Design and Preclinical Characterization of SER-155, an Investigational Cultivated Microbiome Therapeutic to Restore Colonization Resistance and Prevent Infection in Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

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Disclosure Information

The presenting author, Elizabeth Halvorsen, and all co-authors listed are employees and shareholders of Seres Therapeutics

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The Gastrointestinal Microbiome May Be a Key Factor in HSCT outcome

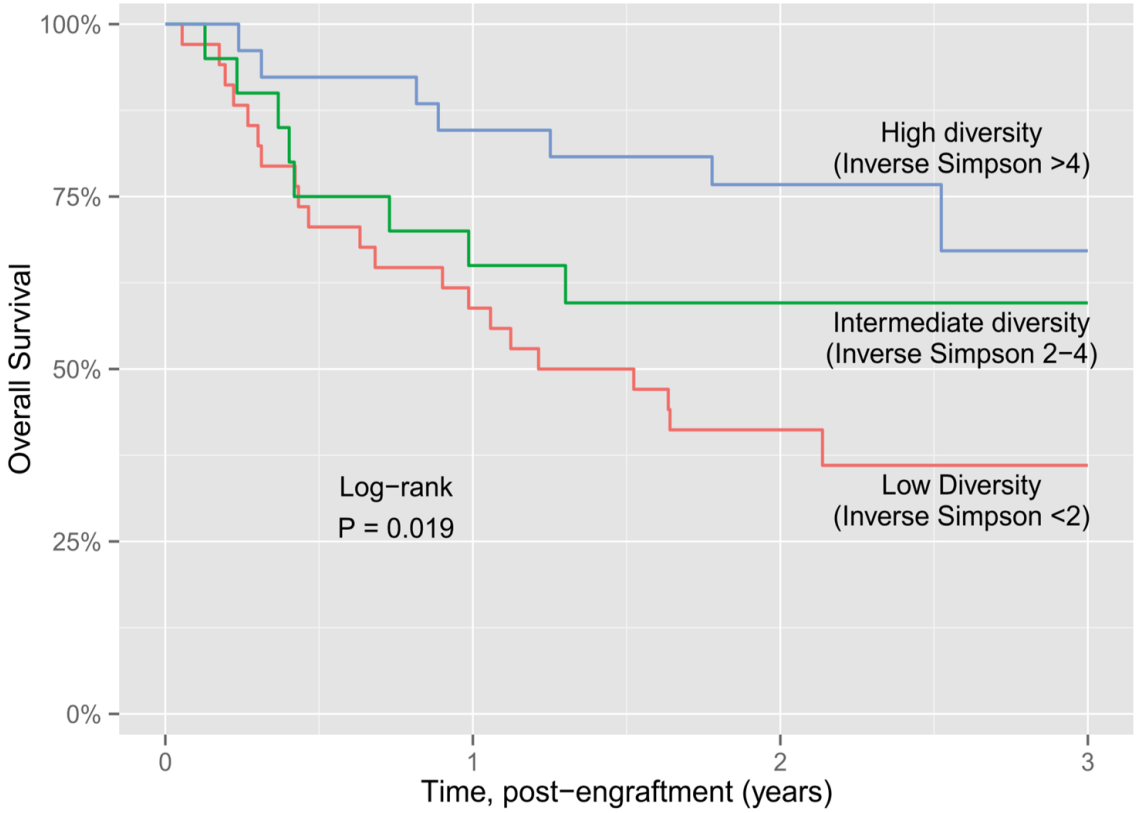
~9,500 allogeneic hematopoietic stem cell transplantation (allo-HSCT) procedures in the U.S. annually

Infection and graft-versus-host disease (GVHD) account for approximately one-third of deaths within 100 days of allo-HSCT

Frequent use of antibiotics during HSCT correlates with increased risk of bloodstream infections (BSIs), GVHD, and mortality

The gastrointestinal tract is a reservoir for potential pathogens that can cause BSIs

Mortality is doubled in patients with low microbiome diversity



Jenq et al, 2015; Taur et al, 2014; Tamburini et al, 2018; Phelan et al, CIBMTR US Summary Slides, 2020

