Elucidation of Gut Microbiome Response to Dietary Fiber Types Using MBRAs

Outstanding Questions:

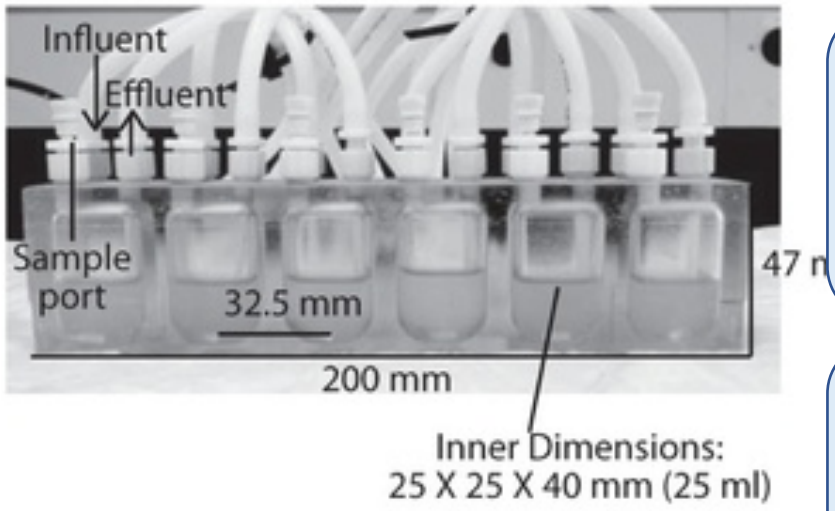
- Which types of fibers result in favorable/unfavorable shifts that are functionally relevant?
- What are the ecological and functional consequences of fiber fermentation on host health?

