Early investments powering the ascent of microbiome therapeutics

After a decade of uncertainty, a trio of clinical trial successes in 2020 is spurring enthusiasm about the potential for effectively treating disease via manipulation of the gut microbiome.

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On 10 August 2020, Seres Therapeutics reported that its flagship product, a purified preparation of stool bacteria known as SER-109, had met its primary end point in a phase 3 trial. Compared with placebo, SER-109 treatment reduced risk of recurrent gastrointestinal infection by the pathogenic bacterium *Clostridium difficile* by more than 30%. Two other microbiome companies have likewise reported success in this indication in the past year. Rebiotix and its parent company Ferring Pharmaceuticals announced positive preliminary phase 3 data from fecal microbial transplantation product RBX2660 in May, and Finch Therapeutics released phase 2 data in June revealing a statistically significant benefit.

Investors have taken notice. Within 24 hours of its announcement, Seres' shares shot up by 460%. By October, the company's market cap was greater than $2.5 billion, and following its phase 2 success, Finch pulled $90 million in Series C funding. More generally, momentum is steadily building for the idea of either turning live microorganisms into medicines or developing drugs that work by modulating the biological activity of our resident bacteria. "Those clinical results have public investors quite interested in the field," said Bernat Olle, CEO and co-founder of Vedanta Biosciences. "But not big pharma yet," he added.

This is mostly true—but not entirely. Companies such as Merck and Co., Gilead, Genentech, and Johnson & Johnson (J&J) have made strong bets on microbiome startups in the past few years. Takeda has forged partnerships worth hundreds of millions of dollars with numerous companies in the microbiome therapeutics space over the past 6 years, including Finch, Enterome, Debiopharm and Nubiyota (Table 1). "We are focused quite heavily, and it is a big investment," said Gareth Hicks, VP and head of gastrointestinal drug discovery at Takeda. "But we've been quite selective so far in the approaches that we're taking."

And some investors in the field see the potential as near limitless. Geoffrey von Maltzahn, a general partner at venture firm Flagship Pioneering, has co-founded multiple microbiome companies, including Seres and Kaleido Biosciences, but agrees that big pharma generally remains skeptical about the field at present—as concerns remain about past trials and a need to further validate the relevance of microbiome modulation in diseases other than gut-centric disorders. Nevertheless, he sees a unique opportunity to develop interventions that have literally been shaped through co-evolution to be inherently well-suited for use in humans. "These medicines categorically have a chance to be safer than your average clinical programs and have a higher probability of success than your average clinical program," said von Maltzahn. "If this is the case, this field is going to go from everybody being skeptical to the vast majority being believers quickly."

A broadening range of indications

The first wave of microbiome startups, including Seres and Vedanta, emerged in 2010, and were born out of exciting progress in academic and medical research. In 2007, the US government embarked on the Human Microbiome Project—a $215 million effort that leveraged cutting-edge genome sequencing technologies to begin profiling the composition and function of the complex commensal communities dwelling within our bodies.

These studies laid the foundation for experiments demonstrating that microbial transplantation in rodents could potentially influence the course of a range of gastrointestinal, metabolic, immunological and other disorders. According to Christophe Bonny, chief scientific officer at Enterome, this makes clear sense from a physiological perspective. "The intestine is both the largest endocrine organ in the body, producing more than 30 different hormones … and the largest immune organ in the body," he said. "More than 70% of all our T cells reside in the intestine." This means that gut bacteria interacting with this tissue could influence critical functions affecting the entire human body, and they have almost certainly evolved to do so throughout human history. "Their life literally depends on ours," said von Maltzahn. There is considerable evidence to support this concept; for example, gut bacteria are known to communicate extensively with the immune system, training it to recognize and respond to true threats while sparing beneficial microbial species.

The earliest demonstrations that microbiome modulation can have clinical benefit in humans emerged from efforts to treat *C. difficile* infection. This pathogen can set up shop in the gut if the resident microbiome has been damaged through treatment with high doses of antibiotics, causing digestive distress and potentially serious long-term health problems. Throughout the 2000s, several academic research groups showed that transplantation with microorganism-laden stool from healthy donors can rebuild the gut ecosystem and reduce the risk of recurrent infection. Today, fecal microbiota transplantation (FMT) is established as an effective therapy for this indication, but its use is limited by the need for donor stool and safety concerns.

