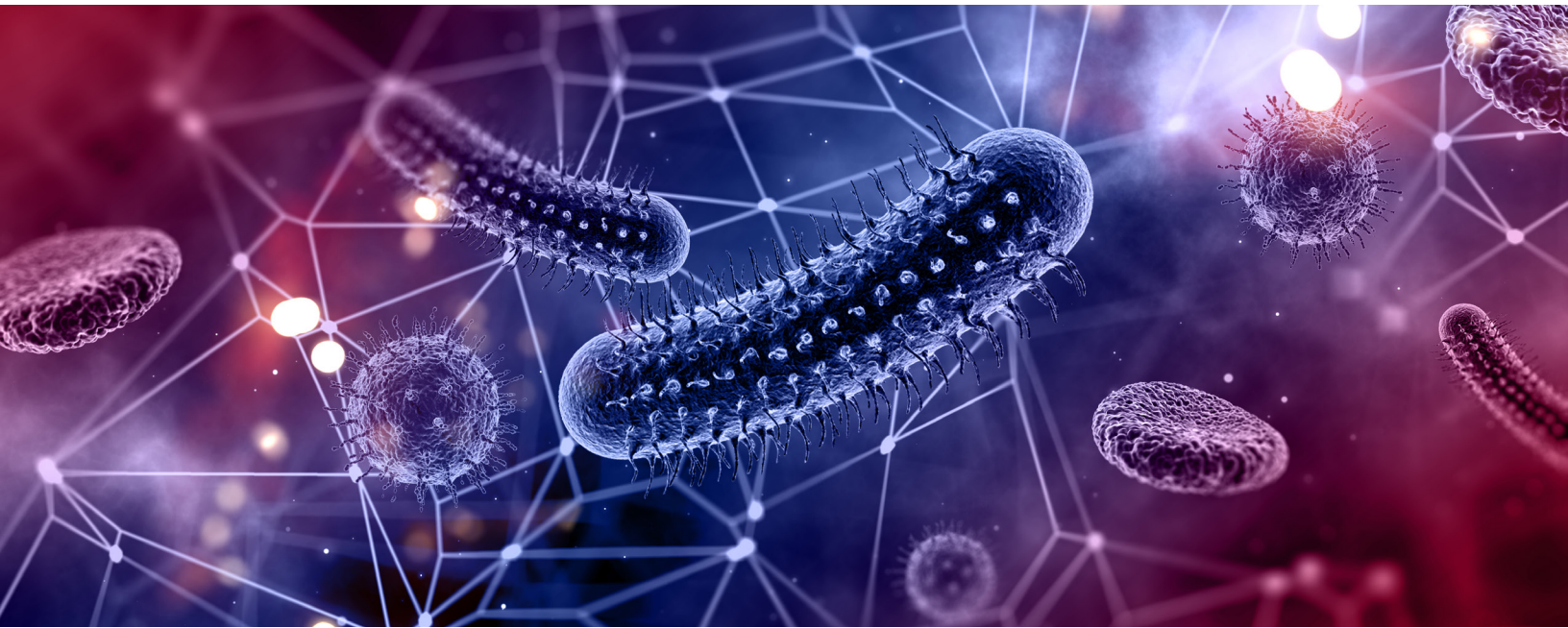


# A Gutsy Combination: The Microbiome and Immuno-oncology



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## Microbes take center stage

With a growing body of pre-clinical and clinical research, the influence of bacteria on human health and disease has emerged from the shadows and into the limelight. The collection of non-human cells living within the gut, skin, and other tissues (collectively referred to as “microbiota” or the “microbiome”), has a profound influence on maintaining normal physiologic function (homeostasis). Disruption of this balance (“dysbiosis”) can influence the development and progression of pathologic disease states such as cancer and autoimmunity.

Studies in both humans and animals reveal the critical importance of diverse microbiota, particularly gut microbiota, in the proper development of the immune system. In the most extreme example, animals raised under sterile conditions (known as “Germ Free” animals) have substantial defects in their immune system. These impacts have been observed both locally—on the immunological mucosal surfaces where many of these bacteria live—as well as systemically: a sterile microbiome is correlated with significant effects on immune cells that reside far away from the gut.<sup>1</sup> While the biomedical community’s understanding of the influence of bacteria on immune development has been steadily expanding over the past decades, the discovery of a link to cancer was truly seminal: in 1995 it was revealed that colonization of the stomach with the bacterium *Helicobacter pylori* increased patients’ risk of gastric cancer.<sup>2</sup> Since then, this type of dysbiosis has been associated with other cancers as diverse as breast and colorectal cancer.<sup>3</sup>

The connection between the microbiome’s effects on the immune system and its role in cancer has converged as modulation of the immune system plays a critical role in the newest generation of cancer therapeutics. The immune system, designed to seek out and destroy foreign invaders such as bacteria, fungi, and virus-infected cells, can also “see” tumors as foreign to the human host. This fundamental paradigm shift in the fields of oncology and immunology has led to approval of several therapies that boost a patient’s immune response against their growing tumors. These agents, called checkpoint inhibitors (CPIs), turn off the “brakes” on the killer cells of the immune system (cytotoxic CD8 T cells) thereby keeping T cells active for longer periods of time. The impressive responses demonstrated by some CPIs, including ipilimumab (an anti-CTLA monoclonal antibody), nivolumab (anti-PD-1), and pembrolizumab (anti-PD-1), have led to FDA approval of six checkpoint inhibitors in 11 tumor types.<sup>4</sup> However, even in the most CPI-responsive tumors, a significant percentage of patients show no response to therapy or eventually relapse. As CPIs generate previously unprecedented long-term responses, researchers are searching for the reasons why some patients derive long term benefit, and some do not.