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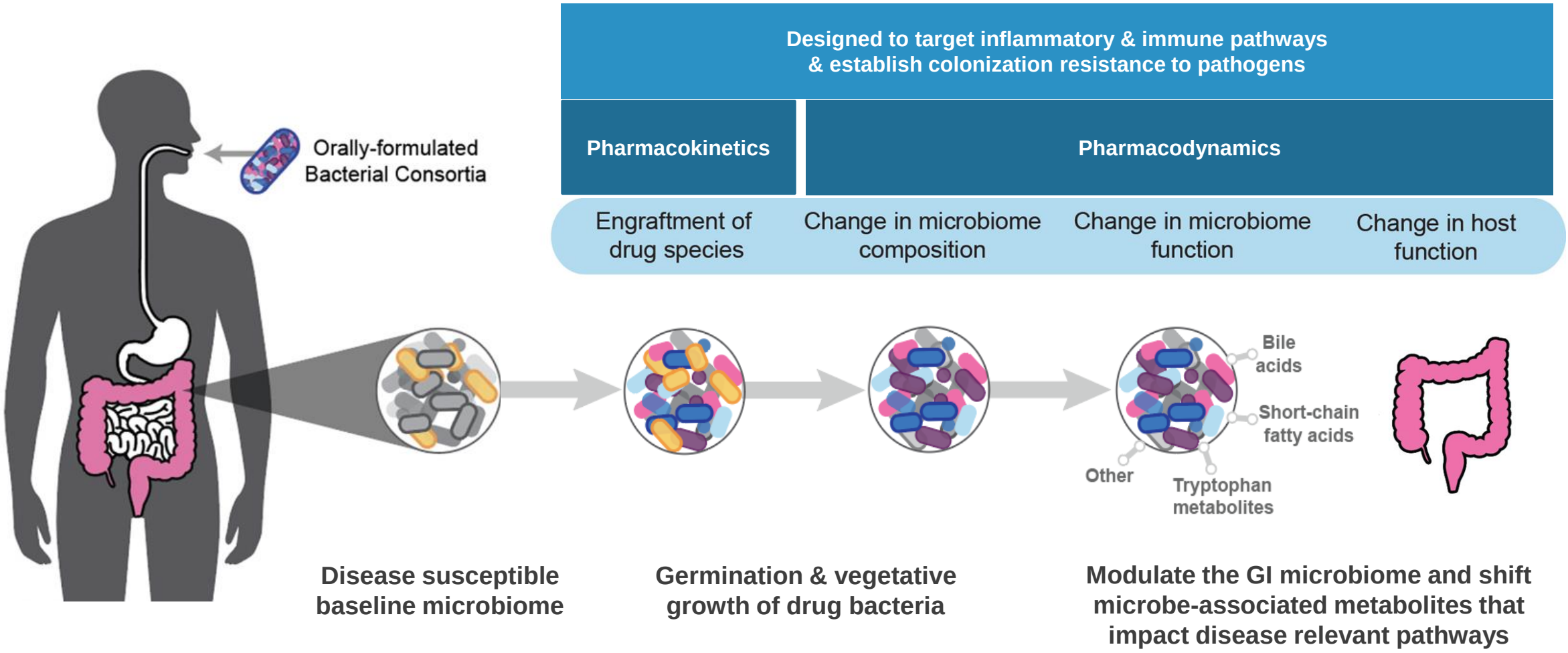
Seres Microbiome Therapeutics are Bacterial Consortia with Specific Pharmacological Properties



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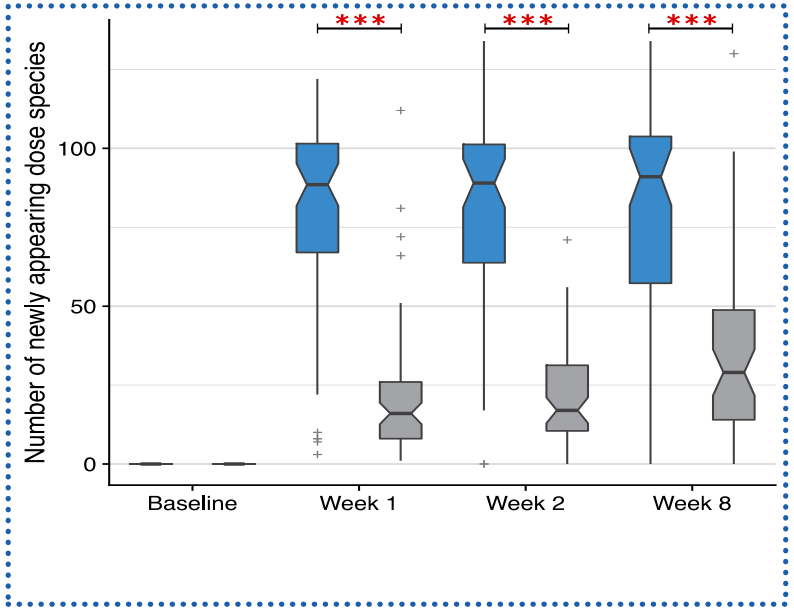
In a Phase 3 Study, Investigational Microbiome Therapeutic SER-109 Led to Rapid Pharmacokinetic and Pharmacodynamic Changes Associated with Clinical Response in *C. difficile* Infection

