Microbiome Live Biotherapeutics as a Novel Approach to Treat Infectious and Inflammatory Diseases

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**Mission**

*To transform the lives of patients with revolutionary microbiome therapeutics*

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- **Location**
  Cambridge, MA

- **Clinical Assets**
  Advanced drug pipeline with Phase 3 & Phase 2 programs

- **Platform**
  Platforms enable early discovery through GMP manufacturing of microbiome therapeutics

- **Employees**
  130+
Seres is developing a novel drug modality that modulates the gut microbiome

_Ecobiotic®_ Live Microbiome Biotherapeutics are encapsulated consortia of commensal bacteria with specific pharmacologic properties

- **Consortia capture breadth of phylogenetic & functional diversity** in gut
- **Mechanisms includes microbial engraftment in GI tract** to restructure the microbiome
- **Designed to target inflammatory & immunological disease pathways simultaneously**
- **Formulated for oral delivery** using current Good Manufacturing Practices (cGMP)
Drugs are designed to target therapeutic microbe-microbe & microbe-host functional interactions in the human gut

<table>
<thead>
<tr>
<th>Microbe-Microbe Colonization Resistance</th>
<th>Microbe-Host Inflammatory &amp; Immune Pathway Engagement</th>
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</thead>
<tbody>
<tr>
<td>Antimicrobial peptides &amp; toxins</td>
<td>Epithelial Barrier &amp; Mucin Integrity</td>
</tr>
<tr>
<td>Pathogen growth inhibition</td>
<td>Epithelial Cell Inflammation</td>
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<td></td>
<td>Local Innate &amp; Adaptive Immunity</td>
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<tr>
<td></td>
<td>Systemic Innate &amp; Adaptive Immunity</td>
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</tbody>
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- **C. difficile Infection**
  - SER-109 (Ph3) & SER-262 (Ph1b completed)

- **Ulcerative colitis**
  - SER-287 (Ph2) & SER-301 (Ph1b in 2020)

- **I-O metastatic melanoma**
  - SER-401 (Ph1b) & PICI/MDACC

- **I-O Disease Expansion**
  - AZ & MSK Collaboration

- **Bacteremia & GvHD IN allo-HSCT / Immunocompromised patients**
  - MSK Collaboration

- **Inflammatory Disease Expansion**

*Reverse Translation Drug Discovery & Development Platform enables building of portfolio based on key learnings across programs*
Human ‘Proof of Concept’ Phase 2: SER-109 for the reduction of C. difficile recurrence

Early engraftment of SER-109 strains was associated with non-recurrence

Increased engraftment was associated with increased production of secondary bile acids

McGovern, Ford, Henn et al. (in revision)
Human ‘Proof of Concept’ Phase 1b: SER-287 for the treatment of mild-moderate ulcerative colitis

Preconditioning with vancomycin followed by daily dosing of SER-287 was associated with clinical remission

Microbially-mediated metabolites that modulate host inflammation & barrier integrity are associated with SER-287 treatment and clinical outcome

\[ p = 0.024 \]

Henn et al. (in revision)
How does the gastrointestinal (GI) microbiome impact antibiotic resistant infection?

(1) The GI tract is home to trillions of bacterial cells; a healthy intact microbiome is essential to preventing colonization with pathogens.

Suau et al, Appl Environ Microbiol. 1999
Kim et al, Nature, 2019
Caballero et al, Cell Host & Microbe, 2017
Pamer, E., Science 2016
How does the gastrointestinal (GI) microbiome impact antibiotic resistant infection?

(1) The GI tract is home to trillions of bacterial cells; a healthy intact microbiome is essential to preventing colonization with pathogens.

(2) Antibiotic resistant & tolerant bacteria rapidly expand in the absence of commensals resulting in domination by a few species.

Ubeda et al, J.Clin Invest 2010
Taur et al, Clin Infect Dis, 2012
How does the gastrointestinal (GI) microbiome impact antibiotic resistant infection?

1. The GI tract is home to trillions of bacterial cells; a healthy intact microbiome is essential to preventing colonization with pathogens.

2. Antibiotic resistant & tolerant bacteria rapidly expand in the absence of commensals resulting in domination by a few species.

3. Domination with multidrug resistant organisms (MDRO) in populations with increased intestinal permeability has been associated with increased risk of bacteremia.  

   Tamburini et al, Nat Med 2018
Ecobiotic® live biotherapeutics may disrupt this path and represent a novel approach to combating antibiotic resistance.

**Treatment with SER-109 reduced VRE Carriage**

- **Baseline** vs **4 weeks post treatment**
- **1x10^3** to **1x10^9**

**SER-109 engraftment resulted in reduction of carriage of antibiotic resistance genes**

- **Results from Seres SER-109 Phase 1 trial**
- **Results from Seres SER-109 Phase 2 trial**
Seres is leveraging clinical insights to design Ecobiotic® live biotherapeutics as a novel solution to MDRO infection

Designed to prevent infection through decolonization & barrier restoration

- Defined consortia of laboratory-grown bacteria

- **Consortia Design:** Leverages insights on species and target pathways from SER-109 & SER-287 trials to define compositions of interest

- **Consortia Screening:** *in vivo & in vitro* models of VRE (shown), CRE, epithelial barrier integrity, & host immunity

Program supported by CARB-X

Vancomycin Resistant Enterococcus (VRE)
Lead candidate can decolonize VRE (data shown) & CRE in vivo

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![Graph showing VRE CFU/g Feces over days after VRE challenge](image)
Conclusions

(1) Clinical studies support potential to use microbiome live biotherapeutics to modulate host inflammation/immunity and to target infection.

(2) Antibiotic resistant infections can derive from reservoirs of antibiotic resistant organisms living in the GI microbiome. Inflammation and barrier compromise facilitate translocation of MDRO bacteria into bloodstream with clinical consequences.

(3) Proof of concept studies suggest microbiome therapeutics can reduce the abundance of antibiotic resistant organisms and genes in the GI microbiome.

(4) Seres is leveraging clinical & preclinical data to develop microbiome therapeutics to take-on the challenge of antibiotic resistant infection.
Thank You

Patients & Participating Clinical Sites
Seres Clinical Trials
Seres R&D, Manufacturing, Clinical, & Regulatory Teams
Support from CARB-X
Collaborations with NHSc & MSKCC

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