



New Technology Commercialization Opportunities and Challenges – Microbiome Therapeutics

by groupH

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Aug 18th, 2021

WHAT IS IT?

- Microbiome therapeutics modify an individual's microbiota (using additive, subtractive or modulatory approaches) with the goal of treating or preventing disease
 - **Additive approach:** the supplementation of the host microbiota with either a new strain or a consortium
 - **Subtractive approach:** the elimination of specific members of an individual's microbiota
 - **Modulatory approach:** the administration of a therapeutic to modulate the composition or activity of the endogenous microbiome
- Microbiome therapeutics generally utilize the following approaches:
 - **Small molecules:** microbiome-informed approaches that manipulate the biology of bacteria and/or host with traditional pharmaceuticals. For example, Enterome Bioscience's small molecule EB8018 blocks the bacterial adhesin FimH to reduce downstream cytokine production
 - **Single-strain bacteria:** live biotherapeutics consisting of only one bacterial species. This approach enables manipulation of the microbiome via bacterial engraftment, while providing a more streamlined approach than complex consortia. Companies such as 4D Pharma are pioneering single strain therapies with the rationale that they are akin to a single API in traditional modalities
 - **Microbial consortia:** live biotherapeutics consisting of multiple species with the rationale that a bacterial community needs to be interconnected to be efficacious. Companies such as Vendanta Biosciences are developing consortia of up to 11 different strains, while Federation Bio is attempting to create highly complex consortia of over 120 different strains
 - **Genetically modified single-strain bacteria:** using bacteria as a vector to synthesize and deliver enzymes or payloads *in vivo* that have a therapeutic effect. Synlogic is currently leading the way with programs for PKU and hyperoxaluria

COMMERCIALIZATION OPPORTUNITIES



General

- The microbiome is important for many aspects of human health and evidence is mounting that shows that an altered microbiome is associated with a wide variety of different diseases. Modifying an individual's microbiome could have therapeutic benefit across disease areas as diverse as infection, autoimmune / immunology, oncology, metabolism, and neurology
- While considerable research has focused on the gut microbiome, other organs like the skin and the vagina could also be amenable to microbiome approaches
- In addition to these therapeutic opportunities, there are also opportunities for manufacturers of small molecule and antibody therapies to improve the profile of their product by improving the dosing/frequency, efficacy, safety, and tolerability. Gut bacteria can affect a drug's PK/PD, and influencing them could affect a drug's half-life, increase response rates and/or deepen responses¹

Recurrent *C. difficile* infection Opportunities

- Recurrent *C. difficile* infection (rCDI) is the most widely known 'use case' for microbiome therapies, has the strongest rationale for microbiome manipulation (due to the strong link between rCDI and the disruption of the colonic microbiota, primarily due to antibiotics), and is the most advanced indication with several products in late-stage development
- Treating rCDI with a microbiome therapeutic has a number of commercial incentives: (1) CDI is the leading cause of hospital-acquired infection in the US and recurrent infection carries a mortality risk, and may necessitate prolonged hospitalization, thereby creating a financial burden on healthcare systems, (2) there are currently few efficacious treatment options for rCDI, (3) patients with recurrent disease form an easily-definable target patient population, which is important for payers, and (4) a new microbiome therapeutic could fit easily into the treatment landscape
- Given this strong case, numerous players are exploring microbiome-based therapies for rCDI; SER-109 (Seres Therapeutics) and RBX2660 (Rebiotix/Ferring) are taking the lead with Phase 3 programs, with others following behind
- SER-109 is on track to be the first microbiome product to market. After the Phase 2 study did not show any statistically significant benefit, the Phase 3 study, using 10x the dose and a different diagnostic approach to select patients with *C. difficile*, demonstrated a significant reduction in re-occurrence of infection compared with placebo at 8 weeks in Aug 2020, with

confirmatory follow-up data at 12 and 24 weeks. However, Seres is continuing an open-label study, since the FDA has stated it will require 300 patients at the marketed dose in the safety database, monitored for 24 weeks, to secure approval. Seres plans to co-commercialize with partner Nestlé Health Science, with its global pharmaceutical business Aimmune Therapeutics taking the lead^{2,3}

