Manipulating the human microbiome to fight inflammatory disorders

Big pharma's interest in the therapeutic potential of modulating the body's own bacterial ecosystem is growing, particularly with regard to the treatment of inflammatory disorders.

BY RACHEL BRAZIL

Fortune declared 2015 "the year of the microbiome." The clinical success of fecal microbiota transplants (FMTs) for treating *Clostridium difficile* infections and studies linking changes in the composition of the gut microbiota to various disorders have moved the therapeutic manipulation of the body's bacterial ecosystems into the spotlight.

"The microbiome space, unlike any other that I have seen in life sciences, has quickly captured the public's imagination with its therapeutic potential," said Peter DiLaura, CEO of Second Genome, one of the pioneering biotech companies in the area. This is mainly because of the unconventional nature of FMT therapy, which involves introducing healthy bacterial flora through infusions of donor stool. In 2013, a randomized, controlled trial showed that FMT was more effective than antibiotics for treating recurrent *C. difficile* infection (*N. Engl. J. Med.* **368**, 407–415; 2013). Dramatic improvements in sequencing technology in recent years have also enabled studies that compare the composition and characteristics of the microbiota in healthy subjects with those seen during disease at multiple levels, including bacterial gene expression and metabolite profiles.

There is still substantial uncertainty about the best way to therapeutically target the microbiome, particularly for indications beyond *C. difficile* infection. Nevertheless, the amount of evidence showing that the gut microbiota can contribute to inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease (*Gastroenterology* **146**, 1489–1499; 2014) is rapidly growing, catalyzing a wave of interest and dealmaking in the field (**Table 1**).

Early movers

Isabelle de Cremoux, CEO of the venture capital fund Seventure Partners, has been interested in the area longer than most. "We identified this field in 2006," she said. Earlier this year, Seventure set up a first-of-its-kind €120 million (~US$130 million) fund, Health for Life Capital, dedicated to microbiome-based innovations.

De Cremoux said that since the June initial public offering of Seres Health, which grossed about $134 million, investors have started to pay attention. Seres is one of the first companies to move from FMTs to the development of a tablet-sized capsule of bacterial spores, dubbed SER-109, to prevent recurrent *C. difficile* infection. Several other leading funds are investing in the area, such as Flagship Ventures, an early investor in Seres, and Woodford Investment Management, which has invested in 4D Pharma, a company that is developing a microbiome screening platform for autoimmune and inflammatory disease therapeutics. The company plans to commence clinical trials with two microbiome-based IBD therapies in 2015.

The pharmaceutical company that has taken the greatest interest in the area over the past five years is Janssen, a division of Johnson & Johnson. The company has a number of partnerships and projects that it has recently complemented by establishing the Janssen Human Microbiome Institute, headed by Dirk Gevers (*Nat. Rev. Drug Discov.* **14**, 305; 2015). Via email, Gevers explained that the institute aims "to build an internal team of expert scientists and match such capabilities with external collaborators." Janssen is also "focusing on pioneering the space and becoming the go-to partner for innovative microbiome projects and talent," he added. In addition to deals with several startups, Janssen has academic partnerships with the University of California, San Francisco, the University of Michigan and the James Cook University in Brisbane, Australia.

Other early adopters with significant microbiome research programs include Novartis, Pfizer, AbbVie and AstraZeneca. But many more companies are keeping an eye on the field. "We are well aware of what's going on. I think it's a matter of watching and seeing what other types of advances are made, in particular with respect to clinical proof of concept," said James Brown, who coordinates microbiome and infectious disease support at GlaxoSmithKline.

"You would be hard pressed today to find a pharmaceutical discovery executive that doesn't list microbiome science as one of the top two or three areas of emerging science that they are watching very closely," said DiLaura.

Table 1. Selected recent major microbiome deals (2013–2015).

Companies involved	Headline	Date announced
Second Genome; Janssen Biotech	Second Genome and Janssen Biotech partner on microbiome-based drug discovery in ulcerative colitis	June 2013
Second Genome; Pfizer	Pfizer partners with Second Genome to research the role of microbiomes in metabolic diseases	May 2014
Synthetic Biologics; Enterome	Microbiome collaboration between Synthetic Biologics and Enterome	June 2014
Mayo Clinic; Seres Health	Mayo Clinic to collaborate with Seres Health on microbiome-based therapies	June 2014
Mayo Clinic; Second Genome	Mayo Clinic to develop Second Genome's microbiome therapeutics	October 2014
Enterome; AbbVie	Enterome and AbbVie to develop novel microbiome-based therapies for Crohn's disease	November 2014
Vedanta Biosciences; Janssen Biotech	Vedanta and Janssen Biotech to accelerate research between the human microbiome and the immune system	January 2015
Alimentary Pharmabiotic Centre (APC), The University College Cork; Janssen Biotech	APC Microbiome Institute and Janssen Biotech to explore the role of viruses in shaping the human microbiome and potential uses in inflammatory bowel disease	March 2015
Evotec; Second Genome	Second Genome and Evotec to discover and develop small-molecule therapies for microbiome-mediated diseases	March 2015
Alimentary Pharmabiotic Centre, The University College Cork; Second Genome	Second Genome to develop anti-inflammatory bowel disease therapies with the APC Microbiome Institute	April 2015