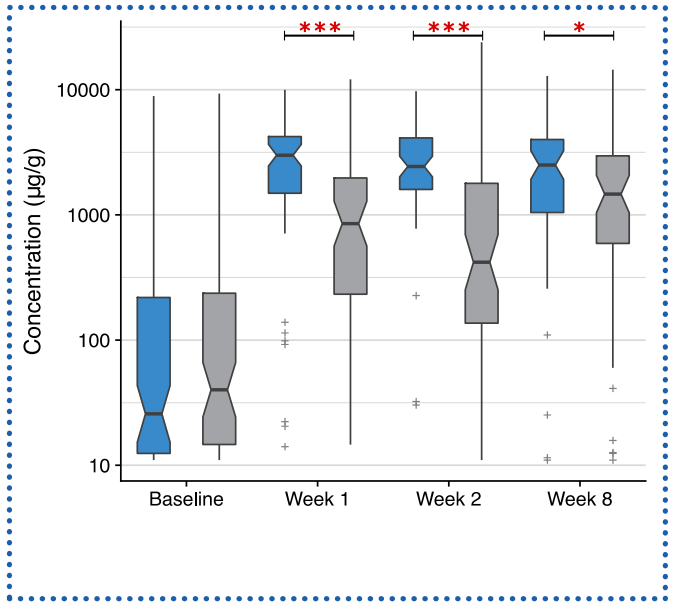
Pharmacokinetics

Engraftment of SER-109 dose species



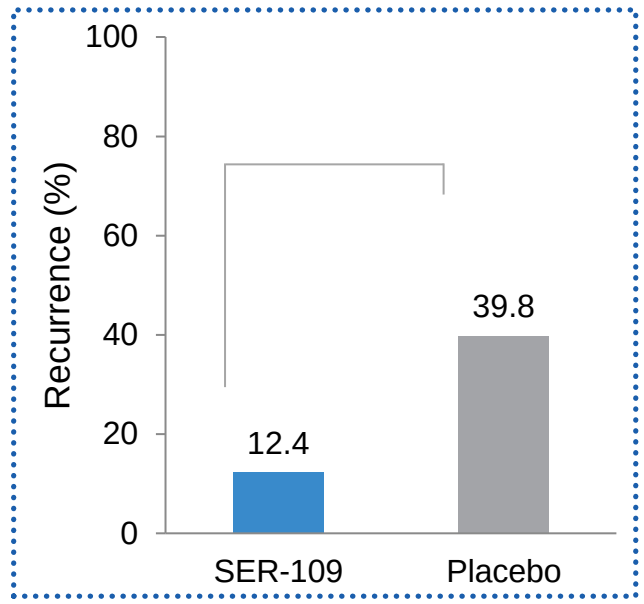
Pharmacodynamics

Increased concentration of secondary bile acids



Clinical response

Reduction in CDI recurrence through restoration of colonization resistance



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Clinical Development of SER-109 Suggests Microbiome Therapeutics May Reduce Carriage of Multi-Drug Resistant Organisms.

(1) In an open-label Phase 1 study of SER-109, carriage of VRE was significantly reduced relative to baseline (Lombardo, IDWeek 2015).

(2) In a Phase 2 placebo-controlled study, engraftment with SER-109 drug product species was associated with a significant reduction in the carriage of anti-microbial resistance genes. (Ford, IDWeek 2018).

(3) In a Phase 3 placebo-controlled study, this finding was repeated: treatment with SER-109 drug product species was again associated with reduction in the carriage of anti-microbial resistance genes (See Late Breaker Talk – Straub, IDWeek 2021).

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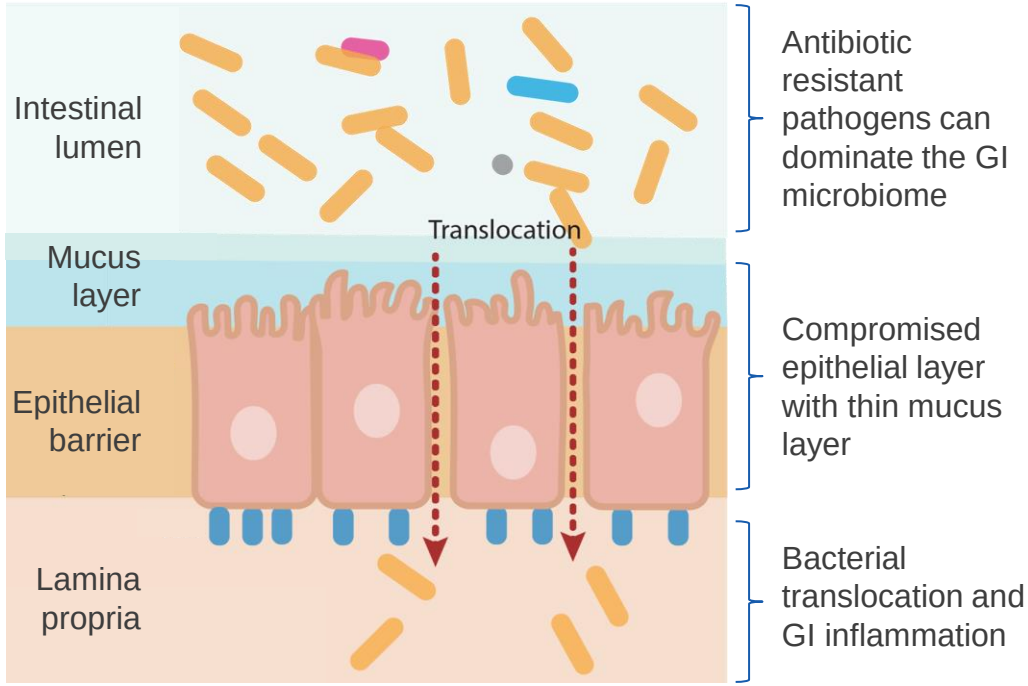
SER-155 is an Investigational Cultivated Microbiome Therapeutic Rationally- Designed to Reduce the Risk of BSI and GVHD in allo-HSCT Patients