Accordingly, many companies have initially focused on this indication as a relatively low risk choice for testing the mettle of their interventions. "The role of the microbiota in this disease is entirely unambiguous," said Olle. SER-109, which consists of a carefully prepared subset of live bacterial spores isolated from healthy donor stool, was the first to enter clinical testing. However, a failed phase 2 trial in 2016 threatened Seres' survival. "It cast a long shadow on the whole live biotherapeutics, 'bugs as drugs' section of the microbiome field," said Mike Romanos, co-founder and CEO of Microbiotica, a microbiome startup spun off from the Wellcome

Sanger Institute in 2016. But Seres bounced back, betting heavily—and successfully—on a phase 3 trial that employed improved diagnostic criteria and a tenfold higher dose of microorganisms. And as the company pursues US Food & Drug Administration (FDA) approval for SER-109, it is possible that a microbiome therapy will enter the clinic sooner rather than later. Such a breakthrough could also have broader implications for preventing other opportunistic infections that arise in the aftermath of high-dose antibiotic treatment. In late September, Vedanta received $7.4 million from the Biomedical Advanced Research and Development Authority—a US government agency focused on medical counter measures against biological threats—with a total of $76.9 million in potential future funding to advance development of its live microbial treatment for *C. difficile*, VE303, which is now in phase 2 (Table 2).

Inflammatory bowel disease (IBD) is another area of active investment—as its two main forms ulcerative colitis and Crohn's disease—are characterized by uncontrolled immunological activity in the intestine. There is compelling evidence that perturbations in the gut microbiome play a central role, where the loss of commensal bacteria that would normally keep the immune system under control either initiates or exacerbates inflammation. Therefore, the restoration of species that soothe the immune system could bring IBD back under control. In 2015, Vedanta entered a deal with J&J to develop IBD treatments based on defined combinations of therapeutically-active microbiota species. The company received $12 million in milestone payments 3 years later, for moving a candidate product into clinical testing, which today is in phase 2. Vedanta has fully taken over development with partner J&J retaining a royalty on the program.

And within just 18 months of its founding in 2016, Microbiotica was approached by Genentech, which proffered up to $534 million to support discovery of microbial biomarkers that might guide deployment of the company's portfolio of IBD therapeutics or reveal new treatment avenues. "They'd been watching the science from our founders at the Sanger Institute and waiting for the company to form," said Romanos. Takeda's partnership efforts are also heavily focused on IBD. As the manufacturer of the widely used anti-inflammatory antibody drug Entyvio (vedolizumab), the company has a strong presence in the IBD space, but Hicks notes that the field is crowded with highly competitive drugs that deliver roughly equivalent clinical benefit. "We don't want to make yet another drug that may have a similar level of activity, but perhaps a little bit better for one patient subgroup," said Hicks. "We want to find something that's fundamentally different."

Certain microorganisms can rouse rather than sedate the immune response, a characteristic that could be useful in bolstering the efficacy of immuno-oncology (IO). Checkpoint inhibitor drugs help stimulate cytotoxic $CD8^+$ T cells to mount a more aggressive attack against tumor tissue. These regimens can deliver durable remission, but many patients fail to respond because they lack a sufficient $CD8^+$ T cell presence at the tumor site. Based on immunological work by scientific co-founder Kenya Honda, Vedanta defined a consortium of bacteria that can efficiently induce activation and mobilization of $CD8^+$ T cells. Its preclinical work caught the attention of Bristol Myers Squibb (BMS), makers of the checkpoint inhibitor drug Opdivo. "We did a collaboration where BMS basically became an equity investor in Vedanta, and they provided drugs for studies that we run," said Olle. This microorganism–drug combination is now in phase 1 testing against various advanced cancers. Several other such collaborations (Table 1) are underway, for example Merck is currently working with both 4D Pharma and Evelo Biosciences to assess whether selected microbial species might bolster the effects of its checkpoint inhibitor drug Keytruda (pembrolizumab).

Many roads to microbiome therapy

Early therapies were built on a foundation laid by the pioneering work with FMT, and several companies are commercializing rigorously standardized and quality-controlled versions of this treatment. Indeed, all three of the most advanced *C. difficile* clinical programs are based on products that are derived from donor stool specimens. This strategy has clear advantages, in that it largely preserves an intact ecosystem of microorganisms with a demonstrated potential to work in concert to deliver clinical benefit.

