

Microbiome partnerships: an expanding network

Partnering activity in the microbiome space exploded in 2016, and with the first inroads into clinical development well under way, 2017 is shaping up as a pivotal year for the microbiome's therapeutic and market potential to blossom.

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For more than a decade, the goals of unlocking the mysteries of the microbiome and harnessing the resulting insights for therapeutic applications have drawn attention from basic researchers, venture capitalists and pharmaceutical executives. However, with the exception of fecal microbiota transplantation (FMT) for the treatment of *Clostridium difficile* infection (CDI), the development of microbiome-based therapeutics—whether they are designed to target the microbiome or to be used as a source of therapeutic compounds—has been slow because of the limited understanding of the complex biology underlying the microbiome's function in health and disease.

Nevertheless, researchers, investors and companies are increasingly coming together to devise new and creative ways to address the challenge. After a burst of research efforts over the past 10–15 years, investors seized the opportunity to support companies in the space (Fig. 1)—for example, in 2014, Seventure Partners established Health for Life Capital, the first fund dedicated exclusively to investment in microbiome companies. Many of the companies have been successful in navigating the funding waters, with one, Seres Therapeutics, even progressing from being a startup in 2010 to launching a successful IPO just five years later. The establishment of a critical number of companies in the space then created further possibilities for partnerships to emerge.

The number of new partnerships established per year worldwide has surged since 2013, with 2016 seeing a nearly fivefold increase in partnering activity compared with that in 2015 (Fig. 1). Although US companies and institutions account for approximately two-thirds of the partners involved in microbiome deals—due mostly to the preponderance of biotechs in the field being founded in the United States—stakeholders in 15 other countries across Europe and Asia provide a solid contribution to the worldwide microbiome partnering network.

The number of active partnerships was close to 70 by the end of 2016, and there is no indication that the momentum with which new ones are established will decrease in 2017 and beyond.

In 2016, the US National Microbiome Initiative was launched, earmarking \$121 million “to advance understanding of microbiome behavior and enable protection and restoration of healthy microbiome function,” and the largest development and commercialization deal to date in the microbiome space was inked between Nestlé Health Science and Seres: \$120 million in upfront payments with a potential total disbursement of over \$1.9 billion. And although 2016 was also the year in which Seres's SER-109, a mix of bacterial spores designed to treat recurring CDI, failed in a phase 2 clinical study—representing the biggest clinical developmental setback to date in

the space—new companies keep sprouting, more partnerships are being established, and novel therapeutic products are reaching clinical stages.

Indeed, the end of 2016 witnessed the launch of Axial Biotherapeutics, a startup focused on harnessing the link between the human gut microbiome and the central nervous system to develop a new class of biotherapeutics, and of Microbotica, a spin-out company from the Wellcome Trust Sanger Institute established to progress multiple live bacteriotherapy programs coming out of the institute's labs. In December 2016, Ferring Pharmaceuticals and MetaboGen inked a multi-year research collaboration to develop a microbiome-based product to prevent and treat intrahepatic cholestasis of pregnancy. In January 2017, Allergan and Assembly Biosciences entered an agreement that grants Allergan worldwide rights to Assembly's microbiome gastrointestinal development programs, and ENTEROME Bioscience announced the launch of a phase 1 clinical study of EB8018, a small molecule it in-licensed from Vertex Pharmaceuticals to treat Crohn's disease.