Hypothesis: Barrier compromise, low microbiome diversity, and concomitant GI domination by potential pathogens drives risk of BSI, GI inflammation, and GVHD in allo-HSCT patients

SER-155 design targets both host and microbiome functions to:

1. **Restore colonization resistance**
2. **Enhance epithelial barrier integrity**
3. **Reduce GI inflammation**



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Compositional and Functional Design Elements of SER-155 to Target Restoration of Colonization Resistance

Decolonize pathogens associated with risk of BSI, GVHD, and mortality

- Vancomycin-resistant Enterococci (VRE)
- Carbapenem-resistant *Enterobacteriaceae* (CRE)

Engraftment of taxa associated with positive clinical outcomes and survival

- *Lachnospiraceae*
- *Eubacteriaceae*
- *Ruminococcaceae*
- *Erysipelotrichaceae*

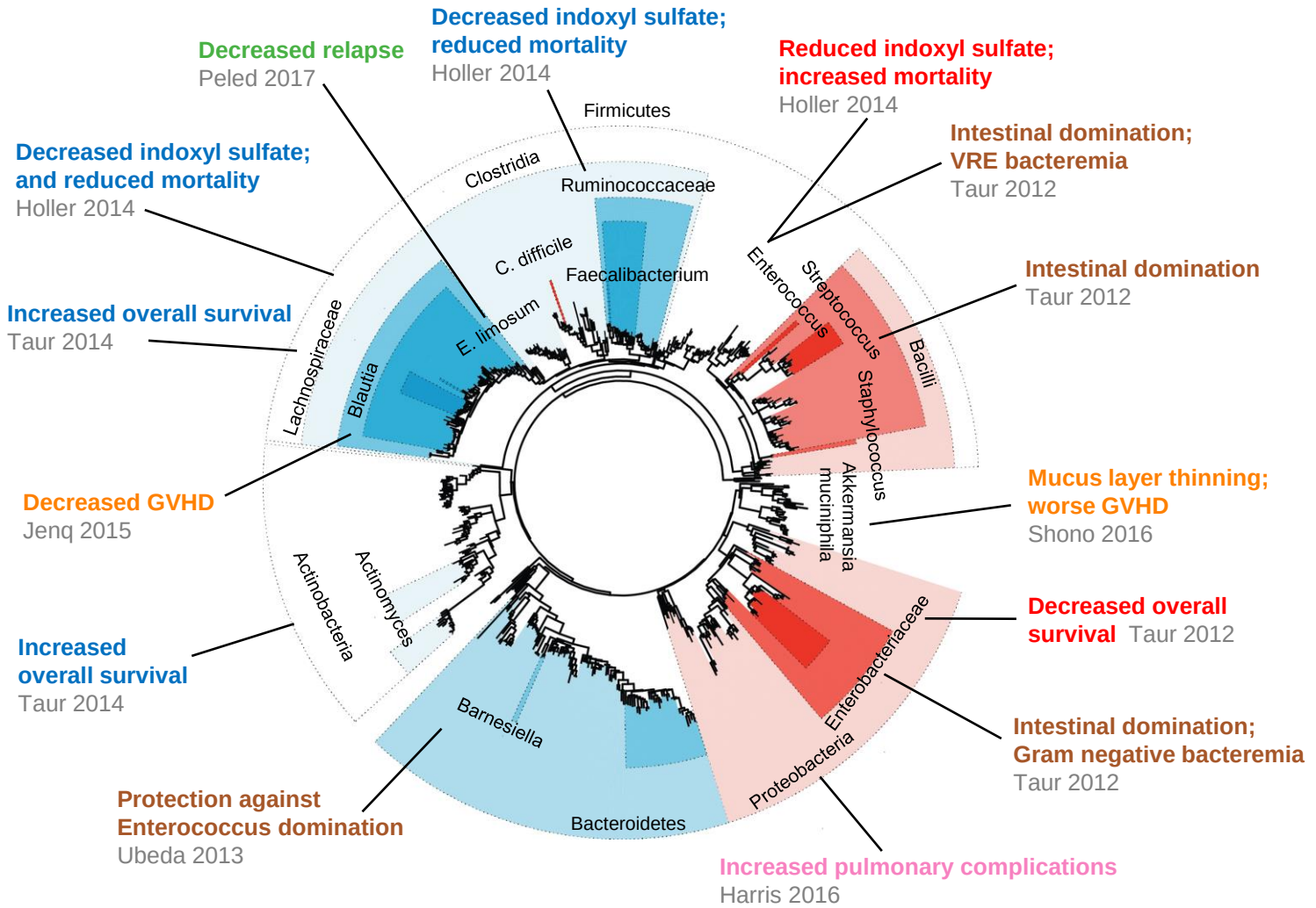

Figure provided by J. Peled, adapted from Taur et al, 2016

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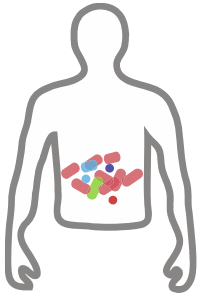
Iterative Reverse Translational Approach to Selecting Strains for SER-155 Starts with Patient Datasets