INPUTS

FIBER
Soluble
Insoluble
Combination

Human Stool
"Healthy"
Colon Cancer

Drugs
Oxaliplatin
5 FU
Antibiotics



OUTPUTS

Microbiome
Composition
Stability
Resilience
Relationships

Metabolome
Global
Targeted:
SCFAs
AAs

OMVs
Protein
Small RNAs
DNA
metabolites

In Vitro

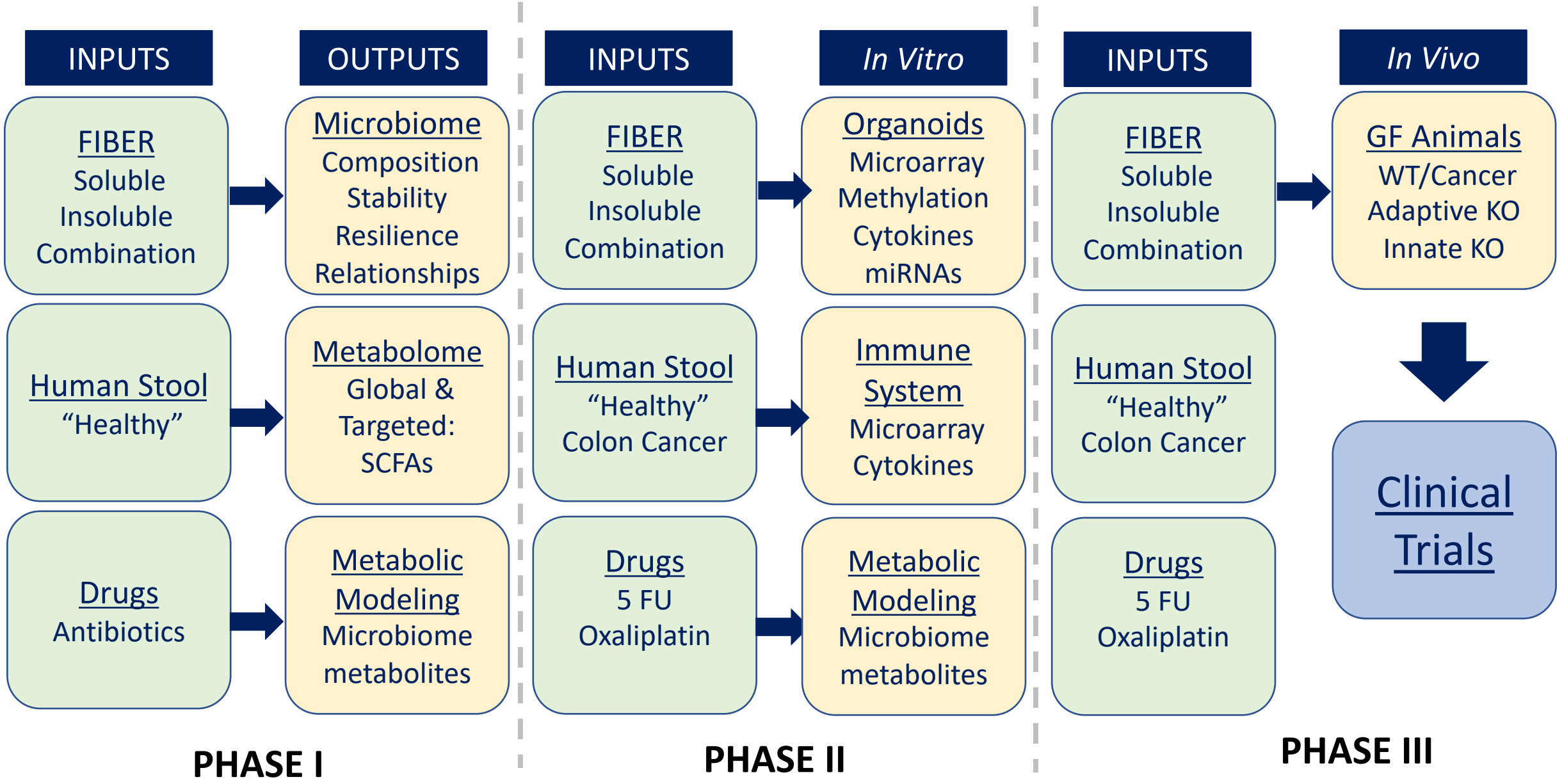
Organoids
Microarray
Methylation
Cytokines
miRNAs

PBMCs
Microarray
Cytokines

In Vivo

GF Animals
WT/CRC
Adaptive KO
Innate KO

Three Phase Strategy for Developing Precision Medicine Prebiotics

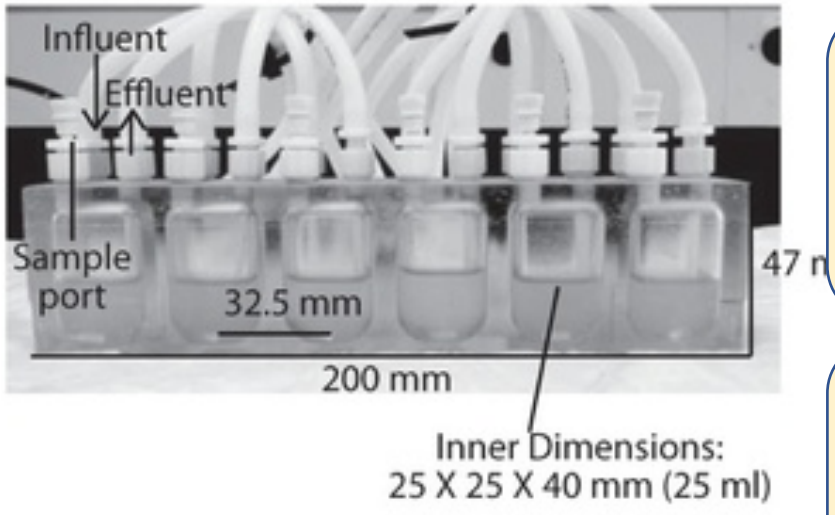


INPUTS

FIBER
Inulin
Resistant starch
Combination

Human Stool
"Healthy" donors

MBRA



OUTPUTS

Microbiome
Composition
Stability
Resilience
Resistance

Metabolites
Global profile
Targeted:
SCFAs

Outstanding Questions:

