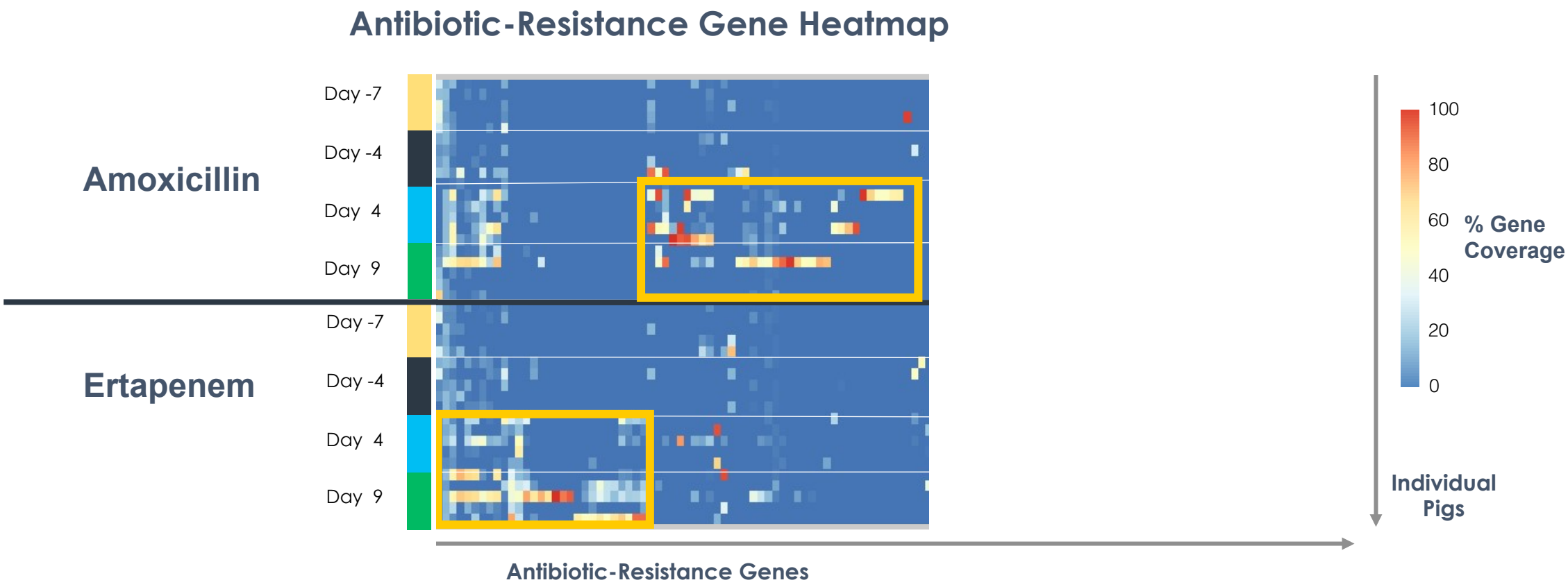
Antibiotic Exposure Rapidly Results in Propagation of AR Genes



A broad spectrum of antibiotic-resistance genes were propagated in response to antibiotic exposure, not just those conferring resistance to β-lactams

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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

Kaleko et al (2016) Anaerobe 41:58
Roberts et al (2016) Clinical Drug Investigation 36:725
Kokai-Kun et al (2017) Antimicrobial Agents and Chemotherapy 41:e02197

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Conclusion

- 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

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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Thank you