The Evolution of Drug Development Targeting the Microbiome

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### Seres Therapeutics Overview

1. **Leading Microbiome Therapeutics Company**
   - Clinically demonstrated approach for treating disease by restoring a dysbiotic (unhealthy) microbiome to a healthy state
   - Integrated discovery and manufacturing platform

2. **C. Difficile Franchise; Positive Phase 1b/2 results for lead candidate SER-109**
   - Potential first-in-field indication for recurrent *C. difficile* infection (CDI)
   - Ph1b/2 study results: 97% clinical cure rate; 87% achieving efficacy endpoint per protocol; no drug-related SAEs
   - Granted Breakthrough Therapy Status & Orphan Designation by FDA

3. **Expanding Pipeline Encompassing IBD, Metabolic, and Infectious Diseases**
   - SER-287 for Ulcerative Colitis: Phase 1b study initiated
   - SER-262 expected to enter clinic in mid-2016 for Primary CDI
   - Additional pre-clinical programs in IBD, metabolic and infectious diseases

4. **Strong Financial and Strategic Position**
   - Founded by VentureLabs, innovation foundry of Flagship Ventures
   - Strong cash position
   - Strategic collaboration with Nestlé Health Science for CDI and IBD assets for ex-US / Canadian markets
Ecobiotic® Drugs – Potential New Frontier in Medicine

- Ecobiotic drugs are consortia of commensal microbes that catalyze a change in the microbiome from a disease state to a state of health
- Capture breadth of phylogenetic diversity of GI microbiome
- Therapeutics areas include ID, metabolic disease, immunology and cancer
- Formulated as oral drugs using GMP manufacturing practices
- No current FDA approved microbiome therapeutics
Business Strategy Prioritizes Indications with Strongest Clinical Data and Scientific Rationale

Pipeline Growth

- Recurrent C. Diff. Infection (SER-109, Ph2 ongoing)
- Ulcerative Colitis (SER-287, Ph1b ongoing)
- Primary C. Diff. Infection (SER-262)
- Infection & GVHD after allo-HSCT (SER-155)
- Liver Diseases (NASH)
- Crohn’s Disease (SER-301)
- Metabolism: Diabetes and Obesity
- Rare Metabolic Diseases
- Immuno-oncology

Process Evolution

Today

- Biologically sourced (SER-109; SER-287)

Future

- Synthetic fermented (SER-262; SER-301; SER-155)
Take Home Messages

• In an emerging field, don’t compound Platform Risk with Indication Risk

• Start with the simplest approach and then add complexity as you generate insight from human studies

• Invest in improved models for drug discovery and mechanism of action studies

• Look to the future—what do patients need and what will the marketplace require?
Don’t Compound Platform Risk with Indication Risk
After antibiotic treatment:

- ~25% No response to certain antibiotics
- ≥60% Clostridium difficile is the #1 Hospital Acquired Infection in U.S.

Primary infection (~640-820k patients)

- After antibiotic treatment: ~25%
- No response to certain antibiotics: 8%

First relapse/reTx (~212-270k)

- ~40%

Second relapse/reTx (~85-110k)

- ≥60%

Third relapse/reTx (~50-65k)

CDC Designated Urgent Threat

- C. difficile disease is an inflammatory infection of the colon which occurs after gut microbes are killed by broad spectrum antibiotic use
- Most common nosocomial infection in U.S.; ~29,000 deaths annually (Lessa et al. 2015. NEJM)
- Growing burden: increased from 4.5 to 8.2 per 1000 patients discharged from 2001 to 2010 (Reveles 2014)
- Economic burden of as much as $4.8B in U.S. acute-care facilities (Dubberke 2012)
- Cost per episode: primary CDI ~$5K, recurrent CDI ~$18K (Ghantoji 2010)
- Breaking the recurrence cycle can result in over $50K per patient savings
Microbiome Disruption is a Correlate of *C. difficile* Infection and Recurrence

Lawley *PLOS Path* 2012
Kelly and Lamont *NEJM* 2008
### Infection

HSCT conditioning results in dysbiosis, and increased risk of infection from gut pathogens

SER-109 demonstrated significant reduction of carriage of gut pathogens\(^1\)

### GVHD

Butyrate producing organisms increase barrier integrity and improve immune homeostasis

GvHD mortality associated with microbiome signature in patients\(^2\)

### Patient Need

~22,000 allo-HSCT per year with high hospitalization and treatment cost (US and EU data)

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**Microbiome Health Correlates with Overall Mortality Risk\(^3\)**

![Graph showing probability of transplant-related death over time post engraftment](attachment:graph.png)

- Log-rank P = 0.003
- Low Diversity (Inverse Simpson <2)
- Intermediate diversity (Inverse Simpson 2–4)
- High diversity (Inverse Simpson >4)
Start with the simplest approach and then add complexity as you generate insight from human studies.
SER-109, a Donor-Derived Product, Enabled Rapid Human POC and Provided Enormous Insights into Ecobiocic Drugs

