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Microbiome Therapeutics to Potentially Transform the Management of Antimicrobial Resistant Infections

FDA/CDC Drug Development Considerations for the Prevention of HealthCare-Associated Infections Workshop

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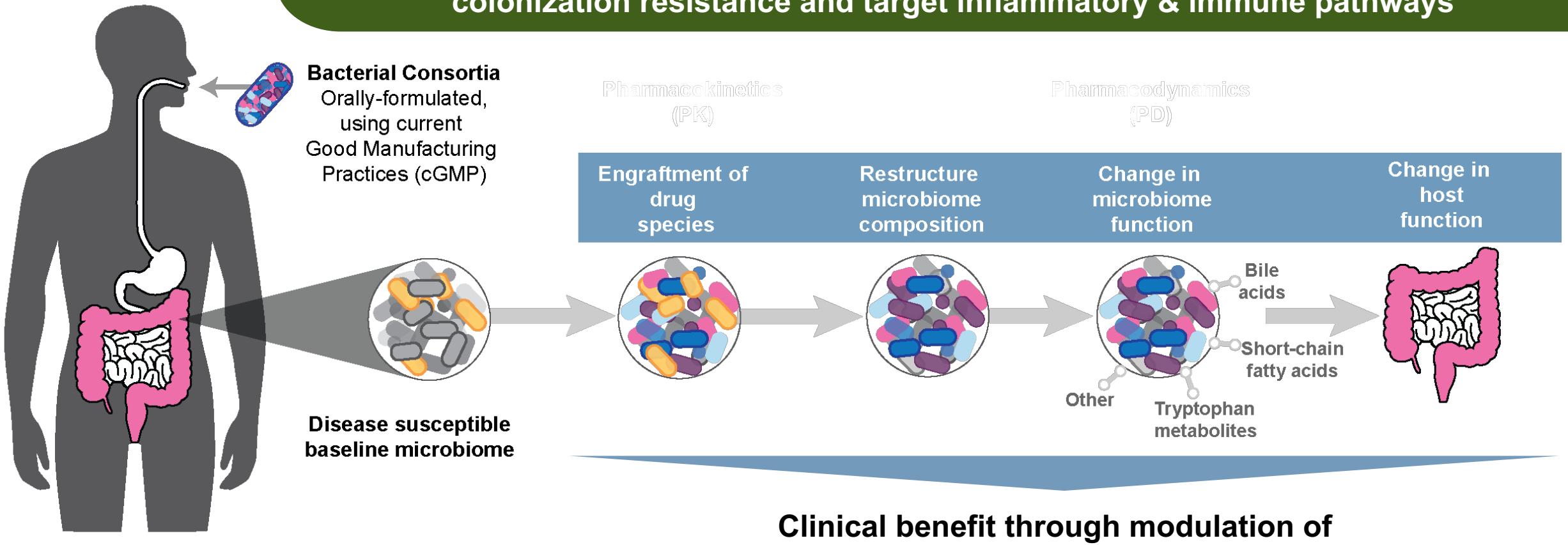
Seres' mission: To transform the lives of patients worldwide with revolutionary Microbiome Therapeutics

Encapsulated consortia of commensal bacteria designed to establish colonization resistance and target inflammatory & immune pathways



Clinical benefit through modulation of multiple disease-relevant pathways

Figure adapted from Henn et al. 2021. Gastroenterology

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Microbiome Therapeutics are a potentially transformative technology in effort to manage Antimicrobial Resistant Infections (AMR)

AMR and bloodstream infections are a major burden to society

World Health Organization

Declared "**one of the world's most urgent threats**"

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

$20 billion excess direct healthcare costs
35,000 deaths per year in US

Bloodstream infections (BSI) major cause of death due to AMR infection

Limited innovation despite substantial and growing impact of AMR

Addressing these challenges **requires new therapeutics with novel mechanisms of action**

Microbiome therapeutics offer **novel mechanisms** with potential to combat infections and AMR

Seres is developing drugs to prevent **infection/bacteremia & decolonize pathogens that carry AMR** in high-risk patient populations

Antimicrobial Resistance Collaborators. 2022. The Lancet; Antimicrobials Working Group fact sheet

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ECOSPOR III: SER-109 was superior to placebo in Phase 3 trial of patients with recurrent *C. difficile* infection (CDI)