- We expect the successful development and commercialization of SER-019 to have a class-effect for microbiome therapies in general as a proof-of-concept

Autoimmune / Immunology Opportunities

- In recent years, studies have highlighted the role of the microbiome in the pathogenesis of numerous autoimmune diseases
- For example, research has shown that both ulcerative colitis (UC) and Crohn's disease (CD) are associated with (1) a reduced diversity of the microbiota, (2) a decrease in anti-inflammatory bacteria, and (3) an increase in pro-inflammatory bacteria. This shift to a dysbiotic state is believed to be a contributory factor leading to intestinal inflammation. Furthermore, Fecal Microbiota Transplantation (FMT) has seen some success with UC in randomized controlled trials in mild-moderate patients
- There is therefore an opportunity for microbiome therapies to target the triggers of inflammation in these inflammatory bowel diseases (IBD) and prevent it occurring. A couple of companies have completed Phase 1 work in IBD, and until recently Seres was testing SER-287 in Phase 2b for UC
- UC has a strong commercial opportunity, driven by the large population size (700,000 cases in the US), the impact that symptoms have on patients' daily lives, and the lack of response to current standard of care (only one in three patients achieves remission)⁴
- Beyond UC and CD, links between disruption of infant microbiome and development of allergic diseases have been elucidated. This scientific basis provides the theoretical potential to prevent allergic diseases by prevention of immune cascades. Siolta Therapeutics is leading the way in developing microbiome therapeutics for the prevention of allergic disease, chiefly atopic dermatitis, food allergy, and allergic asthma in those at high-risk for developing allergic diseases

Oncology Opportunities

- Based on mouse models, there is a scientific rationale for the role of the microbiome in both response and toxicity from immune checkpoint inhibitor therapy⁵. Observational studies in humans with metastatic melanoma have found differences in response to anti-PD1 immunotherapy and separately to ipilimumab (anti-CTLA-4) according to baseline microbiome. Furthermore, a recent study found the FMT overcomes resistance to anti-PD-1 therapy in melanoma patients⁶
- However, this field is in preclinical and early clinical development. Vedanta Bioscience has an ongoing Phase 1/2 study with Bristol-Myers Squibb in advanced or metastatic melanoma,

gastric and colorectal cancer testing nivolumab in combination with VE800, a daily oral therapy consisting of a live bacterial consortium of 11 strains that act in concert to activate cytotoxic CD8+ T-cells. Results are anticipated in 2021⁷

- Given the widespread use of checkpoint inhibitors and the high unmet need for better outcomes in oncology, there is a significant opportunity to improve response rates through microbiome modulation. However, the field is in an early stage with only a few players exploring this option in human clinical trials. If one of these studies demonstrates proof-of-concept, this could propel microbiome therapies quickly in oncology as complements to the key therapy

Neurology Opportunities

- The gut-brain axis link to the microbiome has been solidly established in academic literature and the microbiome has been implicated in numerous CNS indications, such as Parkinson's disease, anxiety, autism, and depression⁸
- Degenerative CNS diseases including Parkinson's disease and Alzheimer's disease have ample commercial incentives for drug development including high unmet need due to lack of tolerable and efficacious therapies for motor and non-motor symptoms, and very large population sizes and associated societal cost
- Psychiatric illnesses including major depressive disorder (MDD) have been linked to inflammation resulting from increases in pro-inflammatory cytokines (IL-6 and TNF- α) and decreases in anti-inflammatory cytokines (IL-19 and TNF- β). Bacterial translocation from the gut can lead to systemic inflammation and has been proposed as a potential mechanism for induction and/or exacerbation of MDD⁹
 - NuBiyota is currently recruiting for a Phase 2 trial of MET-2, an orally administered microbial consortia of 40 different strains of gut bacteria from healthy donors, in people with major depression¹⁰. Primary completion was anticipated in mid-2021
- Scioto Biosciences's SB-121 (orally administered *Lactobacillus reuteri*) is currently recruiting for a Phase 1 trial in autism¹¹
- In addition to the ongoing clinical development, 4D Pharma has multiple ongoing neurology-focused preclinical programs including MRx0029 (*Megasphaera massiliensis*) and MRx0005 (*Parabacteroides distasonis*) aimed at neurodegenerative diseases including Parkinson's disease. To date, *in vitro* data has been published that demonstrates potential neuroprotective properties via reduction of pro-inflammatory IL-6 secretion¹²