Data sourced from Thomson Reuters Cortellis.

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Manipulating the microbiome

Scientists are testing several distinct approaches to therapeutically manipulate the microbiome, and it is not yet clear which of these will prove successful. Apart from FMT, the most advanced approaches make use of bacterial cocktails with the aim of restoring and rebalancing the microbiome; these are being used by companies such as Vedanta Biosciences. In January, Janssen announced that it was investing up to $241 million to license and develop Vedanta's potential IBD therapy, VE202, which is expected to reach the clinic within a year or so. VE202 is a cocktail of Clostridia subspecies that studies suggest encourage the proliferation of regulatory T cells (*Nature* **500**, 232–236; 2013).

The microbiome space has also captured the interest of the food industry, and several companies are developing partnerships in the medical food area. In January 2015, Seres Health announced a further $65 million investment from Nestle Health Science, a subsidiary of Nestle, which increased its total investment to $110 million. The deal will fund phase 3 trials of SER-109 to prevent recurrent *C. difficile* infection, as well as advance Seres' pipeline, which includes treatments for inflammatory disease. Danone is also a key investor in Seventure's Health for Life Capital fund.

But the "bugs as drugs" approach, as DiLaura calls it, has some drawbacks for big pharma. "There are concerns about regulatory frameworks, manufacturing processes and intellectual property protection," he said.

De Cremoux highlighted similar concerns. "There is an environment of uncertainty where big pharma are not comfortable…They don't like products that are not well characterized and identified as unique components."

Charles Mackay, CSO of Pfizer's Inflammation and Immunology Research Unit, said that Pfizer is unlikely to enter the probiotics business. "I think we are much more interested in understanding the pathways whereby beneficial bacteria work and replicating those using a small-molecule drug."

DiLaura agreed that focusing not on the bacteria directly but on the bioactive compounds that are secreted is the strategy that is drawing in big pharma. "I think it has catalyzed an interest and provided a road map to bridge from this incredibly important new understanding of the role of the microbiome in human health and disease to clear drug discovery efforts."

Second Genome is using this approach, and its small-molecule IBD drug candidate SGM1019, for which the target has not been disclosed, is currently in phase 1 trials, with phase 2 trials planned for early 2016. In 2013, the company inked a deal with Janssen to identify microbes and their metabolites with causal roles in ulcerative colitis and ultimately develop new therapeutics.

Another microbiome-based biotech company working on the small-molecule approach is Enterome, founded in 2012. CEO Pierre Belichard said that in addition to developing its own small-molecule drug candidate for Crohn's disease (which it hopes will reach the clinic in 2016), the company is working with three different large pharma companies. He did not disclose details of all three deals, but Enterome partnered with AbbVie in 2014 to develop a rapid and noninvasive test for Crohn's disease based on fecal bacterial DNA analysis.

DiLaura said that microbiome science can also bring a new view to patient stratification. "By bringing a biomarker-centric view of a patient population that includes the microbiome to both the diagnosis and the monitoring of patients, we can get to a more targeted therapeutic population." This is the backdrop for another Second Genome collaboration, with Pfizer, which began in 2014. Together, the companies are carrying out a 900-patient study of the relationship between microbiomic profiles and metabolic phenotypes to better understand disorders such as obesity.

Beyond the gut

Although activity so far has focused on the role of the gut microbiome in *C. difficile* infection and IBD, the microbiome in the gut and beyond could have a role in a much wider range of inflammatory diseases, including the liver disorder nonalcoholic steatohepatitis, airway diseases such as asthma and chronic obstructive pulmonary disease, skin disorders such as psoriasis, and other autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.

The next two to three years will be a crucial time for accelerating efforts to realize the promise of manipulating the microbiome, with an increase in partnerships and involvement from major pharmaceutical companies. Belichard expects 2017 to be the year for significant deals in the space. "[Big pharma] will not move until someone else is really showing that they have a drug in clinical development…But then you will see; they are going to move."

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PETER DILAURA, CEO OF SECOND GENOME