"Those products are great and I think they have regenerated confidence in the sector that this could really be our next major modality," said Romanos, although he also noted clear limitations for stool preparations. "It's not really scalable, and it has some level of risk," he said. As a donor-derived material, it is essential to screen every specimen rigorously for pathogens that might infect the recipient—including SARS-CoV-2, which can be detected in fecal matter of infected patients. In March, the FDA issued a warning about two deaths linked to FMT with stool bank-derived samples that had been contaminated with pathogenic *Escherichia coli*.

Table 1 | Selected deals involving the microbiome (2018–2020)

Date	Microbiome company	Partnering company	Summary
June 2020	Debiopharm	Takeda Pharmaceutical Company	Debiopharm and Takeda partner to develop microbiome therapeutics to treat IBD and other GI disorders.
April 2020	Second Genome	Gilead	Second Genome and Gilead partner to identify biomarkers for five of Gilead's clinical candidates and drug targets for IBD. Second Genome will receive $38 million upfront.
February 2020	Enterome	BIOASTER Institute	Enterome partners with BIOASTER Institute to explore mechanisms of microbiome-derived cancer immunotherapies.
November 2019	Finch Therapeutics	Takeda Pharmaceutical Company	Finch expands its partnership with Takeda to develop microbiome-based therapeutics using Finch's Human-First Discovery platform.
October 2019	4D Pharma	Merck & Co., Inc (MSD)	4D Pharma signs research deal with MSD to develop live biotherapeutics for vaccines. 4D will receive up to $347.5 million in milestone payments as well as an upfront cash payment.
March 2019	Seres Therapeutics	AstraZeneca	Seres announces partnership with AstraZeneca to evaluate microbiome-based therapies on their capacity to augment cancer immunotherapy.
November 2018	Vedanta Biosciences	Janssen R&D	Vedanta signs deal with Janssen R&D to commence phase 1 study of VE2020 for IBD. Through the deal Vedanta will receive up to $12 million in ongoing milestone payments from Janssen.
October 2018	Enterome	Takeda Pharmaceutical Company	Enterome signs licensing and co-development deal—including $50 million up front and up to $640 million in milestones with Takeda—for the development of EB8018 for Crohn's disease.
June 2018	Microbiotica	Genentech	Microbiotica signs $534 million deal with Genentech to develop biomarkers, targets and therapeutics for IBD using its precision metagenomics microbiome platform.
April 2018	Rebiotix	Ferring Pharmaceuticals	Ferring Pharmaceuticals acquires Rebiotix and its microbiota restoration therapy platform and lead candidate RBX-2260 in development for *Clostridium difficile* infection.

GI, gastrointestinal; IBD, inflammatory bowel disease.

Table 2 | Selected financings involving the microbiome (2018–2020)

Date	Microbiome developer	Partnering company	Summary
September 2020	Finch Therapeutics	Various investors	Finch Therapeutics raises $90 million to progress its *C. difficile* infection-targeted microbiome drug.
September 2020	Vedanta Biosciences	Biomedical Advanced Research and Development Authority (BARDA)	BARDA grants Vedanta Biosciences $7.4 million upfront, and up to $76.9 million in total to develop its VE303 *C. difficile* anti-infection program.
June 2020	Enterome	Various investors including Takeda Pharmaceutical Company	Enterome secures €46.3 ($52.6) million in funding to develop its microbiome inflammation clinical pipeline, including EO2401 indicated for IO applications.
December 2019	Vedanta Biosciences	CARB-X	CARB-X grants Vedanta up to $5.8 million to progress candidate VE707 for multi-drug resistant infections. $3.5 million in milestone payments could be awarded.
September 2019	Vedanta Biosciences	Various investors	Vedanta Biosciences raises $16.6 million in series C funding round to support development of its clinical pipeline.
August 2019	Finch Therapeutics	Various investors	Finch secures $53 million in series C financing round to advance its pipeline.
May 2019	Vedanta Biosciences	Various investors	Vedanta Biosciences secures $18.5 million as an extension of its series C funding.
June 2018	Kaleido Biosciences	Various investors	Kaleido raises $101 million in series C funding round.
May 2018	Evelo Biosciences	Various investors	Evelo's IPO secures $85 million to further develop its microbiome candidates.

BMS, Bristol Myers Squibb; CARB-X, Combating antibiotic-resistant bacteria; *C. difficile*, *Clostridium difficile*; IO, immuno-oncology; IPO, initial public offering.

