

TRANSLATIONAL MICROBIOME AT A GLANCE

YOU AND THE MICROBIOME

Person

- 3×10^{13} cells
- 23,000 genes

Microbiome

- 4×10^{13} bacteria
- 2×10^{14} viruses
- 4×10^{12} fungi
- Other microorganisms (archaea, protists)
- ~8 million genes in total

Superorganism

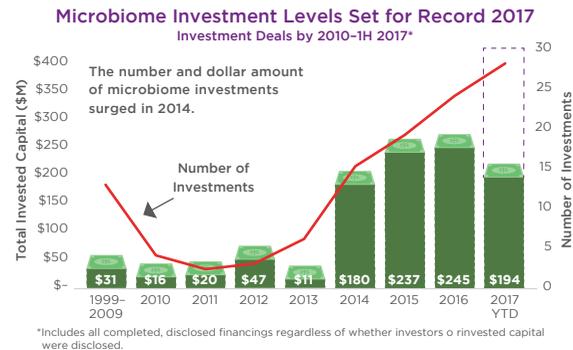
Source: The American Academy of Microbiology: Human Microbiome FAQ

INVESTMENT AREAS

- \$840M invested in microbiome therapeutics since 2010
- Gastrointestinal (GI)/infectious diseases account for 50% of investments

Key areas of microbiome-based therapeutic development:

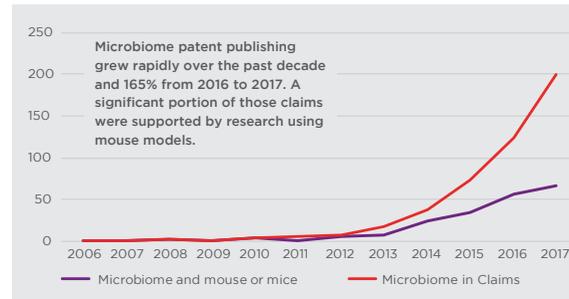
- GI/Infectious Disease
- Cancer/Autoimmunity
- CNS
- Dermatology



Source: Emerging Healthcare: Microbiome Investment Trends. Silicon Valley Bank, 2017

INTELLECTUAL PROPERTY

In 2007 there was one patent published and in 2016 there were 316. This is indicative of growing success despite the challenges in patent law.



- 4D Pharma issued U.S Patent #9,839,655 in Dec 2017 demonstrating reduction of tumors in four different murine models
- University of Chicago issued U.S Patent #9,855,302 in Jan 2018 for treating cancer. Mouse models were critical in supporting claims that gut microbe composition can be manipulated for therapeutic effect.

APPLICATIONS OF GERM-FREE MICE: FMT

Germ-Free

- Di-association**
 - Controllable
 - Host physiology and immunology not normal, but improved compared to the germ-free state
- Complex, partially defined, or undefined microbiota-association**
 - Normal physiology and immunology expected, but is dependent on the nature and origin of the microbial community
- Complex defined microbiota-association**
 - Controllable
 - Unclear how many and what species are required to induce normal host physiology and immunology
- Mono-association**
 - Controllable
 - Host physiology and immunology not normal, but improved compared to the germ-free state
- Simplified microbiota-association**
 - Controllable
 - Host physiology and immunology improved compared to the germ-free and mono/di-associated state, but still not fully normal

Source: Foundational Gnotobiotic Concepts taconic.com/gnotobiotics-concepts

MICROBIOME: DISEASE ASSOCIATIONS

Therapeutic Areas with a Microbiome Link

- ✓ Cancer
- ✓ Metabolic Disease
- ✓ Autoimmune Disease
- ✓ Mental Health
- ✓ Infectious Disease
- ✓ Inflammation

Learn more about Microbiome: Disease Associations

WHAT SHAPES THE MOUSE MICROBIOME?

Husbandry Factors	Experimental & Veterinary Procedures	Internal Factors—Mouse	Microbiology	Personnel	Environmental Factors
<ul style="list-style-type: none"> Cleaning and sterilization procedures of materials Time of last cage bedding change Housing system/cage type Cage density Feed (type and means of sterilization) Water source and treatment with chlorine or acids Bedding material Enrichment material (type and availability) 	<ul style="list-style-type: none"> Therapeutic treatment Compound administration Diet 	<ul style="list-style-type: none"> Pregnancy Diseases Subclinical disorders and infections Genetics Age Stress Gender Activity level Circadian rhythm 	<ul style="list-style-type: none"> The microbiome of the dam/mother (vertical transmission) Exchange of microbes between cages (horizontal transmission) Coprophagia Health standard (list of excluded SPF agents) Environmental organisms Mode of birth 	<ul style="list-style-type: none"> Pheromones Human microorganisms 	<ul style="list-style-type: none"> Room temperature and humidity Air movement and drafts Light cycle

DRUG EFFICACY

Checkpoint Inhibitors Work Best when You Have the "Right Microbiome"

Fecal Microbiota Transplantation (FMT) with non-responder microbiota vs Fecal Microbiota Transplantation (FMT) with responder microbiota.

Anti-PD-1 therapy results in:

- Tumor size ↓ in responder-microbiota mice
- Immune activation ↑ in responder-microbiota mice

Sources: Gopalakrishnan et al. Science 2017; Routy et al. Science 2017; Matson et al. Science 2017