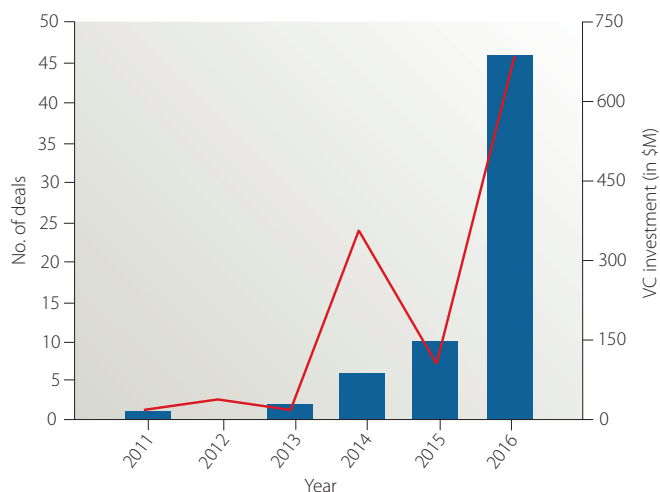


Figure 1: Evolution of the microbiome partnering and VC funding space between 2011 and 2016. Over the past six years, partnering activity in the microbiome space has steadily gathered momentum, with 2016 yielding a bumper crop of new partnerships (blue bars). Venture capital (VC) funding has followed a similar trend, albeit not as smoothly, to also deliver a strong showing in 2016 (red line). Sources: Clarivate Analytics Cortellis; *Wall Street Journal* (see Further Information).

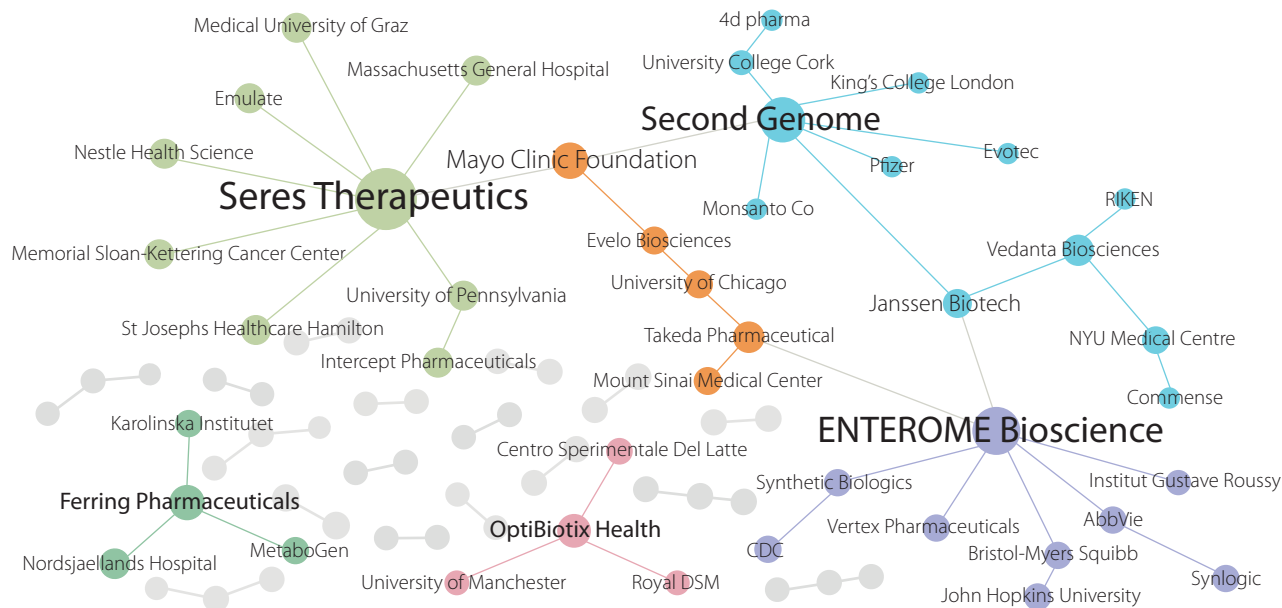


Figure 2: Network of partnerships in the microbiome space as of December 31, 2016. Active partnerships in the microbiome space cluster mostly around one large network consisting of several main nodes (Seres Therapeutics, Second Genome, ENTEROME Bioscience, Vedanta Biosciences and the Mayo Clinic Foundation). Two smaller satellite nodes emerged in 2016 (Ferring Pharmaceuticals and OptiBiotix Health), and several single or double partnerships (in gray) complete the picture. Partners are shown as nodes, and partnerships are indicated by edges. Node and name sizes are proportional to the number of edges. Colors denote different ‘community modules’.
Source: Clarivate Analytics Cortellis.