The NEW ENGLAND JOURNAL of MEDICINE

12.4%
SER-109 Recurrence rate

sustained clinical response rate 87.6%

PRIMARY EFFICACY ENDPOINT RESULTS

Time point	SER-109 (N =89) n (%) of recurrences	Placebo (N =93) n (%) of recurrences	Relative risk (95%CI)	p-value
Week 8	**11** (12.4)	**37** (39.8)	**0.32** (0.18-0.58)	**<0.001 @ 1.0** **<0.001 @ 0.833**

- Recurrent *C. difficile* patients (n=182); all subjects treated with standard of care antibiotics followed by SER-109 or Placebo
- Relative risk exceeded FDA predefined threshold for single pivotal trial
- SER-109 was well-tolerated. Most common reported AEs were flatulence, fatigue, abdominal distension, abdominal pain, constipation, decreased appetite, diarrhea, chills, nausea, & UTI. Three deaths occurred on SER-109 evaluated as unrelated to treatment by the investigators. Full description of safety results in Feuerstadt et al. NEJM. 2022
- ECOSPOR IV (n=289; Open-label) provides additional support for observed efficacy and safety profile

Feuerstadt et al. 2022. New England Journal of Medicine.

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The pathogenesis of *C. difficile* infection is a two-hit process

Disruption of gut microbiome → Leading risk factor for *C. difficile* infection is exposure to antibiotics, which disrupt the microbiome

Exposure to *C. difficile* spores → Disrupted microbiome is susceptible to colonization and vegetative outgrowth of *C. difficile*

SER-109 mechanism targets disrupted microbiota and prevention of *C. difficile* spore germination and vegetative growth

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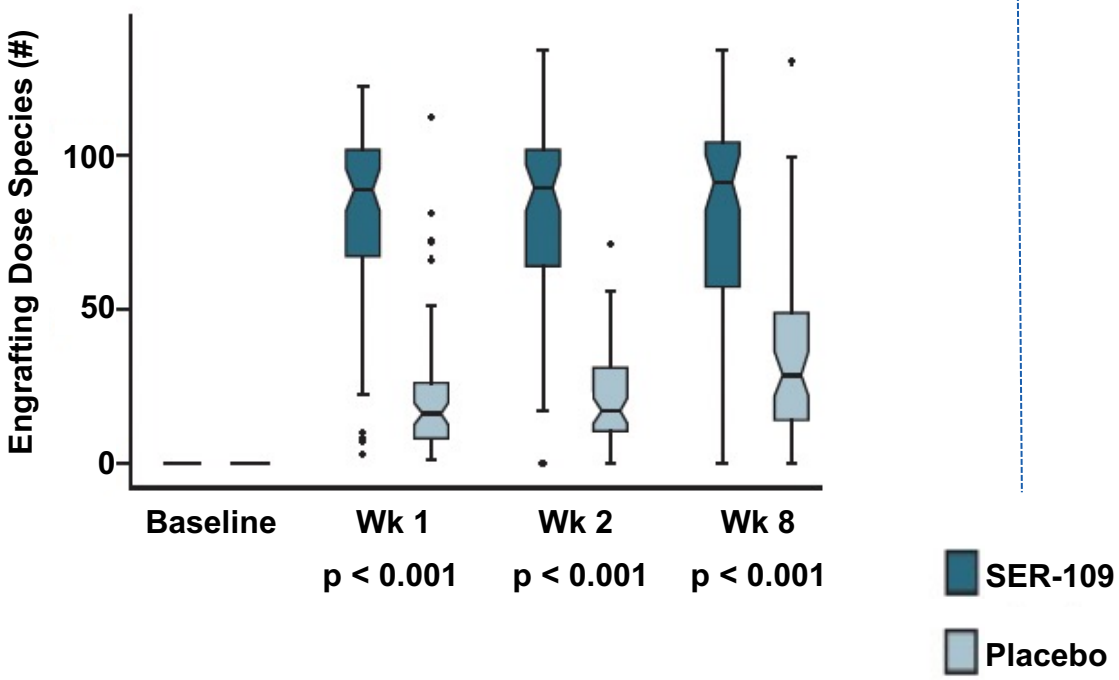
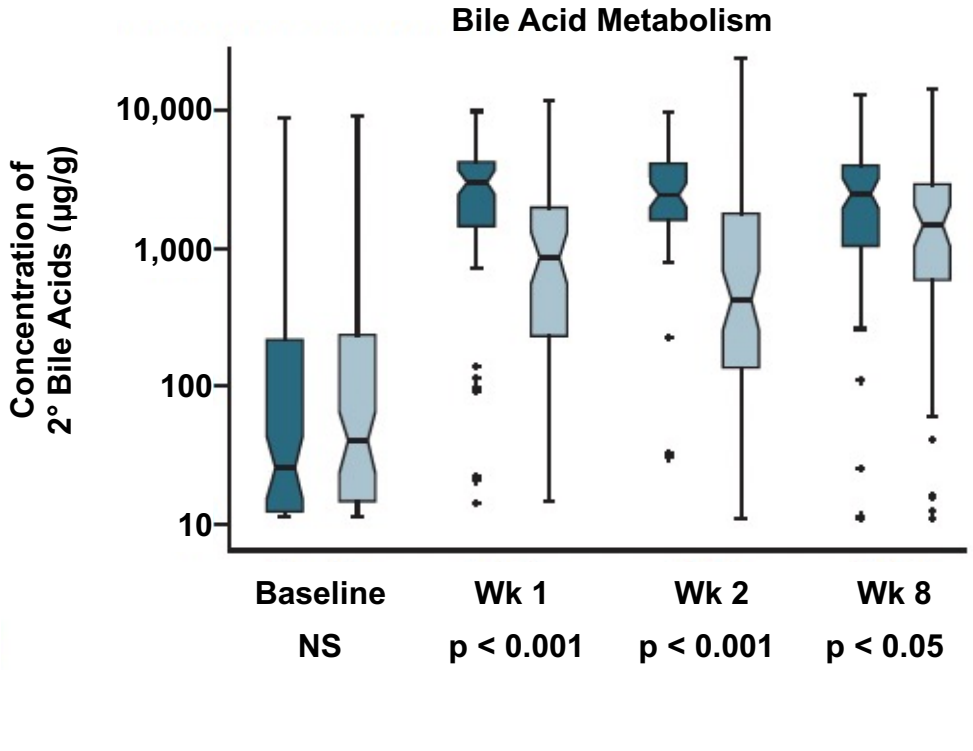
PK & PD: In ECOSPOR III, SER-109 bacteria engraft restructuring the disrupted microbiome and changing its function to inhibit *C. difficile*