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# The connection between the microbiome and IO

Recent studies offer tantalizing evidence that the answer may lie within the bacteria living within a patient's own body. Connecting the dots between microbiome studies, immunology, and oncology is revealing a striking new picture—and potentially, new treatments.

- Starting in animal models of cancer, researchers looked to the diversity of gut bacteria to assess whether there is a correlation to CPI-responsiveness.
- Building on the observation that genetically identical strains of laboratory mice from different commercial sources harbor different commensal bacteria, a group from the University of Chicago identified that the presence of the *Bifidobacterium* bacteria is associated with responsiveness to CPIs.<sup>5</sup>
- Using a series of experiments with mice housed in germ-free and specific pathogen-free environments (i.e., “SPF” mice, whose viscera are colonized only with a defined set of bacteria), a team from France observed that the efficacy of anti-CTLA4 treatment depended on the presence of gut *Bacteroides* species.<sup>6</sup>

Intriguingly, both studies investigated the impact of a treatment called Fecal Microbiota Transplant (FMT). In FMT, fecal material containing gut bacteria are harvested from one individual and transferred to the gut of a recipient. In these models, the landmark finding was that FMT from CPI-responsive animals conferred CPI efficacy to mice previously unresponsive to CPIs. Translating these studies into humans, the French group revealed that antibiotic consumption is associated with a poorer response to immunotherapeutic PD-1 blockade. Profiling stool samples from patients with lung and kidney cancers allowed this team to correlate resistance to CPI with lower levels of the bacterium *Akkermansia muciniphila*.<sup>7</sup>

In January 2018, a group at The University of Texas MD Anderson Cancer Center published two papers revealing a connection between human gut diversity and the efficacy of CPI treatment for metastatic melanoma. They show an association between gut bacterial diversity, and more specifically an abundance of the *Clostridia* family of bacteria, with CPI-responsiveness.<sup>8</sup>

Not to be left out, the University of Chicago group published findings that *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium* were over-represented in the stool of metastatic melanoma patients that responded to CPI treatment, compared to non-responders.<sup>9</sup> Interestingly, these studies took stool samples from patients categorized as responders and conducted FMT experiments on germ-free (GF) mice that are usually unresponsive to CPI therapy. When given FMT from responding human patients, GF mice responded to CPIs with an increased anti-tumor T-cell response.

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Such stark data immediately raises the question: what exactly are the bacteria doing to influence the effect of CPI treatment? Hypotheses abound, and experts interviewed for this study highlighted the variety of possibilities (Figure 1). While a comprehensive review of the potential mechanism that underpins this fascinating axis could worthily consume this entire article, Back Bay Life Science Advisors has highlighted several possible connections.

Primarily, bacteria can directly influence the growth of tumors, promoting many of the hallmarks that characterize a cancerous environment.<sup>10</sup> Tumors arise due to aberrant changes in their DNA code, allowing for unrestrained growth. In various cancer models, bacteria promote this potentially cancer-initiating DNA damage. While bacteria can start the ball rolling by causing DNA damage, they can also help the tumor stay supplied with nutrients (by promoting the growth of blood vessels—a process called angiogenesis) and promote metastases through remodeling of the extracellular matrix, which allows the spread and dissemination of cancer cells throughout the body.