- Purified Firmicute spores from 7 families: *Clostridiaceae*, *Erysipelotrichaceae*, *Eubacteriaceae*, *Lachnospiraceae*, *Oscillospiraceae*, *Peptostreptococcaceae*, & *Ruminococcaceae*
- Oral, single dose drug in 4 capsules
- GMP manufacture of drug by fractionation of spores from human stool
- GMP process preserves spore viability while selectively killing vegetative bacteria, fungi, parasites and viruses; greatly reduces risk of pathogen transmission

Ecology of microbes in spore form that represent a broad phylogenetic breadth
Engraftment of Ecobiotic Strains & Augmentation of Commensals Establish a Diverse, Functional Microbiome

Restoration Stages

- Stabilize Healthy Ecology Function
- Replace Disease Ecology
- Disrupt Disease Ecology

Microbial Population Carriage

- Augmented microbes
- Restored Microbiome
- Engrafted microbes
- Disease microbes

Time Post-Treatment
Clinical Results: Durable Improvements in Total Microbial Diversity

Rapid & sustained change in microbiome through 24 weeks in both cohorts

Microbiome in patients compared to Human Microbiome Project dataset

Unweighted Unifrac Analysis

PCoA Analysis

HMP = green
Pretreatment = red
8-16 wks = yellow
24-27 wks = orange
Seres Marshalled an Exhaustive Characterization of Spore Formers in Humans--A Major Factor in Human Microbiome

- “Sporulation is an unappreciated basic phenotype of the human intestinal microbiota”
- “At least 50–60% of the bacterial genera from the intestinal microbiota of a healthy individual produce resilient spores”
- “Spore-forming bacteria of the microbiota were significantly more diverse than the non-spore-forming bacteria”

Proprietary Library Comprises Over 400 Commensal Organisms, >200 Spore Forming Species and >14,000 Strains

Browne et al Nature 2016
MSKCC Collaborators Have Shown that Human Insights Can be Leveraged in Setting of Immuno-Oncology

There is a microbiome signature in melanoma patients with colitis induced by ant-CTLA4 checkpoint Inhibitions

Different microbiota in colitis vs resistant patients

Members of the Bacteroidetes phylum associate with resistance

Dubin et al *Nature Comm* 2016
Invest in Improved Models For Drug Discovery
Ex Vivo Systems for Screening Responses and Mechanisms Using Human Cells

Human Colonic Tissue

Organoids Derived from Stem Cells

Micrograph of Human Colonic Crypts

Gut-on-Chip

Kim PNAS 2015
Selective Use of Animal Models to Address Mechanism

AB/PAS stain. Dark purple = mucins
Look to the future—what do patients need and what will the marketplace require?
CMC Platform Enables the Translation of Complex Anaerobic Biology Into cGMP-compliant Oral Drugs

Scalable fermentation of unconventional anaerobic and spore-forming microbes

Fermented strains

Biologically sourced

cGMP Isolation of spores from complex biological materials

Formulation, Filling, & Packaging

Development of novel cultivation and germination

Unoptimized

Optimized

Novel QC assays for microbiome characterization, identity, purity, & potency

Absorb.

Lumin.

DPA

Tb$^{3+}$

SERES THERAPEUTICS®
SER-262 is Rationally Designed for *C. difficile* Treatment Based on Insights from SER-109
Characterization of SER-262 Strains for Functions that Prevention CDI

Nutrient competition

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Carboxylic acids

- Fr: Fructose
- Gl: Glucose
- Ma: Malate
- Rh: Rhein
- Li: Lactic acid
- Ce: Citrate
- Tr: Taurine
- Sarc: Sarcosine
- Met: Methionine
- Ile: Isoleucine
- Leu: Leucine
- Ala: Alanine
- Gly: Glycine
- Ser: Serine
- Pro: Proline
- Arg: Arginine
- Thr: Threonine

Amino acids

- Fr: Fructose
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- Pro: Proline
- Arg: Arginine
- Thr: Threonine

Bile Acid Metabolism (bsh or HSDH activity)

- Strain 1
- Strain 2
- Strain 3
- Strain 4
- Strain 5
- Strain 6
- Strain 7
- Strain 8
- Strain 9
- Strain 10
- Strain 11
- Strain 12

26 of 29 C. difficile carbon sources tested are used by the SER-262 strains

10 of 12 strains tested have bile acid conversion activity
SER-262 is a Rationally Designed Product and is the Precursor to a Next Generation of Ecobiotic Drugs

Potent efficacy demonstrated in *C. difficile* murine model

![Graph showing percent body weight change and survival proportions](image-url)

* p≤0.01 PBS CDI compared to SER-262, SER-109 and No C. diff on Days 2 through 6

p≤0.001 PBS CDI compared to SER-262, SER-109 and No C. diff through 6
Leading the Microbiome Revolution