Metabolism Opportunities

- The occurrence of microbial dysbiosis has been linked to metabolic disorders including diabetes and obesity, which are large and growing indications in the US and other developed nations. The gut microbiota clearly contributes heavily to many metabolic functions including bile acid and choline transformation, fermentation and absorption of indigestible carbohydrates, and production of vitamins and amino acids¹⁴

- The commercial opportunity for these indications is based on the extremely high prevalence of metabolic diseases and the intense pressure they exert on healthcare spending, and the poor compliance for standard of care therapies that require chronic administration. This dynamic leads to high visibility on payers' radars and a commercial double-edged sword, as payers closely scrutinize new therapies, but also are open to alternatives that can build evidence of reduced healthcare spending. Development of therapies that can deliver long-term results from a small number of administrations and therapies with improved compliance are highly desired by clinicians and payers. Microbiome therapies have many of the properties that could fill this need, but remain largely preclinical at present
- In addition, a large variety of rare genetic disorders including phenylketonuria and hyperoxaluria among many others affect discrete components of the metabolic system and may potentially be amenable to microbiome therapy
 - Synlogic is using genetically-modified bacteria to deliver enzymes into the human gut and has achieved proof-of-concept (1) lowering Phe in healthy volunteers and patients with phenylketonuria (PKU) with SYN1618, and (2) consuming oxalate in the GI tract and reducing oxalate in the urine of healthy (for treating Enteric Hyperoxaluria (HOX) with SYN1618)¹⁵

COMMERCIALIZATION CHALLENGES



General Challenges

- Microbiome science is in its infancy and brings research and clinical development risk: The scientific rationale that a microbiome therapeutic can be used to treat some indications is 'strong', such as recurrent *C. difficile* infection, 'moderate' for autoimmune / immunology and oncology, and 'exploratory' for others, such as metabolism and neurology. Therefore, drug developers need to accept the risk of developing the proof of concept as part of their development program. A good analog is Alzheimer's disease where drug developers tested the underlying 'amyloid hypothesis' while testing the safety and efficacy of their therapies
 - Imperfect translational animal models: The microbes in mice are different from those in humans, making translation of animal data to humans almost impossible. This can slow down and complicate preclinical work, where developers will need to build additional *in vitro* and *ex vivo* models. While some progress has been made with humanized gnotobiotic mouse models, this lack of established preclinical models adds risk to early clinical work
 - Person-to-person variability of endogenous microbiome: Different individuals can harbor vastly different microbiomes, influenced by their geographic location, genetics, diet, age, mode of birth, medication history, and other factors. As a result, individuals

can start therapy with very different baseline microbiome profiles and developers need to understand how these differences can impact the safety of their product and result in different efficacy / response rates across individuals