- •Which types of fibers result in favorable/unfavorable shifts that are functionally relevant?
  - •Which types of fibers prevent pathogen colonization – c. diff, ETBF, E. coli pks, MRSA
  - •Which types of fibers prevent development of biofilm formation
  - •Which types of fibers results in the most diversity or highest amount of competition/stability
  - •Which types of fibers create the resiliency to stressors – pH, temperature, O2 (e.g. what is the buffering capability)

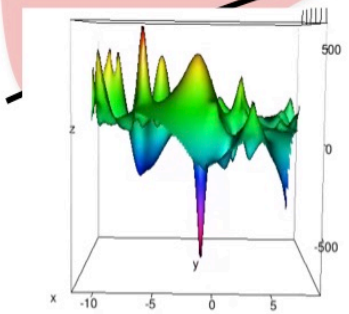
- •What are the ecological and functional consequences of fiber fermentation on host health?
  - •How do different fibers alter the microbial community to protect from colon cancer development
  - •How do different fibers alter the microbial community to modulate stem cells/CSCs

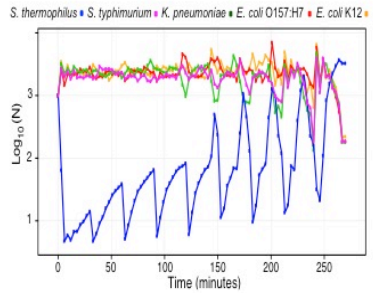
Specific Aims:

1. Determine model community changes in composition and metabolism after exposure to inulin or resistant starch
   - Measure alpha and beta diversity after inulin or resistant starch exposure in three model stool communities
   - Determine changes in short chain fatty acid and metabolism after inulin or resistant starch exposure in three model stool communities
2. Measure ability to resist pathogen colonization by c. diff, MRSA or enterotoxic B. fragilis in fiber-exposed stool community
3. Quantify ability to recover from antibiotic challenge in fiber-exposed stool community

3-step Pipeline for Probiotic Design

Candidate probiotic therapies





Step I

Static Simulations

Static simulation of potential probiotic therapies based on community metabolic metabolism.

Endpoints: Engraftment and *C. diff* interaction scores,

Q: Which probiotics can engraft and block C. difficile?

Step 2

Dynamic Simulations

Dynamic simulation of how microbial population reacts to candidate probiotics based on interactions and nutrient conditions.

Endpoint: Long-term stability assessment

Q: Are candidate probiotics stable and effective over time?

Step 3

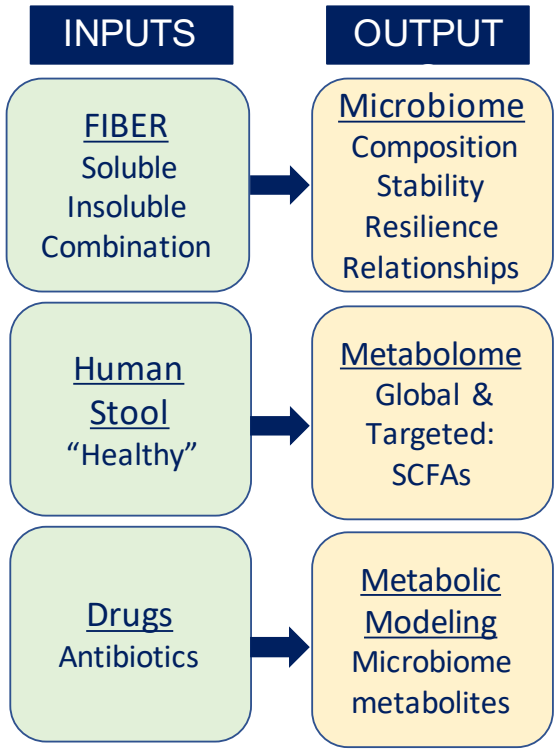
Humanized Mice

Germ-free mice inoculated with human stool will be administered probiotics to test engraftment and ability to prevent *C. diff* infection..