Diversified partnerships

Microbiome-based therapeutics come in many flavors, from the probiotic approach of FMT for CDI and the synthetic cocktails of particular bacterial strains deemed beneficial for certain conditions, to the isolation of active compounds from the microbiome or the identification of small-molecule therapeutics capable of modulating specific microbiome pathways. Similarly, partnering in the space follows many paths, and potential stakeholders in research, biotech and pharma approach it differently.

From 2013, early movers such as Janssen Biotech and the Mayo Clinic Foundation established joint ventures with Second Genome and Vedanta Biosciences, and with Seres and Second Genome, respectively. The focus of these collaborations was on the early development of therapeutics for gastrointestinal conditions such as inflammatory bowel disease (IBD), ulcerative colitis and colorectal cancer.

As one of these early movers, Second Genome consistently grew its areas of interest and network of collaborators to include other pharma stakeholders (Pfizer in 2014 for research in the obesity and metabolic disease spaces), biotech companies (Evotec in 2015, with a broad focus on inflammatory disease) and academic institutions (University College Cork in 2015 for IBD, and King’s College London in 2016 for eczema and food allergies). In 2016, Second Genome further diversified its partnerships by joining the agricultural biotechnology company Monsanto in efforts to develop microbiome-based solutions for insect control.

Janssen cemented its role as a first mover among pharma companies in the microbiome space by establishing the Janssen Human Microbiome Institute in 2015 to build a global collaborative network to translate the science of the microbiome into therapies and diagnostics for autoimmune diseases and other microbiome-related conditions. Janssen followed this in early 2016 with a deal with ENTEROME to develop therapies for Crohn’s disease—a collaboration that contributed to ENTEROME’s recent clinical-trial announcement (see above).

Against this backdrop of early movers, the field has quickly developed a sense of confidence in its possibilities that has triggered the entry of numerous new players into the partnership game. Biotechs such as Seres, Vedanta and ENTEROME greatly expanded their networks of collaborations in 2016. And the pharmas Bristol-Myers

Squibb, Takeda Pharmaceutical and AbbVie partnered with biotech and academic institutions to advance more basic and clinical research in gastrointestinal disorders and cancer.

By the end of 2016, the combined set of collaborations had resulted in a network of activity that illustrates the momentum in the space (Fig. 2). About half of all active partnerships clustered around one large network consisting of several main nodes (Seres, Second Genome, ENTEROME Bioscience, Vedanta and the Mayo Clinic Foundation). This strong interconnectivity reflects the natural tendency of stakeholders to combine resources to advance the field. Janssen, Takeda and the Mayo Clinic in particular provide some of these links, and the large biotech players—Seres, Second Genome and ENTEROME Bioscience—are expanding their pipelines to encompass products not only in the gastrointestinal disorder space but also increasingly in other disease areas, including cancer and other inflammatory and autoimmune diseases.

Two smaller satellite nodes—Ferring Pharmaceuticals and OptiBiotix Health—emerged in 2016 around the search for new therapies for reproductive health and gastrointestinal disorders, and around microbiome-specific high-throughput screening technologies, respectively. A number of players with single and double partnerships complete the picture, many of which could well expand their partnership networks in 2017 and beyond.

Overall, the picture is very dynamic and interconnected, and suggests a high level of focus and efficiency in terms of resources. The substantial number of partnerships not tied into the larger network contribute points of additional innovation and ideas to the entire space. Such a combination of more established players with many new ones continuously emerging in the partnering scene can be regarded as a deep ‘pipeline’ of assets and ideas for a burgeoning field in need of creativity and diversity to address the many scientific, developmental and regulatory challenges it faces.

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FURTHER INFORMATION

Wall Street Journal: <https://www.wsj.com/articles/microbiome-companies-attract-big-investments-1474250460>