SER-109 bacteria engraft durably & rapidly to restructure microbiome



SER-109 bacteria shift gut metabolic landscape following engraftment



N = 182 patients enrolled; figure shows data for 143 patients with evaluable baseline sample
Feuerstadt et al. 2022. New England Journal of Medicine.

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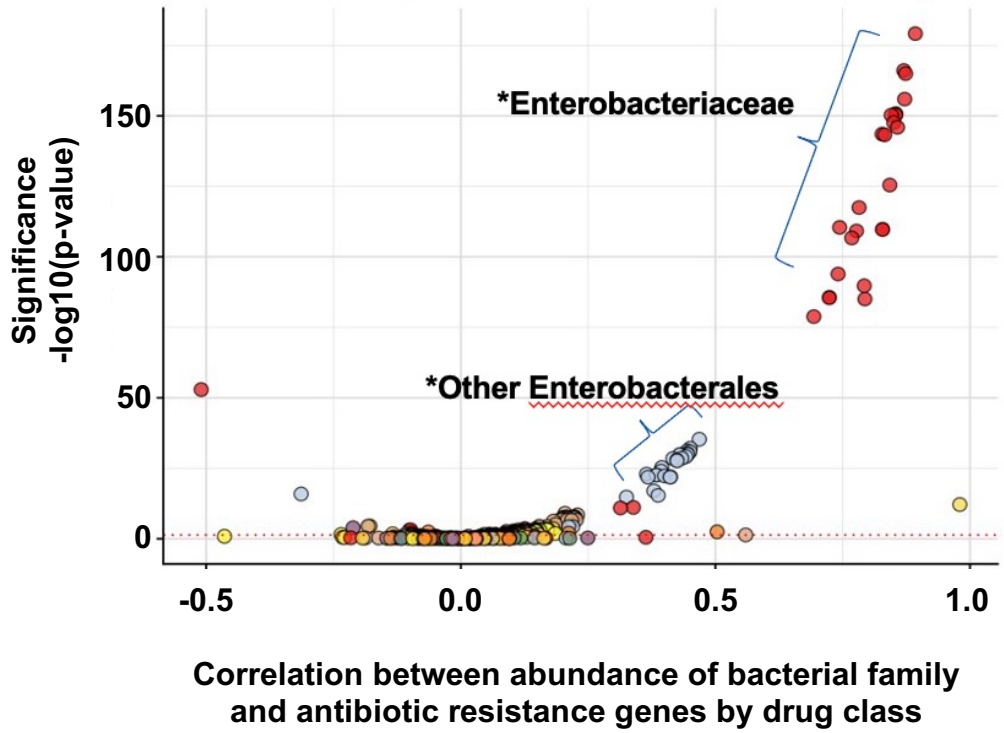
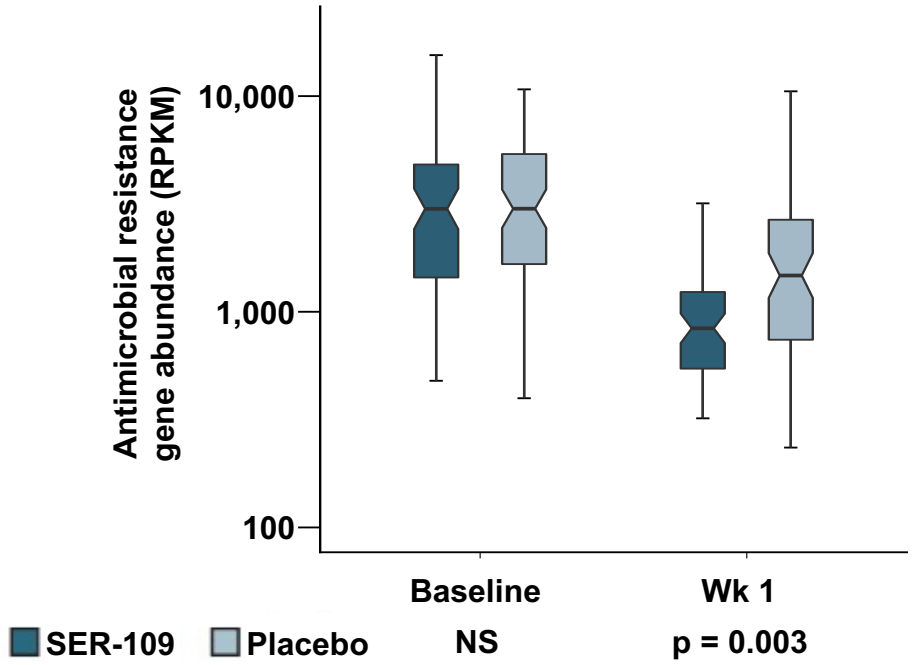
PK & PD: ECOSPOR III data support that microbiome therapeutics can reduce pathogens that can harbor antimicrobial resistance

SER-109

Reduce Proteobacteria* associated with antimicrobial resistance genes



Reduced antimicrobial resistance gene carriage



Results based on *post hoc* analysis of SER-109 Phase 3 study data; presented at IDWEEK 2021 & PACCARB 2021

