MicrobiomeTimes
REPORTING ON THE ERA OF THE MICROBIOME

SANDWALK Bioventures

Microbiome drug development: 2022 in review.

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Abstract

Microbiome therapeutics offer a novel mode of treating disease and improving health outcomes of the world. With wide-ranging potential applications from inflammatory bowel disease to depression, the opportunity to revolutionize treatment options is astounding. Leveraging a year of important research updates, funding rounds, and academic papers, this report compiles the most significant industry news pertaining to microbiome drug development in 2022. It finds that the regulatory approval of three companies (Rebiotix, BiomeBank, and Proge Farm) comes at a timely manner. The closure and downsizing of some microbiome companies are not singular to the microbiome industry but are nevertheless negative for the field. It identifies investment into the microbiome market has not decreased but has shifted to favor fewer but more mature companies. Preferred investment modality has shifted to 'simpler" modalities like small molecule, and from the infectious disease application to oncology instead. Key scientific research is highlighted in the following areas: tumor microbiomes, synthetic consortia, antimicrobial resistance, the gut-brain axis and microbiome and autoimmunity. High profile acquisitions in the field foreshadow a potential 2023 M&A trend, whereby companies resist closure by consolidating. The expected April 2023 approval of SER-109 by the US FDA for Seres Therapeutics will likely boost investor confidence in the market.

Introduction

For the microbiome therapeutics market, 2022 has been a year of high highs and low lows. We saw the first US FDA approved fecal microbiota product in Rebyota®, but witnessed industry juggernauts like Kaleido downsize or close altogether. Whilst it could appear the microbiome therapeutics industry has faced reduced investment in 2022, it has remained stable – receiving the same investment as 2021, which was a record-breaking year for the field. This report will outline the achievements and failures of the sector in 2022, describing significant events, academic breakthroughs, and financial analysis.

The year in highlights

Dictated by macroeconomic trends, such as a divestment from the biotherapeutic sector, 2022 saw some microbiome companies struggle to stay afloat. Conversely, we saw the world's first regulatory approval of an FMT in both Australia and in the USA. In this section, we will discuss the regulatory breakthroughs of the fields, as well as some other major events of this past year.

Regulatory momentum

This year will be remembered as a tipping point for regulatory affairs, with Rebiotix, BiomeBank, and Proge Farm all receiving regulatory approval for some of their products.

Claiming the title of the first-approved microbiome therapeutic of the year was Proge Farm as in July, Switzerland's authority SwissMedic approved its LBP *L. plantarum* P17630 as a topical treatment for vaginitis and prevention of recurrent vaginal mycosis. Whilst an important regulatory step, it should be noted that this authorization may not open the EU market for this drug easily and that drugs based on microbes do indeed exist in many western European countries, although they were originally authorized many decades ago, when pharmaceutical regulations where significantly different to the current ones.

The world's first approval of a donor derived microbiome drug was received by BiomeBank for its FMT product. Targeting recurrent *C. difficile* infection, it was approved by Australia's

Therapeutic Goods Administration on November 9th 2022.

Representing regulatory progress in the USA was the approval of Ferring's-Rebiotix's RBX2660, which was authorized for recurrent *C. difficile* infections, making it the first fecal microbiota product holding a marketing authorization from the US FDA.

Also in the USA, Seres Therapeutics is awaiting an approval for its Biologics License Application for SER-109 – a live biotherapeutic product also indicated for recurrent *C. difficile* infections. The company expects a decision by April 26th, 2023.

Struggles, layoffs, shutdowns, repositioning – and some notable deals

This year has been challenging for the biotech industry, and the microbiome therapeutics sector has not been an exception. Despite the field's positive regulatory outcomes, it has faced many high profile set-backs.

One case that hit the headlines was 4D Pharma's placement into administration after it failed to secure a loan. The company was subsequently delisted from both AIM and NASDAQ in the summer.

Year 2022 also resulted in major **workforce reductions** for the biotech and pharma sector. In fact, over 100 major pharma and biotech companies have announced significant job cutting events between January and December.

Examples of this in the microbiome space include Vedanta, Synlogic and Finch Therapeutics. The downsizing of Finch's workforce occurred after Takeda announced the end of their 2017-signed deal, involving two drug candidates for Crohn's Disease and Ulcerative Colitis.