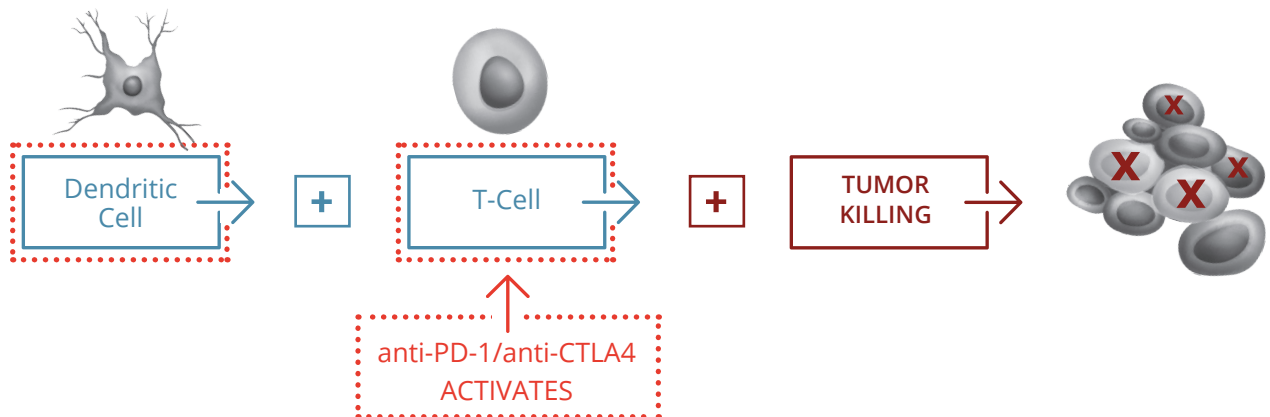
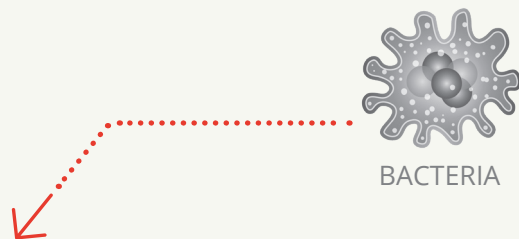
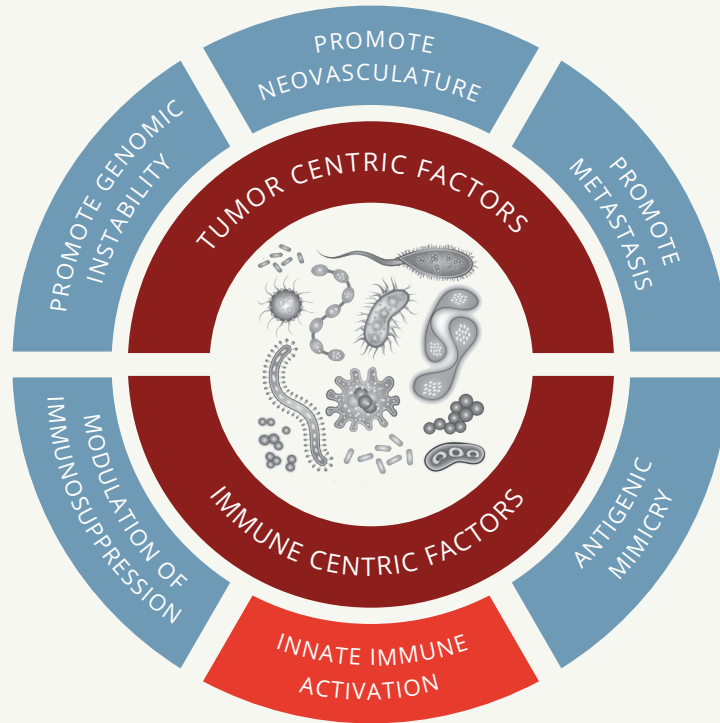
Beyond the so-called “tumor-centric” effect of bacteria, there also are a variety of ways bacteria can impact an immune system trying to mount a counterattack against tumors. These pathways affect both the innate and adaptive arms of the immune system. As the sentinels of the immune system, innate immune cells (such as macrophages and dendritic cells) are the first line of defense for the body. Continually surveying tissues throughout the body for potential invaders, these cells come equipped with “Pattern Recognition Receptors” (PRRs). PRRs sit on the surface of the cells and are activated in the presence of evolutionarily conserved molecules harbored by bacteria, fungi, and viruses, which are collectively referred to as “Damage Associated Molecular Patterns” (DAMPs). Once PRRs engage DAMPs, these innate immune cells become activated, secreting immune stimulatory cytokines, and importantly, serving as a bridge to activate the “adaptive” arm of the immune system (T cells and B cells). These cells then seek out, identify and destroy infected cells. Indeed, many of these bacterial DAMPs are used to increase the efficacy of vaccines (e.g., vaccine “adjuvants”). This is one pathway by which the presence of bacteria and their constituent components is understood to influence the immune status of a patient receiving immunotherapy. For example, *Bifidobacterium* are known to activate Dendritic Cells, allowing them to properly stimulate T cells properly. Indeed, this influence can have a direct impact on the efficacy of immune-based interventions. In a mouse model of colon cancer, treatment of mice with a DAMP-based adjuvant effectively controlled tumors but not in mice grown under germ-free conditions, revealing the influence of the microbiota on the mouse’s innate immune cells.<sup>11</sup>

In addition to their effect on T cells through the innate arm of the immune system, host bacteria can have a direct effect on T cells. In addition to DAMPs, byproducts of microbial metabolism, such as polyamines and short-chain fatty acids (SCFA) can have profound influence on T cells. Again, considering cancer-promoting effects first, they can attenuate immune responses, “helping” the cancer to grow.<sup>3</sup> Certain polyamines suppress T cell proliferation and turn off the production of a critical growth factor, Interleukin-2, which is needed to help

Figure 1:  
Microbiome, tumor, and immune-system interactions

## Tumor- and Immune-centric Mechanisms of Cancer

In addition to acting directly on tumors and the tumor microenvironment to promote tumor growth (top), microbes can also affect the activity of the immune system either activating immune cells (bottom).



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activate killer T cells. In effect, this pathway stops the T cells from undergoing the rapid proliferation needed to produce an army of “clones” necessary to eradicate a tumor. The connection between SCFAs and the promotion of tumors come from their influence on a class of cells called T regulatory cells. Generally considered “bad actors” in the IO space, T regulatory cells (known as Tregs) function to dampen immune responses, switching off their cytotoxic T cell compatriots. Microbially derived SCFAs support the development of Tregs, thereby potentially inhibiting the effect of immunotherapies. However, like any complex system, exceptions exist, as some experimental models show SCFAs may promote anti-tumor immunity rather than inhibit it.