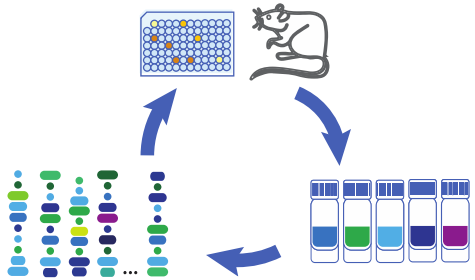
Disease Target Identification

Multiple longitudinal patient GI microbiome datasets analyzed to identify species of functional interest for SER-155 design



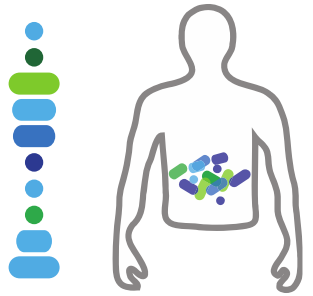
Hit and Lead Identification

Preclinical screening of candidate consortia *in vitro* and *in vivo* for ability to restore colonization resistance, enhance epithelial barrier integrity, and reduce GI inflammation



Final Clinical Candidate

For each strain in lead candidate consortia, finalize safety assessments and optimize manufacturing parameters for IND submission



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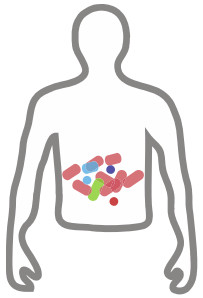
Reverse Translational Approach to Designing and Identifying SER-155, Starting with Patient Datasets

Disease Target Identification

Multiple longitudinal patient GI microbiome datasets analyzed to identify species of interest for SER-155 design

- Observational datasets from adults undergoing HSCT (MSKCC, Univ. of Cologne)
- Interventional datasets from adults receiving Seres investigational microbiome therapeutics (SER-109, SER-287, and SER-262 clinical trials)



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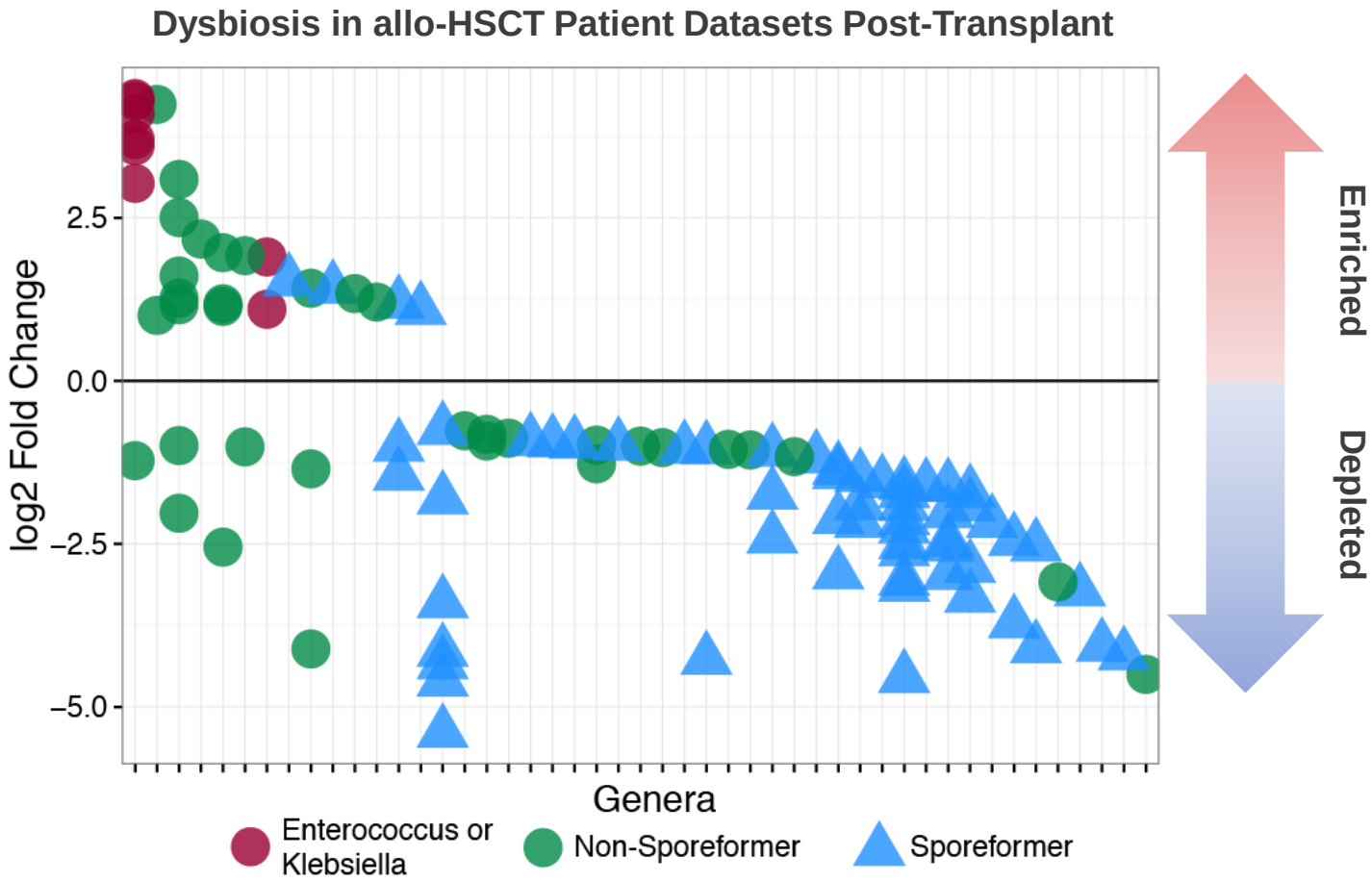
Multiple Longitudinal Patient GI Microbiome Datasets Were Analyzed to Identify Species of Interest for SER-155 Design