Unfortunately, many microbiome drug development companies **could not survive** the economic (and regulatory) headwinds. Arguably, the most remarkable case was industry titan, Kaleido Biosciences, which shut down after regulatory discrepancies with the FDA and its failure to find a buyer.

This was not an isolated case – we have registered **over 10 microbiome drug development companies shutdowns this year** alone.

The relatively recent microbiome boom led to the existence of many microbiome-targeted therapeutic companies, many of which had immature technologies and a lack of clinical data. Some shut down as a result of being able to secure the capital required to persist in the microbiome arena. Whilst, around a dozen companies in 2022 **repositioned** themselves as enablers and service providers (such as discovery and preclinical CROs or manufacturers) or have steered towards different applications ranging from oncolytic viruses developers to food or cosmetic ingredients creators.

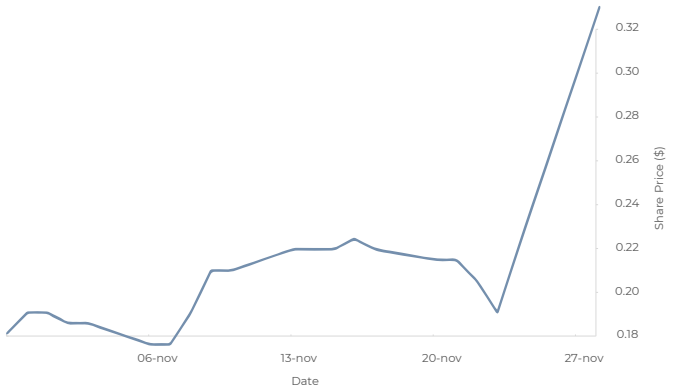
Whereas some big players seem to be retreating from microbiome therapeutics, others continue to expand. For example, **Nestlé Health Science** signed two major deals this year. The first one concerned the US and Canada marketing rights for **Seres**' SER-109 and involved an upfront payment of USD 125 M, up to USD 525 M in milestones and 50% of the commercial profits on marketing the therapeutic. The second was a research collaboration and licensing

agreement around **Enterome**'s lead immune disease drug candidate EB1010 for food allergies and inflammatory bowel disease, which will enter clinical trials in 2023. The deal involved € 40 M in cash and stock from Nestlé, plus additional payments if certain clinical and sales milestones are hit, as well as royalties on sales of any therapeutic candidates that win approval.

Merk & Co. / **MSD** has also continued to expand its strategic collaborations in microbiome science this year, as the company signed a clinical trial collaboration with Korea's **Genome & Co** to test the safety and efficacy of the latter's immuno-oncology microbiome therapeutic, GEN-001, in combination with Merck's blockbuster Keytruda®, in patients with biliary tract cancer.

Two microbiome biotechs have been particularly active this year. The first is **Microba**, which in April inked a partnership with **Ginkgo Bioworks** to use the latter's high throughput screening capabilities to identify potential therapeutic candidates for autoimmune diseases in Microba's extensive strain bank. More recently, Microba secured a significant investment from **Sonic Healthcare**, a multibillion-dollar diagnostics services business. After the operation, Sonic will control 20% of Microba's stake.

Microba share price, daily ($) Source: BLOOMBERG



The other one is **Xbiome**, which in January signed a licensing and collaboration agreement with **Aurealis Therapeutics** for the clinical development and commercialization of Aurealis' investigational candidate AUP-16 for diabetic foot ulcer, other chronic wounds, and inflammatory disease, in Greater China. In April, Xbiome acquired M201, a clinical-stage candidate for Ulcerative Colitis, from **Assembly Biosciences**.

In July, **Cidara Therapeutics** announced a licensing deal with **Melinta Therapeutics** around its antifungal drug rezafungin in exchange for €30M upfront.

Strategic Investments & Acquisitions

After two acquisitions of microbiome technology companies by major biopharma players in 2021, in December 2022 the skincare giant **Beiersdorf** announced the **acquisition** of a majority stake in skin microbiome player **S-Biomedic**, after years of successful collaboration.

In November, **Holobiome** acquired **AsiaBiome** to expand its microbial collection and datasets, and to gain further insights into the microbiome makeup in Asian countries.

These operations show that interest remains in therapeutics developers. However, most moves in 2022 involved **enabling technologies** like **manufacturing** with **Recipharm**'s acquisition of **Arranta Bio**; **multi-omics analysis** with **Clinical Microbiomics'** acquisition of **MS-Omics** and **Ilya Pharma**'s strategic investment in the bioanalytical company **Nordic Bioanalysis**.