One last intriguing way in which microbes affect anti-tumor immune responses is through a process called “molecular mimicry.” Each T-cell contains a unique receptor (known as a T Cell Receptor, TCR) which recognizes a unique peptide sequence, a molecular “flag” which allows the T cell to distinguish an infected or diseased cell from healthy tissue. Interestingly, researchers have discovered many bacterial peptides have surprising similarity to antigens found on tumor cells.<sup>12</sup> In effect, these bacterial peptides can activate T cells harboring TCRs, preparing the body’s T cells to “see” a cancer cell and subsequently destroy a cancer cell. As a result, these bacterial peptides could allow T cells to get a jump start in recognizing a growing tumor, in effect acting as a “vaccine” growing in a patient’s own body.

## Corporate development in the microbe space

This body of evidence has not gone unnoticed by companies, which are aiming to capitalize on these discoveries. Back Bay Life Science Advisors cataloged the activity of organizations who are harnessing these microbial pathways to improve cancer treatment (Figure 2, and chart). These companies broadly fall into a few categories based on the approach they are using to commercialize bacteria-based therapies in oncology:

- **Fecal Microbiota Transplant** - As previously discussed, this approach involves harvesting stool sample from a patient of interest (a CPI responder, for example) and transfers their microbiome into another patient.
- **Defined Microbial Cultures** - Certain bacteria and groups of bacteria are associated with superior responses to CPI; with this approach, companies are developing treatments based on defined cultures of single or multiple bacteria.
- **Phage** - Bacteriophages (or “Phages”) are bacteria’s natural “viruses,” infecting bacterial cells with genetic material. Their ability to target and alter the genetic code of bacteria makes Phages an ideal candidate to selectively target and kill bacteria or alter their genetic makeup, “tuning” a patient’s existing bacteria for immune response.

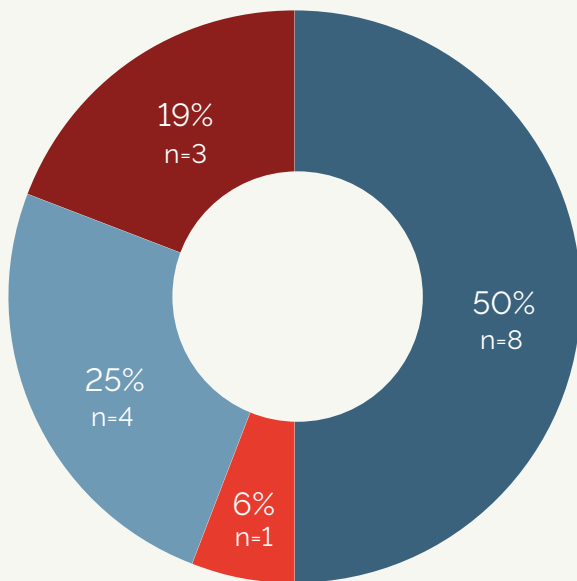
- **Small Molecules and Biologics** - With several identified bacterial constituents that alter immune responses (e.g. SCFAs, sugars, etc.), some organizations are skipping the bacteria altogether and delivering bioactive molecules alone.
- **Vaccines** - Some companies are harnessing the concept of “molecular mimicry” to use bacterial antigens that overlap with tumor antigens to induce an antitumor immune response.
- **Synthetic Bacteria** - With the advent of high-throughput sequencing, there is the potential to create synthetic bacteria harboring specific properties beneficial to an anti-tumor immune response.

The flurry of results in basic research has caught the eye of VCs, who have invested ~\$500M in these companies over the past two years (Figure 3). As this science enters “primetime,” some companies have raised money from the public capital markets, most recently Evelo, who closed an \$85 million IPO in May 2018.<sup>13</sup>

Figure 2:  
Industry approaches to the harnessing the microbiome in oncology

## TECHNOLOGY Type

n=number of companies



- Vaccines
- Small Molecules/Biologics
- Phage
- Bacteria

## BACTERIAL Approaches

### FECAL MICROBIOTA TRANSPLANTS (FMT)

Maat Pharma



### MULTIPLE (DEFINED CULTURE)

Assembly Biosciences

Vedanta

Seres



### MONOCULTURE

Evelo

4D Pharma



### TO BE DETERMINED/SYNTHETIC

Biomica

Synlogic



\*Includes vaccines, probiotics, and polysaccharide compounds derived from bacteria