- Impermanence and malleability of the microbiome: An individual's microbiome population changes over time and also in response to disease. Ulcerative colitis (UC) patients for example, have undergone years of exacerbations and remittance, and the microbes that triggered the beginning of the inflammatory cycle can be different than those found mid-cycle. Furthermore, given the long and complex journey that UC patients may have suffered for months or years under the care of a primary care physician and received misdiagnoses, exacerbations may have shaped the microbiome. It is often not clear if 'dysbiotic microbiome' is the cause of or the result of disease. This increases trial risk and introduces uncertainty
- Stable engraftment of therapeutic microbes into the endogenous microbiota is necessary if long-term efficacy is therapeutically desirable: The introduced microbiota need to exist and persist in the host's endogenous ecosystem. As a solution, some development programs are pre-treating / conditioning with a targeted antibiotic to 'open up an ecological niche' for the therapeutic microbes to occupy
- Long-term side-effects are unknown (safety Catch-22): The very same rationale that the microbiome is associated with numerous areas of health (across GI, metabolic, CNS, etc) also raises the potential for therapies that manipulate the microbiome to have long-term effects, that have not yet been elucidated
- Regulatory challenges: Since microbiome-based therapies represent an entirely new category of treatment, there is a lack of an established regulatory pathway for developers to follow. The FDA has defined a Live Biotherapeutic Products (LBP) category and in 2019 the EU has accepted LBPs as a new category of medicinal product.¹⁷ While the FDA has partly laid out its regulatory requirements for LBPs, the EU has not yet. Given that (1) individuals have such varied baseline microbiomes at the start of therapy, (2) that an individual's microbiome can be affected by many host and environmental factors that are 'in play' during therapy, and (3) that the long-term safety consequences of manipulating an individual's microbiome are not known, regulators are taking a cautious approach and may require longer-term data that could slow down development timelines
- Manufacturing microbiome therapeutics at scale is more difficult than for chemical manufacturing: Manufacturing cells reliably at commercial scale is challenging and a key step for developers to crack. Manufacturing quality (i.e. purity and potency), consistency (i.e. minimizing batch-to-batch variations) and stability (i.e. maintaining efficacy throughout shipping and storage) are all likely to receive a high level of regulatory scrutiny. Ultimately, manufacturing at scale remains a key barrier to commercialization, even in the face of encouraging clinical results
- Biocontainment is a concern for some types of microbiome therapeutics: The escape of engineered microorganisms into the environment that may lead to unintentional colonization beyond the target patient population. This is more of a concern for live therapeutics that contain genetically modified material, such as microbes introducing a therapeutic enzyme

function. Conditional kill switches that prevent engineered microbes from replicating outside of the target host tissue have been developed

- Intellectual property protection remains challenging: Patent law prohibits patenting naturally occurring materials as ‘composition of matter’ patents, presenting a unique challenge for new microbiome therapies. Therefore, developers may need to rely more on ‘formulation’ and ‘use’ patents, which have historically been regarded as weaker¹⁸
- Competitive threat from Fecal Microbiota Transplantation (FMT): FMT involves taking stool from a healthy person and delivering it, typically as an enema, to the recipient. Scientific evidence of the potential for microbiome therapeutics has been built, in part, on research with FMTs. However, the availability of FMT approaches, such as homemade approaches (e.g. Facebook sample swapping) or stool banks will represent a significant low-cost off-label competitive threat to proprietary microbiome therapies. FMTs have a number of weaknesses: (1) patient deaths have resulted from pathogen-contaminated transplants leading the FDA to issue a safety alert over the potential for viruses, pathogenic bacteria, or parasites to be transmitted to a recipient, (2) it can be challenging for patients to identify the most appropriate donor, (3) enemas are an unattractive route of administration, (4) FMT is only loosely regulated, and (5) FMT is challenging to provide at-scale. While proprietary microbiome therapies aim to have the advantage in terms of clinical evidence, manufacturing CMC standards, safety, and more palatable RoA, the low-cost threat remains
- Analyst sentiment and investor appetite will ‘wax and wane’ while microbiome developers advance the field: When SER-109 failed its Phase 2 study for recurrent *C. difficile* infection in 2016, the field saw investment dry up³. It later got a boost when the same product hit its Phase 3 primary endpoints, but a frost may be setting in after the recent failure of SER-287 in Phase 2b for UC¹⁹. Microbiome developers will need navigate this changing sentiment