Financial analysis

Whilst several high-profile biotechs were forced to downsize their operations, with significant deals coming to an end, the market's investment has not decreased. Opting for a 'quality over quantity" approach, investors are investing more money into fewer companies. This section will describe investment trends in the space, offering explanation for the patterns.

Impact of the macroeconomic and geopolitical situation - although not dramatic

Investment in microbiome drug development technologies has obviously not been immune to global circumstances. For some investors, there is a sentiment that microbiome therapeutics are too high-risk. Some are even becoming skeptical towards this field, given its regulatory uncertainties and its currently limited clinical validation.

After a first quarter in which investment figures in the field continued with the strong upward trend from 2021, a sharp decline in both cash and number of operations happened in April.

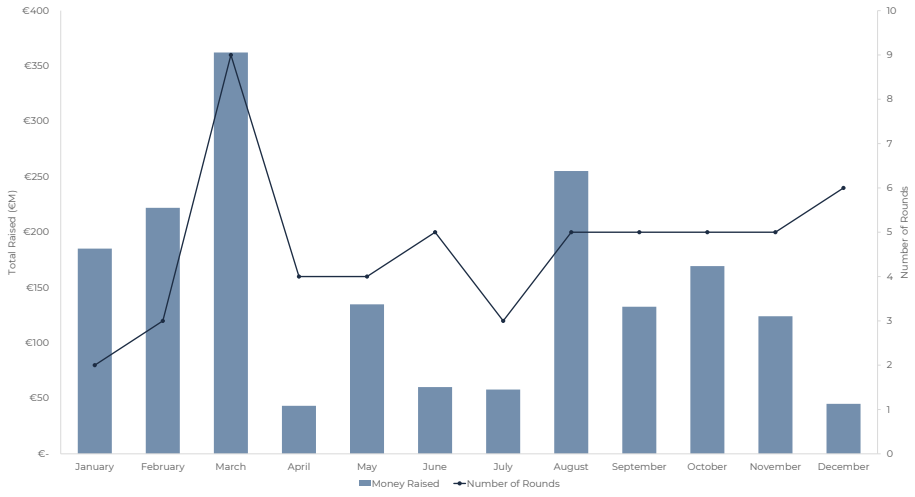
However, if we look at the period between January and December **2022**, we see that a total of **€1.8Bn** have been invested in this sector, which does **exactly match the figure for the same period of 2021**, which was in turn the record year of microbiome therapeutics investments.

Where we see significant differences is in the **number of operations**, which **fell by 30% in 2022** compared to 2021. This means that companies that were able to raise funds did so with bigger checks. In fact, the **average round** (from Seed to Series D) has been over **2x larger than in 2021**.

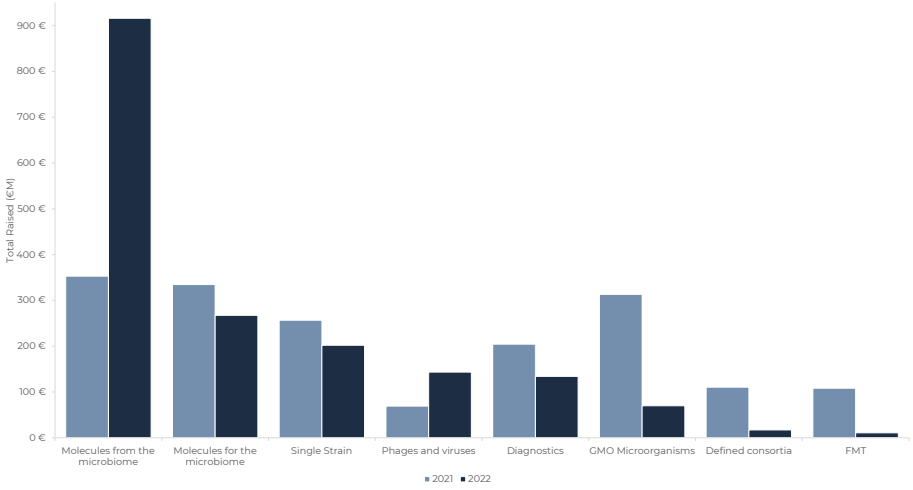
Also, in line with the broader context, microbiome drug development companies have raised capital largely in the private market. In 2021, a total of €755M were raised in the form of **public placings** in 23 operations. These figures dropped to €340M **(down 55%)** in 15 operations **(down 35%)** around the globe in 2022.