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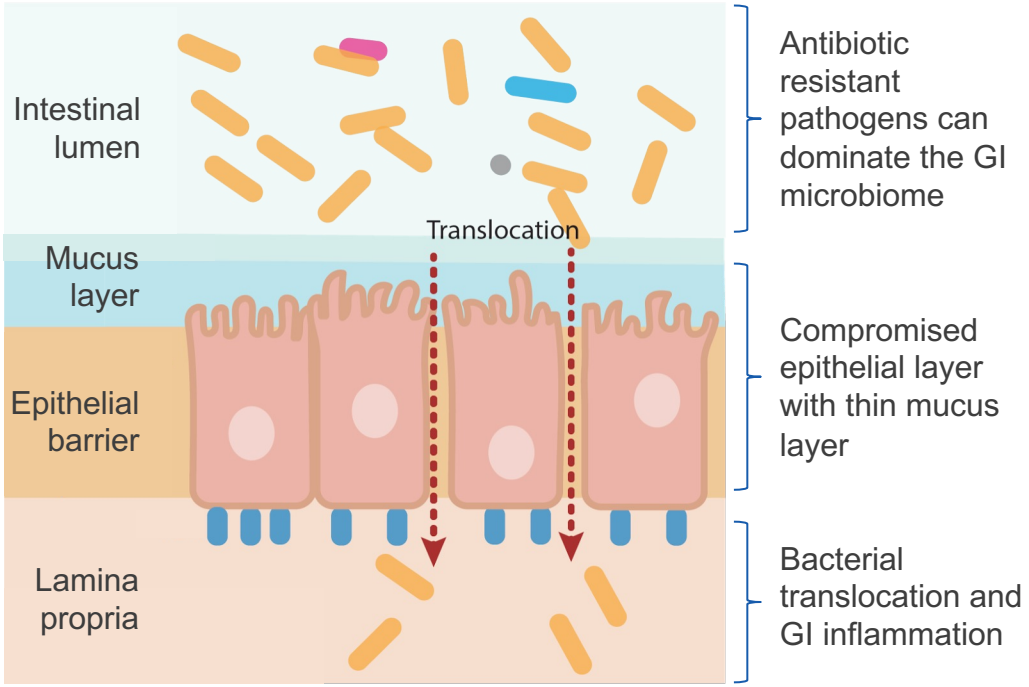
Microbiome therapeutics have potential to reduce infections, bacteremia, & antimicrobial resistance through multiple mechanisms

Infection & AMR

Disrupted Gastrointestinal Microbiome is Reservoir for Potential Pathogens



Microbiome Therapeutics

Restore colonization resistance and potentially decrease patient-to-patient transmission potential by preventing pathogen growth via nutrient competition and other functional mechanisms

Enhance epithelial barrier integrity and reduce likelihood of translocation to bloodstream by preventing/repairing epithelium and mucosa damage

Modulate immune response by improving immune homeostasis and reducing inflammatory responses

Microbiome consortia therapeutics likely can circumvent known resistance mechanisms of traditional antibiotics

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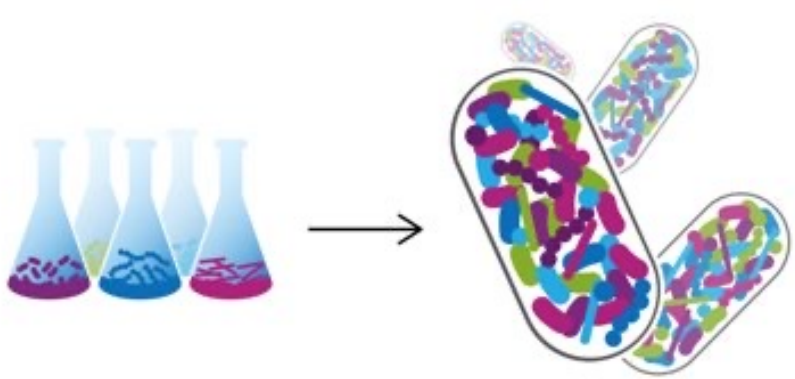
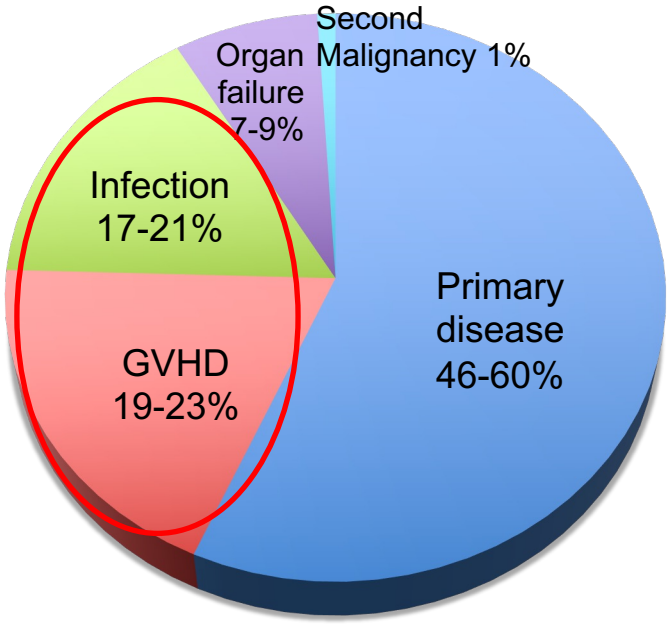
SER-155 is a cultivated consortium designed to target VRE & CRE infection and to modulate immune responses associated with GvHD