Recurrent *C. difficile* infection (rCDI) Challenges

- Treating rCDI with a microbiome therapeutic could become a crowded space. In addition to Seres Therapeutics and Rebiotix/Ferring in Phase 3, Vedanta Biosciences and Finch Therapeutics have products in Phase 2, with others in Phase 1 development. If successful, this level of competition will decrease the market share for each player, and increase the need for these products to differentiate themselves
- *C. difficile* infection guidelines already give physicians leeway to try FMT in patients with recurrent disease. Particularly within this treatment landscape, it will be important for developers of proprietary microbiome therapies to differentiate from FMT. Until clear differentiation is established, guidelines and clinical practice may be slow to switch, leading to slow commercial uptake of proprietary microbiome products
- Microbiome therapeutics could also face competition from new small molecule therapies (such as emerging antibiotics) also in development to treat rCDI, that could further reduce the market opportunity

Autoimmune / Immunology Challenges

- In ulcerative colitis (UC), microbiome therapies face a number of challenges:
 - Firstly, the exact etiology of UC is unknown and the disease appears to be multifactorial and polygenic. Etiologic factors potentially include genetics, immune system reactions, diet, antibiotic use, NSAID use, low levels of antioxidants, psychological stress factors, and a smoking history. Given this complex picture, the exact role of the 'dysbiotic microbiome' is unclear, and questions remain regarding whether microbiome manipulation can be effective therapeutically
 - Ulcerative colitis (UC) is already a complex treatment landscape with multiple therapeutic classes in use: 5-aminosalicylates (ASA) and corticosteroids for mild-moderate patients and aTNFs, vedolizumab, ustekinumab, and tofacitinib for moderate-severe patients, followed by surgery. Microbiome therapies need to find their best fit into the treatment landscape, where the mechanism of preventing inflammation will have the most effect; as an example, Seres is testing in mild-to-moderate UC patients with inadequate response to ASA
 - The UC market is likely to become even more competitive in the future, with additional aIL-23s, S1P1Rs, JAK inhibitors and other classes in development, making it even more important to find the ideal positioning in the treatment landscape. This will include understanding the best timing in a patient's disease for the microbiome therapy to be most effective, and whether it can be combined with existing treatments
 - As with all the new therapies, it will also be important to understand which products payers consider to be the appropriate pricing reference points – current treatments for mild-to-moderate patients are priced considerably lower than the premium-priced biologics used for severe disease, meaning much lower pricing potential for microbiome therapies targeting mild-to-moderate patients
 - The very recent failure of SER-287 in Phase 2b for UC highlights the challenges and risks of developing a new therapeutic class; Seres hopes to gain insights from this study that can be used to inform its next generation candidate for UC
- Microbiome treatments aiming to prevent autoimmune diseases have a different set of challenges:
 - While it is widely acknowledged that preventing disease is preferable to treating disease once it has occurred, preventative therapies need to be (1) particularly safe and convenient, since they are being used in individuals without disease, and (2) used in individuals with the greatest change of developing the disease – to minimize use in individual who do not go on to develop disease
 - For preventative therapies, payers typically want a tightly defined target patient group – to minimize the cost of providing therapy to individuals who will not receive benefit – and both physicians and payers want to avoid exposing these individuals to the side-effects and/or risks of a novel therapy unnecessarily. As an example, in its Phase 1b study, Siolta Therapeutics focused on individuals with a positive skin prick test to two or more allergens, and those with a family history allergic disease in its Phase 2

- Preventative microbiome therapies also need to employ novel clinical development strategies, since an individual's microbiome can already be established by 3 months of age, giving a narrowly defined window where prevention of autoimmune disease is possible. Testing novel therapeutics in individuals so young is challenging and has a very high safety bar

Oncology Challenges

- While there is a compelling rationale to improve the response rates for widely used for immune checkpoint inhibitor therapy, several barriers exist:
 - Questions remain on the optimal target patients for therapy – should therapy be given to all patients, or only those with a certain microbiome profile that would most benefit from manipulation?
 - Oncologists who are unfamiliar with microbiome therapies will need to be provided with a clear and compelling mechanistic rationale describing a causal relationship between a patient's microbiota, the nature of the microbiome therapy, and CPI response, in order to drive prescribing
 - There is also a risk that combining two immunostimulatory agents and the potential to worsen gastrointestinal side-effects from CPIs
 - Competition from low-cost FMT from identified CPI-responders
 - Furthermore, big pharma with CPIs on the market, may be reluctant to open 'Pandora's box' and dig into response rate and target patient selection. This could hurt deal making for microbiome biotechs in this indication