Companies seeking significant amounts of capital which did not want expose themselves to the volatility of public markets entered into operations significantly greater than the historical averages in this industry, and even in **mega-rounds**, which were almost unheard of in microbiome therapeutics. Some of these operations were used as a proxy to an IPO, whereas some other companies with plans to IPO did raise what looks like bridge rounds expecting better tailwinds in the near future.

It should not be forgotten, however, that 2022 has been an extremely challenging year for biotechnology in general, and for therapeutics in particular. After two years of breathtaking growth, investment in the broader biotherapeutics sector dropped by around 50% in 2022. Therefore, the stagnant numbers we see in microbiome drug development investment may not be ideal for a young and developing field, however, the broader picture tells us that investors have not completely lost confidence in it.



Shifting investment mood: less appetite for risk

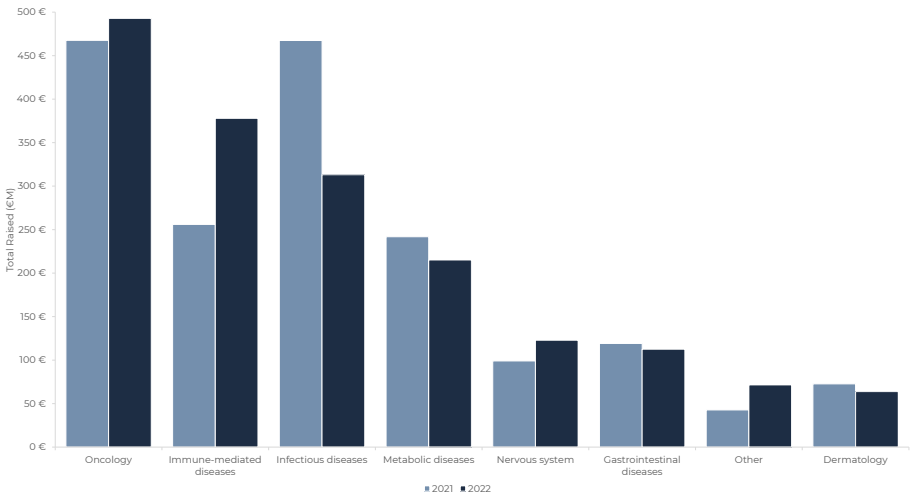


Some clear **risk-mitigation strategic trends** can be identified from money influx in this industry in 2022.

The first and most evident one is purely **financial**, and consists in that investors are betting on **later-stage and safer opportunities**. Whereas the number of operations fell by 30% in all financing rounds, the number of Series C events increased in number in 2022. More remarkably, the average size of Series C events more than doubled, going from € 29M in 2021 to € 66M in 2022.

In 2022, *Molecules from the microbiome / Drugs from bugs* capturing almost 50% of all the funds of the industry, close to 3x from the previous year. *Molecules for the microbiome / Drugs for bugs* ranks second, lagging behind the number one spot significantly. Investment in therapeutic approaches with more complexity, which captured significant amounts of funding in previous years, such as GMO, Defined consortia and FMT saw their investment drastically reduced. The shift to "safer" approaches could be due to **scientific and regulatory** risk-mitigation strategies, as this year's two top categories have clearer regulatory pathways, simpler manufacturing needs and are better understood by Big Pharma. After COVID's fever for them, microbiome-based diagnostics also lost traction over the last 12 months.

Another risk mitigation factor identified from investment metrics is a **market** one. For obvious reasons in the midst of the pandemic, Infectious diseases were the most invested application cluster in 2021, whilst in 2022, Oncology led in investment significantly, followed by Immunology. Investment in Infectious diseases has significantly dropped from 2021. Also, 2022 is the first year in the industry's history that Dermatology applications show negative (even if slight) investment growth. These priorities closely mirror investment patterns from VCs in the broader biotherapeutics landscape.



Science advances untiringly

Microbiome research continues to yield exciting results, which may be translated in the coming months or years. Here is our top-10:

1. Tumor microbiome – and *mycobiome:* Until recently, it was believed that tumors were sterile. Lately, however, researchers have shown cancer tissue contains microbial communities and it appears that some bacteria may impact cancer activity and treatment response.