Infection & AMR





- Investigational consortium of **unique, human commensal bacterial strains**
- Cultivated and encapsulated for **oral delivery**
- **GMP manufacturing** of bacteria in both spore and vegetative formulations

- Phase 1b trial designed to **assess safety** and SER-155 **drug pharmacology**
- Will evaluate **decolonization of pathogens** as well as **incidence of infections** and **GvHD**, the two leading causes of mortality at 1-year post-transplant

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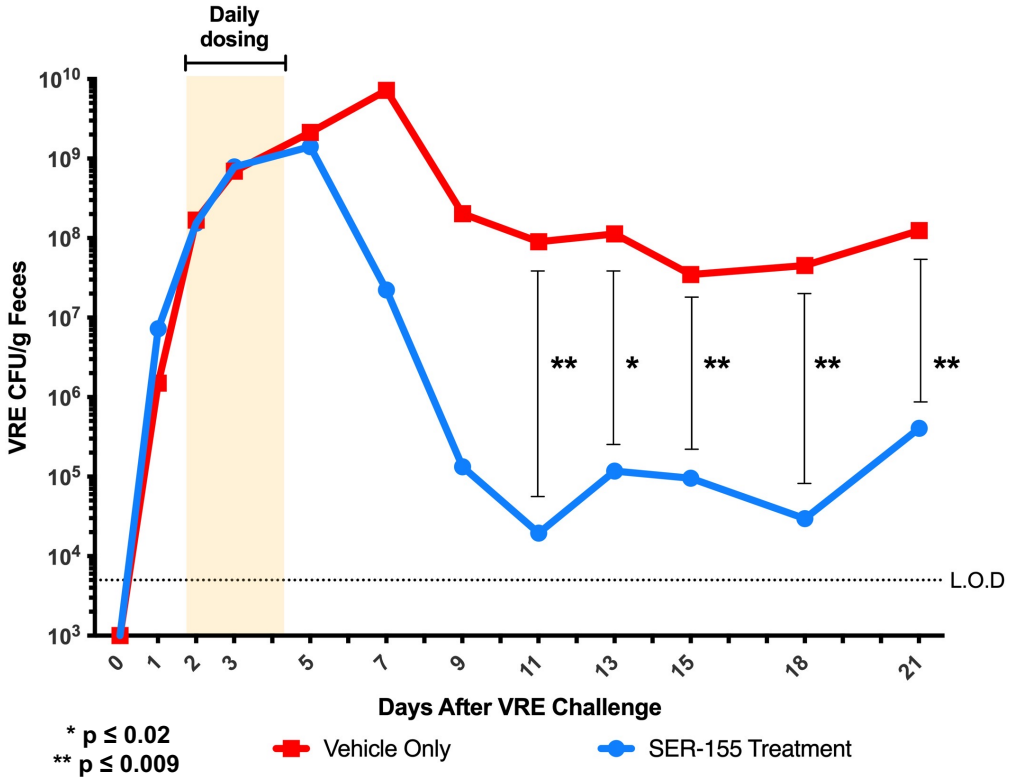
Lead optimization: SER-155 leads to a reduction in VRE and CRE colonization *in vivo*