1) **Observational datasets** from allo-HSCT patients at MSKCC and Univ. of Cologne were used to identify taxa depleted post-transplant and associated with reduced risk of BSI and GVHD

2) **Interventional datasets** from adults receiving Seres investigational microbiome therapeutics were used to further refine SER-155 candidate consortia to select species with a high probability of engrafting in the GI

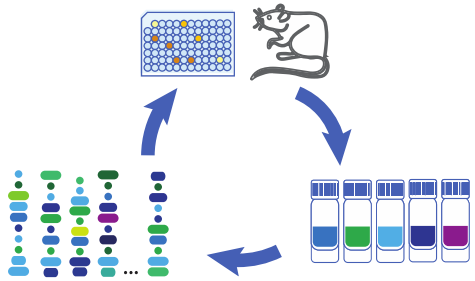


Reverse Translational Approach to Designing and Identifying SER-155, Starting with Patient Datasets

Hit and Lead Identification

Preclinical screening of candidate consortia

- Utilize Seres human-commensal strain library (>35,000 strains) to design and construct consortia
- *In vivo* and *in vitro* assays to screen for the ability to:
  - Inhibit and outcompete VRE, CRE & other pathobionts
  - Enhance/protect GI epithelial barrier integrity
  - Reduce GI inflammation



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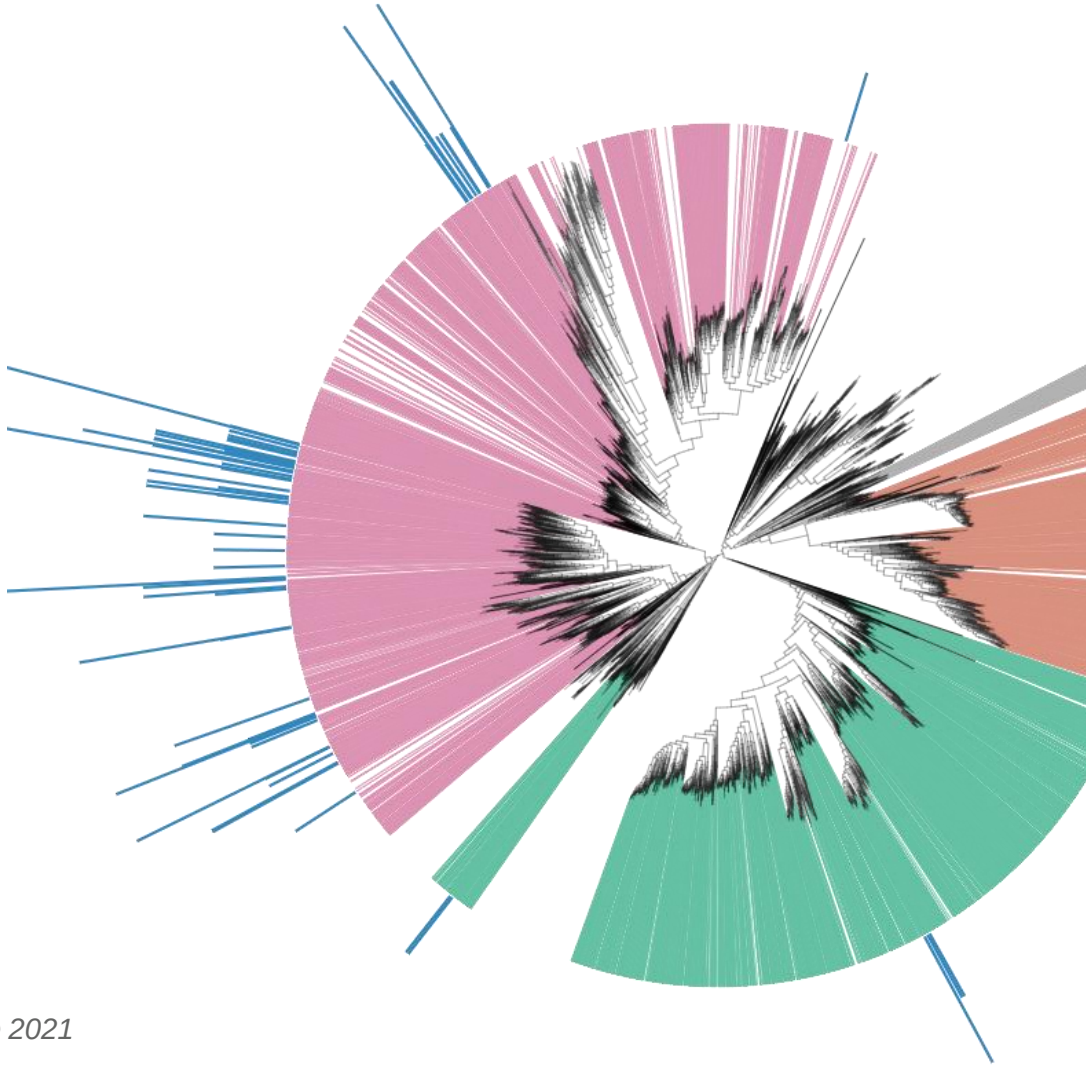
Breadth of Candidate Consortia Evaluated in Hit-to-Lead Identification for SER-155