WHAT TO GET RIGHT



General

- Very early on, developers need to form close working partnerships with their respective regulatory authorities to review and refine their clinical trial strategy, especially since this is a new therapeutic category and regulators are taking a cautious approach
- Microbiome companies are developing diagnostic tools in tandem with their therapeutic development – monitoring how the therapeutic intervention changes an individual's microbiota, the duration of engraftment, and how a patient's baseline microbiome profile affects

treatment outcomes and safety. These tools have the potential to assist in optimizing the consortia during development and driving patient selection for trials

- The bulk of intellectual property protection for microbiome therapies is currently focused on 'formulation' and 'use' patents, rather than 'composition of matter' patents, since many of these therapies are derived from natural sources. These patents are generally viewed as weaker, and microbiome developers are turning to additional protections where they can. One such example is the use of orphan drug designation to extend the exclusivity window by 7 years
- As development progresses, developers will need to engage with payers, physicians, and patients, who may be unfamiliar with microbiome therapeutics, to provide early class / mechanism education
- Significant investment will be needed to build the market: Microbiome therapeutics is a nascent field with a relatively small number of players. The area has started to gain traction, with several companies signing research collaborations. Of the big players, Johnson & Johnson, Takeda and Nestlé Health Science are taking the lead; BMS and AZ are exploring options to complement their oncology pipelines, as is AbbVie in metabolic and inflammatory diseases
 - As the microbiome pipeline matures, greater involvement from established players, and a shift from research collaborations to commercialization deals (such as the recent update to the Nestlé and Seres collaboration in rCDI) will be necessary to provide the commercialization and marketing muscle needed to build this new market
- Launching an entirely new therapeutic class: A key part of building the market will be to raise awareness and understanding of these new therapies across all stakeholders. During launch readiness, deeper engagement will be necessary to:
 - Provide physician education on MoA, treatment setting, role of diagnostics, route of administration, etc
 - Provide physicians with guidance on how to counsel patients on topics such as the concurrent use of probiotics, whether a change in diet could be beneficial or detrimental to treatment outcomes, etc
 - Understand the positioning of microbiome therapeutics in the care pathway for each indication and provide clear differentiation from existing options
 - Differentiate proprietary microbiome therapies from FMT, being clear that (1) they are a safer option, (2) consist of an approach that has been specifically designed and tested for the indication / use case, and (3) represent a more palatable option for patients
 - Map stakeholders' barriers to adoption and develop strategies to overcome them
- As with all new products, microbiome therapies need to build a clear clinical and economic value proposition for payers, with a late-stage development plan that generate the supporting evidence needed. Developers will also need to understand which products payers consider to be the appropriate pricing reference points, and how relatively cheap 'homemade' FMTs or

those obtained from stool banks are considered in the pricing landscape of the target indication

WHAT CAN GROUHP OFFER?



groupH can conduct...

- Technology scans of next-gen microbiome technologies (small molecules, single-strain bacteria, microbial consortia, genetically modified strains)
- Market-mapping to identify leading microbiome companies
- Scenario planning workshops to understand the implications of different possible future markets to product positioning and the clinical development plan
- Early TPP testing and development to optimize product positioning in the treatment landscape, refine value proposition, identify any commercial challenges or barriers to prescribing, and inform clinical strategy
- Robust opportunity assessments and forecasts including epidemiology, market landscape, commercial forecasting, pipeline and competitor analysis, and market access
- Pricing, reimbursement, and access research in major markets to understand the payer landscape, characterize the value proposition, understand the payer value elements in the TPP, assess the evidence generation against payers' needs and understand the implications of any gaps, understand the price potential and rationale and any potential access restrictions for given price points, and identify any potential market access hurdles and develop potential approaches to overcome these hurdles
- Strategic competitor role-play workshop to understand how competitor activity could shape the future treatment landscape, future patient segments, and remaining unmet needs, to refine product positioning



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