Companies like Seres employ rigorous purification processes to isolate the desired subset of species while weeding out pathogens and contaminants. But many are instead focusing on live therapeutics assembled from hand-picked, experimentally defined consortia of cultured microorganisms. Finch's newer programs have shifted in this direction, and this is the strategy being employed at Vedanta and Microbiotica. This entails detailed comparison of the microbiota of healthy versus unhealthy individuals, followed by rigorous computational analysis to identify meaningful strain signatures associated with those two states, and finally, functional characterization of the candidate strains in relevant bioassays. Romanos notes that his company's co-founders at Sanger identified roughly 13,000 different bacteria that comprise the healthy gut microbiome, but initially lacked detailed genomic data for most of these. "We can now isolate all the gut bacterial species from any human … and then get the genome sequence fully assembled of all of them," he said. These kind of rich data accelerate the identification of disease-related strains, and subsequent assembly of therapeutically-useful combinations. Such strategies could also appeal to regulators, and Olle notes that the FDA's willingness to back trials based on donor-derived communities should bode well for therapies that employ hand-picked consortia. "There hasn't been any hurdle that the FDA has put in front of companies that has kept the field from advancing," he said, "and I think they've taken the view that generally, this is likely to be a class of drugs that is relatively safe."

But building a consistent drug product from a defined mixture of bacterial strains is no mean feat, and the challenge grows with the number of species involved. Many gut microorganisms are difficult to culture, and the formulation process must accommodate the particular quirks of each bacterial component. Vedanta has invested considerable time and resources into building an in-house manufacturing pipeline that can overcome these complexities. "We know exactly what's in our product and we can make it by a fermentation process that is truly scalable, where making 10 L of product uses the same process as making 2,000 L," said Olle. Other companies are opting to outsource, and there has been considerable activity in the contract development and manufacturing organization (CDMO) space for live microbial therapeutics, including a $101 million partnership between Lonza and Chr. Hansen to build contract production facilities in Denmark and Switzerland.

A few companies are pursuing a simpler alternative, in which therapeutic benefit is derived from a single microbial strain. For example, 4D Pharma has more than half a dozen clinical trials underway for indications ranging from IBD to asthma to COVID-19, each employing a 'monoclonal' preparation of bacteria to achieve immunomodulation. Such preparations greatly simplify the manufacturing and formulation process, and have drawn some investor interest. In October 2019, 4D inked a deal with Merck for the development of microorganism-based vaccines that could net the startup $347.5 million. Another single-species company, Evelo Biosciences, drew $85 million for its initial public offering (IPO) in May 2018. But others in the field are hesitant about this approach, which may not deliver the punch of multiple species operating in concert. "This is one area where we haven't elected to partner, as of today at least," said Hicks. "We just thought … if you could have four mechanisms in your pill rather than one, why wouldn't you?"

Enterome is one of several companies, as well as Kaleido Biosciences and Second Genome, that are pursuing an entirely different approach, where the focus is on the biologically active molecules produced by the microbiome, rather than the microorganisms themselves. "We have sequenced more than 20 million full genes from the gut microbiome," said Bonny. "For me, it's a bit like going into the Amazonian rain forest and picking leaves and things to try to find something you could make into a drug." The focus is on molecules that are already being produced in the gut, and are therefore, by definition, suitable for use in humans.

The company has already identified a bacterial signaling pathway that can be targeted to treat Crohn's disease, and recently moved a promising drug candidate into phase 2 trials in partnership with Takeda. Several other promising candidates are also in the pipeline, including molecules that either stimulate an anti-tumor immune response or suppress harmful inflammation. The company has drawn more than $90 million in venture funding in the past 2 years, and is partnering with companies like BMS who want to take advantage of the company's vast and unique library of microorganism-derived drug candidates. Bonny touts the fact that discovery processes like Enterome's fit naturally into existing drug screening and development procedures. But, as with the single-species interventions, it remains to be seen whether this will offer the breadth or durability of effect of live, multi-species consortia.

With many candidates now being tested in complex clinical scenarios such as IBD and IO, hopes are high that the field will get the big win it needs to get serious buy-in from the pharma industry. And if these trials vindicate the idea of achieving a systemic clinical response via the gut bacteria, all manner of neurological, autoimmune, and other indications may be on the table. Von Maltzahn is optimistic that the industry may be on the verge of an inflection point. "I think it is unimaginable that there won't be a gigantic category of microbiome therapeutics ahead of us," he said. "At Flagship, we think that the biology is important enough that there will be multiple Genentech-like companies in this field."

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