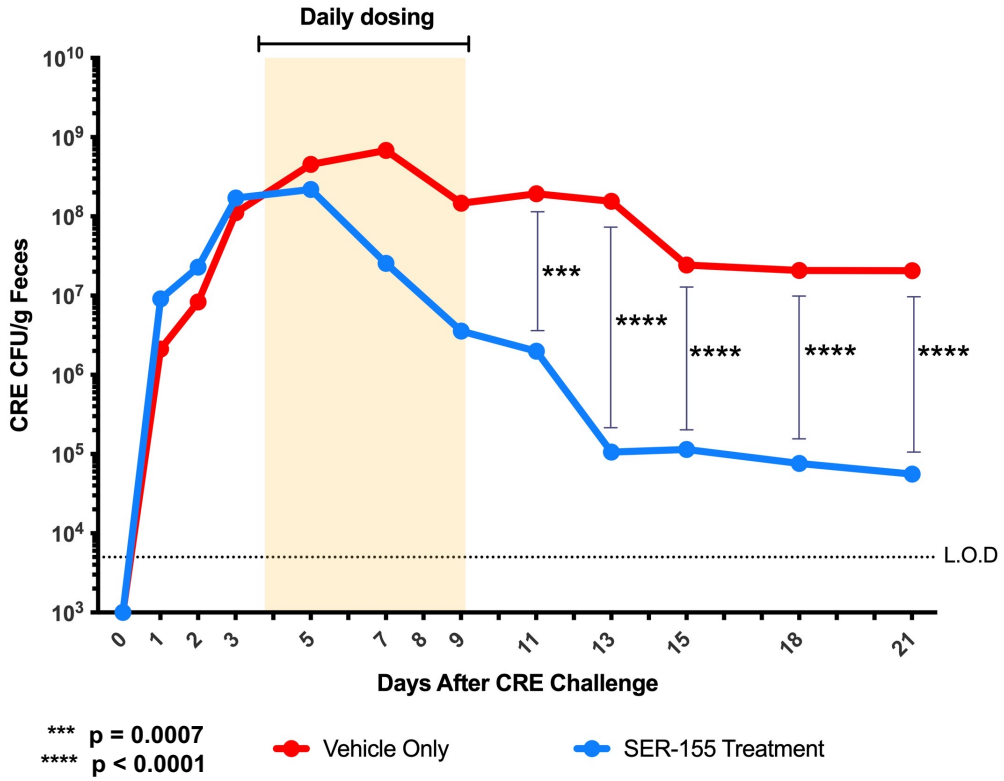
Infection & AMR

- SER-155 can decolonize CRE (carbapenem-resistant Enterobacteriaceae) and VRE (vancomycin-resistant Enterococci) in *in vivo* specific pathogen-free mouse models
- Enterococcus species and Enterobacteriaceae specifically linked to infection and GvHD

Declining titers of VRE



Declining titers of CRE



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Lead optimization: SER-155 designed to prevent translocation of bacteria into bloodstream and reduce GvHD

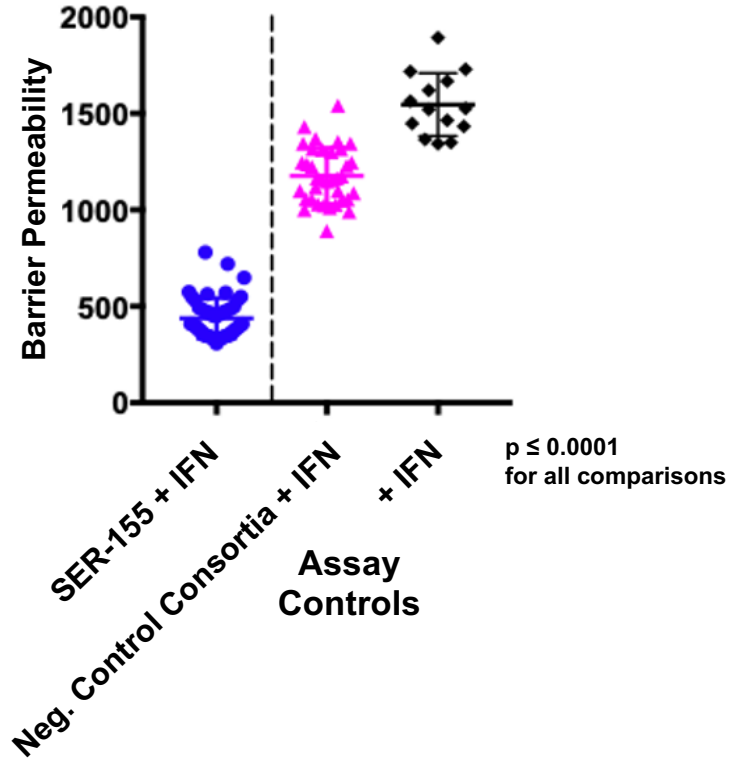
Infection & AMR

Consortia strains **optimized for production of metabolites** that:

- *Prevent Translocation:* Enhance epithelial barrier integrity, mucosal homeostasis & tight junction gene expression
- *Reduce GvHD:* Increase T*reg* differentiation and decrease proinflammatory T Cells

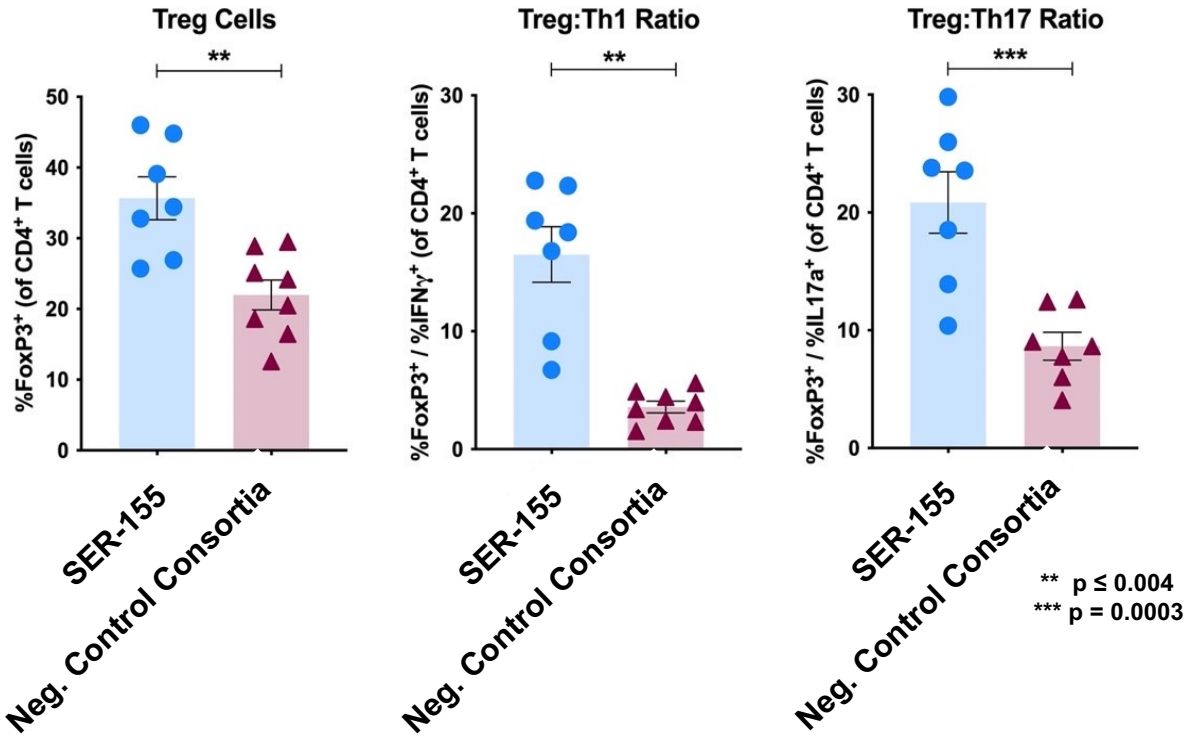
Epithelial Barrier Integrity

(in vitro primary colonic epithelial membrane assay)



Immune Modulation

(in vivo germ-free mouse model)



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Moving microbiome therapeutics from concept to reality in AMR

Infection & AMR

Microbiome therapeutics are potentially a transformative technology with novel mechanisms to combat infections and AMR

Seres is developing drugs to prevent **infection/bacteremia & decolonize pathogens that carry AMR** in high-risk patient populations

Discovery & Development Considerations for Successful Translation

- Continue to improve **translatability of preclinical screens & models** for lead optimization
- Continue to enhance **methods to evaluate PK, PD, & dosing strategies**
- Refine understanding of **patient subpopulations on disease pathogenesis & drug pharmacology**
- Develop **drug formulation strategies** that optimize patient access & can capture breadth of microbial biology
- **Scale GMP manufacturing** for use of broad breadth of microbial strains in drugs

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Thank You

Patients & Participating Clinical Sites in Seres Clinical Trials

Seres R&D, Manufacturing, Clinical, & Regulatory Teams

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Nestlé HealthScience

CARB-X
Combating Antibiotic-Resistant Bacteria

Memorial Sloan Kettering Cancer Center

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