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With money and science coalescing around new companies, Back Bay Life Science Advisors took a close look at the state of clinical development to see how the drug pipeline is evolving (Table 1). That there are only four academic/industry collaboration studies (as of end of year 2018) in this area highlights the nascent state of the field. Two of these trials, run out of the University of Chicago and the University of Pittsburg, are recruiting patients for Phase 2 trials targeting PD-1 refractory melanoma patients, albeit with different mechanistic approaches. For the latter, Merck and their academic colleagues are enrolling an FMT trial in which donor material from PD-1-responsive melanoma patients is transferred into patients whose cancers have progressed despite treatment with an anti-PD-1 mAb. This in-human clinical study closes mirrors published pre-clinical data showing that FMT from human CPI responders turns previously non-responder mouse strains into responder strains. The Evelo/Merck/University Chicago study uses Evelo's orally-delivered monoclonal microbial product, EDP1503, alongside Merck's anti-PD-1 mAb, pembrolizumab, in melanoma patients that are either naïve to anti-PD-1 treatment or those previously treated unsuccessfully with pembrolizumab. 4D Pharma plc, in collaboration with Merck and MD Anderson, has commenced a Phase I/II trial for its oral, single bacteria strain MRx0518 in combination with pembrolizumab in patients with metastatic cancers across multiple tumor types who have failed prior anti-PD-1 therapy.

A third approach takes the middle ground between FMT and a single-defined bacterial monoculture treatment. The Seres/MD Anderson/Parker Cancer Institute partnership is planning a Phase I study of Seres SER401, which aims to orally deliver a defined consortium of multiple bacteria.

While primary readouts from these trials are not expected until 2021/2022, the field will be closely assessing the progress on a few fronts. First, as in any oncology study, analysts and investors alike will try to read the tea-leaves regarding early efficacy data. Beyond the normal caveats of small sample sizes in early studies, interviewed experts noted that any signals may be attributable to the improvement in outcomes normally seen in transferring patient care from general hospitals to specialty cancer centers, rather than the specific microbiome intervention used in the study. This is particularly true in the absence of a strong pharmacokinetic (PK: how the drug substance moves through the body) and pharmacodynamic (PD: how the drug substance is hitting its target and exerting its effect) data connecting the intervention and the outcome.

Second, but equally important, will be the safety data that emerges, given the concern that combining two immunostimulatory molecules could exacerbate the autoimmune gastrointestinal side effects seen with some CPI's.<sup>14</sup> Nevertheless, development of autoimmune-related colitis, particularly when combining multiple immune stimulatory agents may be a dose-limiting toxicity but on the other hand, it could also offer a mechanistic proof of principle. As one expert summed up during an interview with Back Bay Life Science Advisors: "it is challenging to imagine increasing gut-related immune system signaling while decreasing the risk of colitis."

Figure 3:  
Companies Perusing Microbiome Approaches in Oncology

COMPANY	TYPE	EXAMPLE ASSETS	HIGHEST PHASE OF DEVELOPMENT	TECHNOLOGY DESCRIPTION
4D Pharma	Monoculture	MRx0518	Phase I/II	Ongoing collaboration with Merck for evaluating the combination of pembrolizumab and MRx0518 (NCT03637803) in patients with metastatic tumors; additionally, in a placebo-controlled study as neoadjuvant monotherapy in patients with solid tumors
Assembly Biosciences	Bacteria- Multiple Culture	NA	Discovery	Oral delivery system for live biotherapeutic products to the lower GI tract
Biomica	Bacteria- TBD	NA	Discovery	Bioinformatics platform to identify and characterize microbes to enhance IO, Initial results are expected till the end of this year
Biomx	Phage	NA	Discovery	Synthetic biology platform to identify targets and engineer phage to drug relevant pathways
Eligo Bioscience	Phage	NA	Discovery	Delivery of CRISPR payload via Phage to selectively kill pathogenic bacteria
Enterome	Vaccine	EO2401 (GBM); EO520 (partnered w/ BMS); EO510 (various)	Preclinical	Developing Vaccine against microbial peptides that mimic tumor associated antigens , also discovery program for microbe related biomarkers and neoantigens
Evelo	Bacteria- Monoculture	EDP1503	Phase II	Orally-delivered strains derived from a single clone, considering Colorectal cancer, renal cancer, and melanoma tumor indications
Kaleido	Small molecule/ Biologics	NA	Discovery	Microbiome Metabolic Therapies (MMT) platform to increase/ decrease metabolites or generate changes in the Microbiome toward a desired therapeutic outcome
Locus Biosciences	Phage	NA	Discovery	Use Phage delivering CRISPR to bacteria and modulate immune responses
Maat Pharma	Bacteria- FMT	MaaT033	Preclinical	Lead assets addressing cancer treatment related side effect
Second Genome	Small molecule/ Biologics	NA	Discovery	Platform to generate and evaluate small molecules, peptide biologics, and bacterial strains that modulate microbe-human interactions- Computational pipeline of therapeutic bioactive molecules for assay evaluation
Seres	Bacteria- Multiple Culture	SER-401	Preclinical	Developing SER-401 based on defined taxa found in CPI responders, Phase I in planning stage
Symberix	Small molecule/ Biologics	NA	Discovery	Focus on addressing toxicity associated with chemotherapeutics to reducing dose-limiting toxicity
Symbiotix	Small molecule/ Biologics	SYMB-104	Preclinical	Developing polysaccharide compounds derived from Bacteroides fragilis to modulate activity of regulatory T cells
Synlogic	Bacteria- Engineered	NA	Preclinical	Engineered probiotic bacteria carrying a set of optimized genes
Vedanta	Bacteria- Multiple Culture	VE-800	Preclinical	Developing therapeutics based on defined consortia of bacteria, IND expected soon

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## Turning a bug into a drug: regulatory and IP issues

Along with these advances in basic and early clinical science, the FDA has begun the process of sorting out when bacteria can be considered a “probiotic” versus a “drug,” and if the latter, how they might be considered within the established drug development path.