Endpoint: *In vivo* validation

Q: Do the candidate probiotics work in vivo?

Clinical Trials



PHASE I

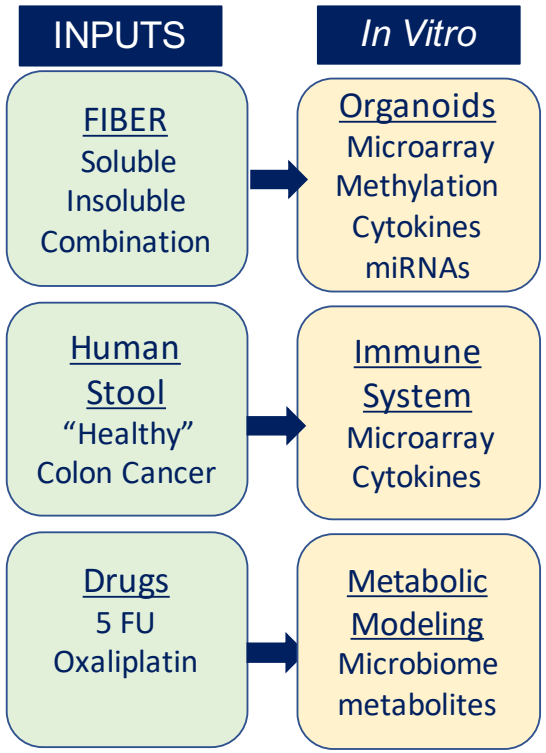
Fiber-Microbiome Modeling

-Microbial community response to dietary prebiotic fibers

-Resistance to ETBF or *C. difficile* infection

-Model nutrient-metabolite interactions

Q: Which dietary fibers prevent pathogen invasion?



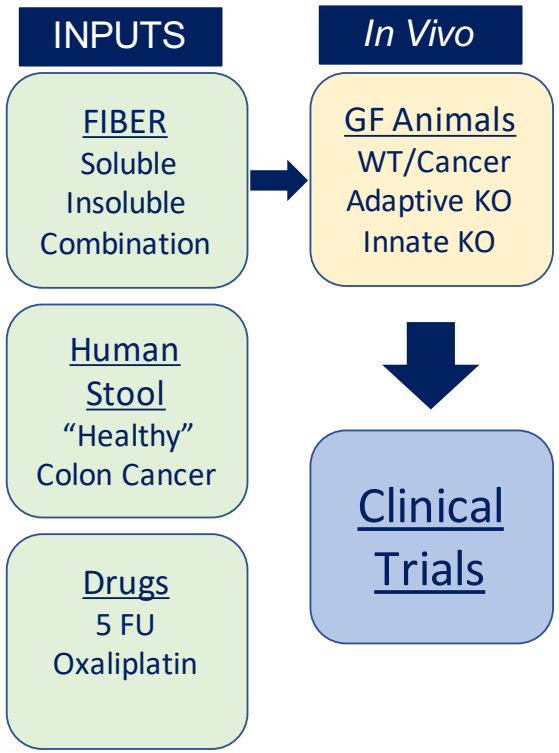
PHASE II

Fiber Conditioned Microbiome Response

-"Healthy" vs colon cancer stool community response to fibers

-Fiber conditioned microbiome response to immune system

Q: Which dietary fibers promote a favorable immune response in healthy/cancer stool communities?



PHASE III

Candidate Fiber Testing

-Germ free mice humanized with fiber-conditioned microbiome

-Fiber conditioned community effect on host tumor response

-Fiber conditioned microbiome response to cancer therapy

Q: Does the fiber conditioned microbiome improve response to cancer therapy?