Over 50 candidate consortia containing different combinations of nearly 150 species were designed and tested *in vitro* and *in vivo*



Blue lines indicate species tested and length of lines indicates increasing number of strains within a species tested

- Actinobacteria
- Bacteroidetes
- Firmicutes
- Verrucomicrobia

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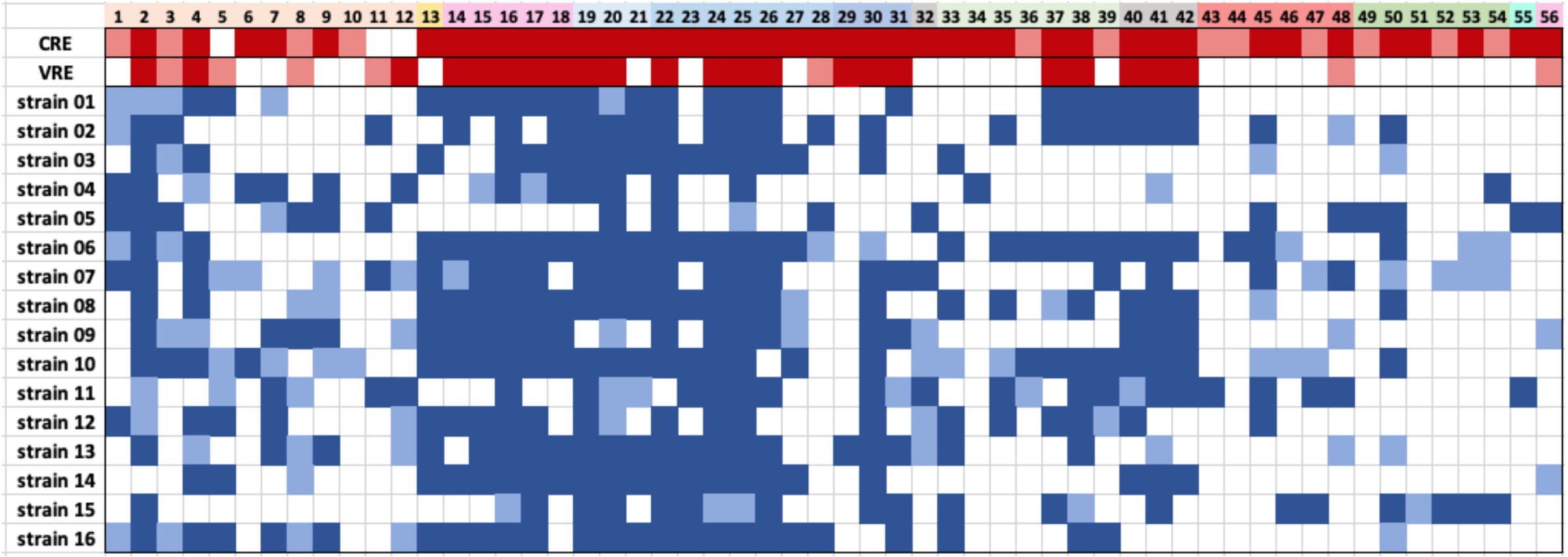
SER-155 Strains Can Compete for Nutrients to Restore Colonization Resistance Against Relevant Pathogens VRE and CRE

Carbon source utilization profiles of VRE, CRE, and SER-155 strains were assessed across 85 carbon sources