In 2016, the FDA took initial steps to pave a regulatory pathway for microbiome therapies with the publication of CMC (Chemistry, Manufacturing, and Control) guidelines for Live Biotherapeutic Products (LBPs). An LBP is defined as a product that 1) contains live organisms; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine. This guidance was discussed at an FDA workshop held in September 2018, gathering clinicians, researchers, industry experts, and patient advocates to discuss key issues around clinical, manufacturing, and regulatory issues associated with microbiome therapies. In brief, microbiome therapies will be regulated as biologics, requiring an Investigational New Drug (IND) application and clinical trial data with standard clinical trials with standard outcomes for efficacy and safety, when the sponsor makes claims regarding the impact of a bacterial product on a disease state. However, initial efforts to define regulatory guidance for microbiome therapies have focused on areas like *Clostridium difficile*-associated diarrhea, which have advanced through the clinic and are now in later-stage clinical trials, whereas much of the work in immunology remains an academic pursuit. Regardless a few key considerations emerge:

- **Pharmacodynamics and Pharmacokinetics:** As noted above, defining the “how’s” and “whys” of the manner in which the drug substance moves through the body (PK) and exerts its biologic effect (PD) are critical in the regulatory process. Regarding PK, a key question will be developing standardized assays to track the delivered bacterium/bacteria. A complicating factor is the ability to determine which bacteria found in patients’ bodies are a result of the “drug” and which may have been the result of natural colonization processes during the treatment period. During the recent FDA workshop one biotech, Vedanta, noted they are developing sensitive assays to separate out the bacteria introduced by the LBP.<sup>15</sup> With respect to PD, without a clearly biologic mechanism/target tied to the bacteria treatment, the question of how much bacteria to dose and how often, will remain a critical question.
- **Safety:** An important component of any IND is a thorough evaluation of long-term safety versus efficacy benefit. Regarding the use of bacteria or bacterial derived products in oncology, multiple experts voiced concerns regarding the long-term safety implications of modulating a patient’s gut flora when changes in the gut microbiome have been tied to diverse diseases from diabetes to Parkinson’s Disease.<sup>16</sup> In addition

Figure 4:  
Active Trials

SPONSORS	TECHNOLOGY/ APPROACH	PATIENTS	STAGE, STATUS, AND TIMELINE	CLINICAL TRIAL HIGHLIGHTS
	<p><b>FMT from PD-1</b> responder patients</p>	<p>Advanced melanoma</p>	<ul style="list-style-type: none"> <li>Phase II</li> <li>Currently enrolling</li> <li>Primary completion end of 2021</li> </ul>	<ul style="list-style-type: none"> <li><b>TRIAL:</b> NCT03341143</li> <li><b>INTERVENTION:</b> FMT + pembrolizumab</li> <li><b>PATIENTS:</b> 20 advanced melanoma patients, PD-1 (nivolumab or pembrolizumab) resistance/refractory</li> <li><b>OUTCOMES:</b> Primary (3 years)- ORR at 3 years; Secondary (4 years) - change in T cells, change in innate/ adaptive immune subsets, T-cell function, association of PD-1 response with common gut microbiota (changes in bacterial abundance, bacterial diversity)</li> </ul>
	<p><b>EDP1503:</b> orally delivered monoclonal microbial product</p>	<p>Advanced melanoma</p>	<ul style="list-style-type: none"> <li>Phase II</li> <li>Currently Enrolling</li> <li>Anticipated primary completion 2H2021</li> </ul>	<ul style="list-style-type: none"> <li><b>TRIAL:</b> NCT03595683</li> <li><b>INTERVENTION:</b> EDP1503 + pembrolizumab</li> <li><b>PATIENTS:</b> 70 Advanced melanoma naïve and refractory to PD-1 therapy</li> <li><b>OUTCOMES:</b> Primary (2 years) - response rates; secondary (2 years) - PFS, AEs</li> <li>Additionally, Evelo is planning open-label study of EDP1503 microsatellite stable (MSS) CRC patients, 1st Line RCC patients, and additional PD-1 relapsed patients, expected to dose first patients in 1H 2019</li> </ul>
	<p><b>MRx0518:</b> Live biotherapeutic – oral, single bacterium strain</p>	<p>Metastatic cancer (multiple tumor types) Solid tumors</p>	<ul style="list-style-type: none"> <li>Phase I/II: combination with pembrolizumab</li> <li>Phase I: neoadjuvant monotherapy</li> </ul>	<ul style="list-style-type: none"> <li><b>PHASE I/II:</b> NCT: 03637803; MRx0518 + pembrolizumab; up to 132 patients with metastatic cancer who failed prior anti-PD-1 therapy; Outcomes: Primary – safety/ tolerability, anti-tumor activity; Secondary – antitumor effect (RECIST, iRECIST); estimated primary completion 2023</li> <li><b>PHASE I:</b> MRx0518 neoadjuvant monotherapy; up to 120 treatment-naïve patients with solid tumors due to undergo surgery; Outcomes: primary – safety/ tolerability; secondary – tumor response, survival, immunological biomarkers and microbiome profiles</li> </ul>
	<p><b>SER401:</b> oral consortium of live bacteria</p>	<p>Melanoma</p>	<ul style="list-style-type: none"> <li>Planning Stages</li> </ul>	<ul style="list-style-type: none"> <li><b>TRIAL:</b> TBD</li> <li><b>INTERVENTION:</b> SER-401 + undisclosed anti-PD-1 mAb</li> <li><b>PATIENTS:</b> Advanced, metastatic melanoma patients</li> <li><b>OUTCOMES:</b> TBD</li> </ul>