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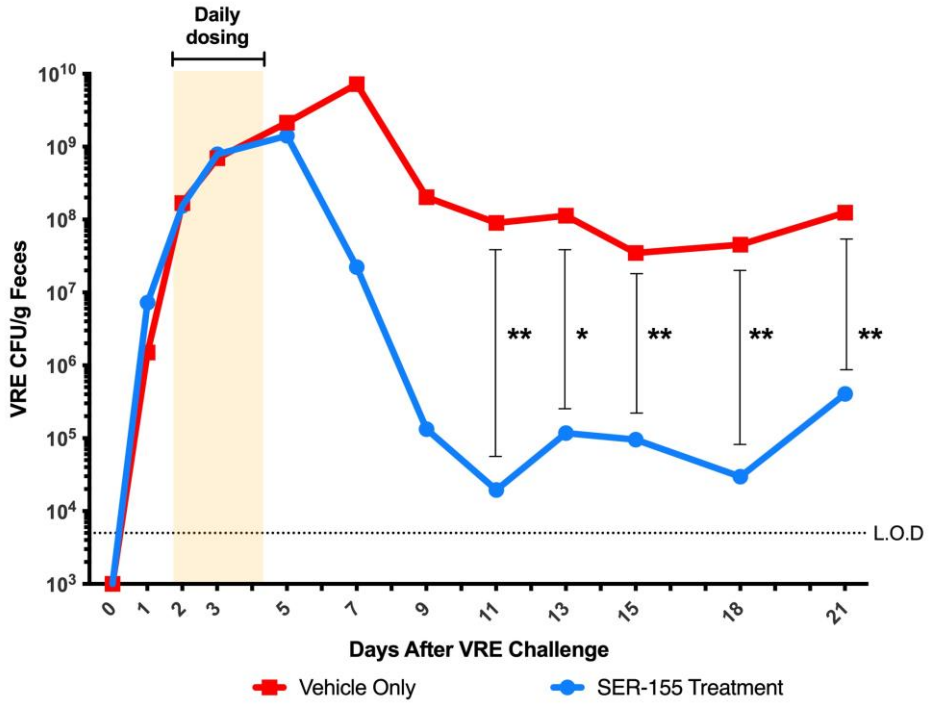
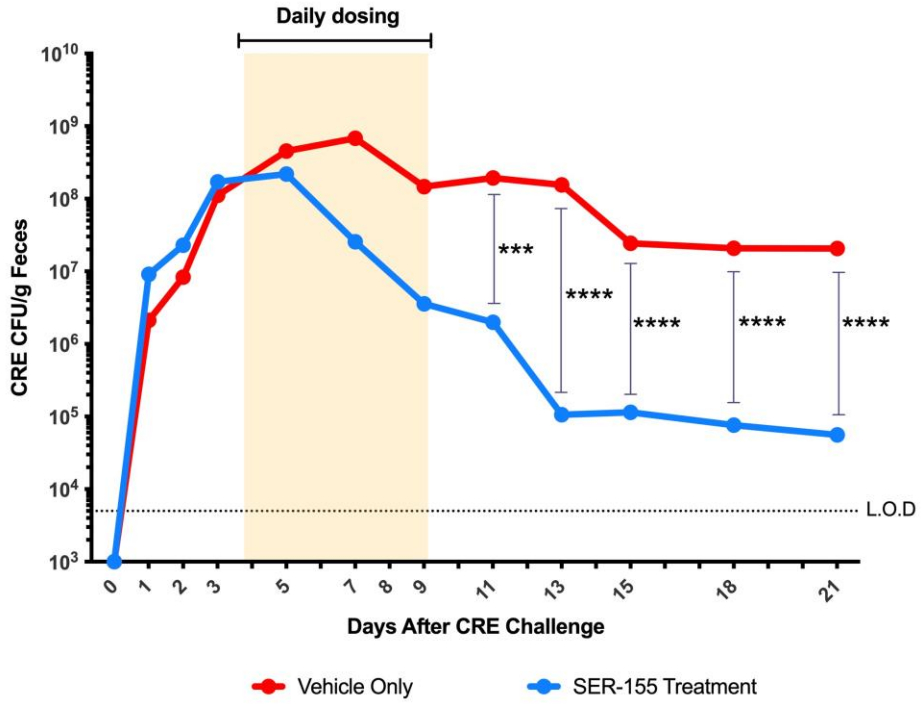
SER-155 Leads to a Reduction in VRE and CRE Titers *In Vivo*

In vivo, candidate consortia were evaluated in mouse models of VRE and CRE colonization and oral administration of SER-155 led to a 2-3 log reduction in VRE and CRE titers compared to untreated mice

Declining titers of VRE after SER-155 dosing



Declining titers of CRE after SER-155 dosing



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Conclusions

- SER-155 is an investigational cultivated microbiome therapeutic designed to reduce the risk of bloodstream infection and GvHD in adults undergoing allo-HSCT by restoring colonization resistance, enhancing epithelial barrier integrity, and reducing GI inflammation

- Preclinical assessments *in vitro* and *in vivo* support the ability of SER-155 to reduce VRE and CRE titers and restore colonization resistance

- A Phase 1b clinical trial evaluating SER-155 in allogeneic HSCT patients is currently enrolling (NCT04995653)

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Acknowledgements

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UNIKLINIK KÖLN

CARB-X
Combating Antibiotic-Resistant Bacteria

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Thank You

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