Sources: Back Bay Analysis, clinicaltrials.gov, company websites and press releases, Nature 2018 557:482-484; JMP Initiation of coverage for Evelo

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to the long-term health effects, another concern of particular relevance to the oncology population is the impact of disseminated infections in a population that is comorbid.

- **CMC:** Compared to a chemical or biologic entity there may be unique regulatory issues applicable manufacturing of microbial products, including ensuring consistent product between batches (of relevance to FMT where the initial substance is taken from human samples), potential to require genomic sequencing and/or other assays to determine purity and potency of each batch, among others.

In addition to the regulatory considerations that must be taken into account when considering the commercialization of these technologies, the extent to which patents may be used to secure market exclusivity loom large. This topic is complex and multifaceted, with implications that span regulatory and investment considerations. Rachel Sachs, law professor at Washington University in St. Louis, provides a thorough and thoughtful review of the relevant issues in the *Michigan Law Review*,<sup>17</sup> and we would highlight four main points of relevance to biotech investors:

- With the historic precedent that natural compounds (including organisms) cannot be patented, how and if “composition of matter” patents (e.g. the structure, sequence, etc. of the active drug substance), which historically have been the most valuable patents for small molecules and biologics, apply to organismal cocktails, remains to be seen.
- As a result, the importance of “formulation” (e.g., how a drug product is delivered into the body) and “use” (e.g., deploying a drug substance for treatment of a specific disease or diseases), which are generally thought to be less strong patent types than “composition of matter” may become more critical.
- Further, the use of alternative mechanisms to protect market exclusivity, such as the FDA’s orphan drug development path may be a critical component to value creation. This has been an effective strategy in other areas where sponsors are trying to create pharmaceutical-grade natural products (e.g. cannabinoid based medicines to treat seizure and other neuropsychiatric disorders).
- Lastly, in contrast to small molecule and biologic medicines, which take industrial-level investment and know-how to make drug products, the fact that microbiome products (such as probiotics or FMTs) lend themselves to small scale or “home-brew” processes may make the potential to prosecute patent infringement difficult (e.g., it may be difficult to identify the “infringer” when it is a patient or physician compared to another pharmaceutical corporation).

While Sachs rightly points out that this has done little to chill innovation, how this evolves will be an important factor in the commercial success of these therapies.

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## How physicians deploy these agents—today and in the future

With intriguing clinical associations in the literature and impending clinical data readouts, physicians are already struggling to incorporate existing data into day-to-day practice. Doctors are increasingly confronted with answering these challenging questions, since patients frequently ask if there is anything they can do to change their microbiome to improve the likelihood of a successful outcome. The microbiome was a hot topic at the 2018 annual meeting of The American Society of Clinical Oncology. The issue of how this should influence oncology practice was raised during several sessions.

Back Bay Life Science Advisors conducted targeted interviews with the physician scientists most familiar with the evolving IO space to understand if, and how, the current understanding of the relationship between the microbiome and cancer has translated into the clinic.

One key question currently swirling among the field is the impact of concurrent antibiotic use alongside CPIs. Initial clinical reports that spurred interested connected the use of antibiotics with lower CPI responses in both animal models and small cohorts of human cancer patients. Emerging data from larger groups of patients, including some presented this year at ASCO, make this association more strongly, indicating that use of antibiotics is associated with lower rates of Progression Free Survival (PFS) and Overall Survival (OS).<sup>18</sup> However, the impact of this data is still evolving within the clinical community. Interviewed physicians were divided on how they now counsel patients on the use of antibiotics—some physicians said use of antibiotics if necessary while others wait for more definitive data.

As one expert said: “Everyone asks about antibiotics and the microbiome. I’m surprised by the data... I would expect the antibiotic effect would be subtler because antibiotics don’t just affect ‘bad organisms’ or ‘good organisms’ because we have unselective classes of antibiotics. We need to look at larger data sets. I don’t go out telling my cancer patients antibiotics are bad or good; if someone really needs one I am not going to withhold. In my mind, the data just argues for the rational use of antibiotics which we know anyway.”

Moreover, oncologists are grappling with the use of OTC probiotics and how to counsel patients regarding changes in diet that could affect their gut microbiome. With broader coverage of the impact of diet on gut health, one clinician noted the number one question he is asked from patients regarding their course of treatment is whether they should be altering their diet and/or taking probiotics.

While many of the ongoing industry and academic-sponsored trials are looking to prospectively demonstrate an impact of FMT or bacterial cultures on patient outcomes, there are two key fundamental questions that are top of mind for clinicians: why there is discordance between bacteria species and

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CPI responses? And, what is the definitive mechanistic link between changes in microflora and treatment response? Regarding the former, each of the studies connecting CPI responders and non-responders to the presence of specific bacteria has identified a different genus and species of bacteria. As one physician put it: “What we have right now is a lot of association studies that do not agree with each other, nor make sense.” While multiple reasons may account for these differences (such as the way species were identified (e.g. differences in specific genetic evaluation, various stool collection techniques, and differences in geography, etc.) it begs the question of whether treatment will need to be specifically tailored to individual groups of patients based on race, geography, diet, etc.

From a mechanistic perspective, none of the studies has pointed to a definitive “smoking gun” proving that the presence of certain bacteria may predict superior outcomes to CPIs. While many potential pathways are implicated, physicians clearly want to understand which of the many factors are critical in conferring CPI responsiveness in a specific tumor type. While some companies have released preliminary data demonstrating an effect of their bacterial strain on the innate immune system,<sup>19</sup> the field has yet to agree on the influence of any one bacteria is solely the result of one or two defined cellular or mechanistic pathways. However, a recent report published by Vedanta Biosciences and their collaborators began to dissect the molecular and cellular mechanisms whereby microbial strains isolated from human fecal samples can induce IFN $\gamma$ + CD8 cells, which are critical for immune mediated tumor rejection.

While physicians realize the influence of bacteria may be multifactorial, and some for-profit development-stage companies may have generated proprietary data, this is seen as a stage-gating step for many physicians before they would recommend a microbe-based treatment. The key difference here is between correlation and causation: as more than one expert told us, just because a bacterium is there and is associated with a type of disease state does not mean it is the cause. Perhaps a unifying answer will come from “deep sequencing,” looking at not only the species of bacteria but also the genes they have “turned on.” Regardless of bacterial species, it is necessary to show specific proteins or signaling pathways that are associated with response to CPIs, regardless of how which or how many of an individual bacterium may be present.

In addition to these fundamental issues, how these potential treatments, if approved, will be rolled into clinical practice raises several questions:

- If a therapy based on a defined bacteria or bacterium is approved, in which patients will it be deployed? If a therapy based on giving a patient a capsule full of “Bacteria X” is approved, will it be used in patients that currently do not harbor “Bacteria X”? What about those who currently contain “Bacteria X” in their gut? If trials are conducted without screening for a patient’s gut bacteria (e.g., no pre-selection based on presence or absence of bacteria), it could raise the questions of how much of a good thing is too much, especially when the specific mechanisms have yet to be elucidated.

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- Research to date has focused on the impact of bacteria on CPI-responsive tumors such as melanoma, NSCLC, RCC, and others that currently respond well to immune therapies.
  - Further, there is some intriguing data that beyond increasing the efficacy of CPIs, microbial treatments may help alleviate side effects associated with CPIs.<sup>20</sup> Yet the same microbe-based treatment that increases the efficacy of CPIs may not be the same that will quell CPI-related side effects as the two goals are opposed (i.e., increasing the immune response to increase anti-cancer efficacy and decreasing the immune systems collateral damage to protect non-cancerous tissue). In short, one might not be able to have the cake and eat it, too.



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## Conclusion

With initial scientific reports as a backdrop, scientists, clinicians, and investors are racing to understand how the trillions of bacteria living within us be harnessed to fight cancer. There are still numerous questions leaving one wondering if the investment has outpaced the science:

- While organizations may be rightly keeping data private, clinicians and basic scientists agree that there is a panoply of ways in which a bacterium could enhance – a detailed mechanism may be necessary to give oncologists comfort with deploying a new therapy, with the understanding a microbial targeted therapy could mediate its effect through multiple paths.
- With a disease such as cancer where the primary goal of the treating physician is to eradicate the growing tumor, the long term effects of microbe-based interventions on gut, metabolic and CNS health have yet to be enumerated. To appreciate this perspective one need not look further than the variety of other disease areas companies are targeting with bacterial based therapies
- From a corporate and investment perspective the issue of market exclusivity will need to be carefully evaluated. Traditional patent protection may not be available to some therapies currently in the clinic and therefore additional mechanisms (e.g. Orphan Drug Designation) and creative patent coverage must be considered.

Regardless, the potential return on investment is staggering. Current market leaders in the CPI space have recently posted upwards of \$8 billion in sales within the current indication set.<sup>21</sup> Even in the most responsive tumors, a subset of patients respond; the majority of patients do not respond and discontinue treatment. Therefore, a microbial treatment that improves responses may be an extremely valuable asset in its own right and to the value to companies that currently market CPIs as a product that also increases the utilization of CPIs within established markets. Even more tantalizing is the opportunity to open up tumors where responses to immunotherapies have been historically poor. Tumors such as Glioblastoma multiforme, ovarian cancer, pancreatic cancer, among others, some of the most fast-growing tumors, have not been responsive to single-agent CPI intervention. With such clinical and economic potential, the next few years will be critical in assessing whether the fascinating early stage data will translate to meaningful patient outcomes.

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# Notes

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