Between October and November, a number of papers by independent groups reported that bacteria live inside cancer cells worsening disease prognosis, boosting cancer's immunosuppressive protein production, and that members of the gut microbiome can significantly inactivate chemotherapy agents. Although microbiome science has classically focused on bacteria, this year the importance of fungi *(mycobiome)* in oncology was highlighted. For instance, a study published in September was able to detect fungi (often intracellular) in all 35 cancer types studied. Furthermore, intra-tumoral fungi stratified clinical outcomes, including immunotherapy response, and early-stage cancer detection could be done by analyzing fungal cell-free DNA.

2. Microbial microrobots: Leveraging on that capacity of microbes to colonize tumors, researchers were able to create biohybrid bacteria–based microrobots to direct them towards solid tumors to release therapeutic payloads by using magnetic fields or ultrasounds.

3. Life-saving capacity of bacteriophages: 100 years after Felix d'Hérelle's experiment showing that phages could be used to treat disease, two experimental phage treatments yielded promising results this year. In May, a team in the US published their positive results in the use of phages to treat an *M. abscessus* infection in a boy with severe cystic fibrosis, to control the infection for more than one year until a donor lung became available. In September, a paper by European scientists described how they saved a toddler's life which got a drug-resistant infection after an organ transplant with a custom-made phage cocktail.

4. Synthetic microbiomes: Led by Michael Fischbach, researchers at Stanford were able to create a fully functional and invasion-resistant synthetic microbiome. It consisted of over 100 bacterial species, and was successfully transplanted into mice. This is the most complex and well-defined synthetic microbiome designed to date, and it opens the possibility to edit complex consortia and gain better mechanistic insights in microbiome-microbiome and microbiome-host interactions.

A bacterial cell culture from the Fischbach lab. (Image credit: L.A. Cicero)

5. Consortia communication: Researchers were able to make complex synthetic consortia engage in complex communication by using DNA messaging with a plasmid conjugation-based communication channel. Inter-microbial communication is one of the main limitations for the design of complex microbial communities capable of expressing sophisticated behaviors.

6. More connections between microbiome and autoimmunity: A celebrated study published in October described how a new species of bacteria, *Subdoligranulum didolesgii*, can trigger the formation of autoantibodies that may lead to rheumatoid arthritis (RA). Researchers identified that 20% of people diagnosed with RA or people who produce RA-associated antibodies had *Subdoligranulum didolesgii* in their intestine. *Subdoligranulum didolesgii* had not been described as a member of the healthy microbiome before, so it is speculated that the presence of *S. didolesgii* may contribute to RA-associated auto-antibody production.

7. Further evidence on the gut-brain connection: A large-scale study published in December identified an association between 13 microbial taxa and depressive symptoms, potentially through the implication of these microorganisms and the synthesis of several neurotransmitters involved in the disorder. A month earlier, results from also a large cohort suggested that patients suffering from Parkinson's Disease

have a significant alteration of over 30% of microbial species, genes and pathways compared to healthy controls, and provided some potential mechanistic insights on disease onset and progression. These findings reinforce the hypothesis that at least some cases of Parkinson's may have a microbial trigger and actually start in the gut to later expand to the brain.

8. New warnings about the next pandemic: Antibiotic resistance has been described as the next potential pandemic since COVID-19. Studies published throughout the year, analyzing data from 2019, concluded around 10% of the 13.7 M infection-related deaths globally can be attributed to antimicrobial resistance. One pathogen–drug combination alone, methicillin-resistant *S. aureus*, caused over 100,000 casualties, while six more each caused between 50,000 and 100,000. It is estimated that by 2050 the number of deaths associated with antibiotic resistance could reach 10M cases per year (for context, official statistics say that COVID has caused around 7M deaths worldwide so far). This year we also learned that pathogenic bacteria can travel from the gut to the lungs more easily than thought.

9. Unexpected trans-generational implications of microbiome communities and interventions: Unintended outcomes of FMT have been under the spotlight. For instance, cases of infections transmitted between donors and recipients of FMT led to several warning letters by the FDA. Additionally, the case of a woman treated with FMT who developed new-onset obesity after receiving stool from an overweight donor received attention some years ago. This year, further complexity was added to the FMT subject when investigators reported for the first time that FMT microbes can be transferred not only between individuals but also between generations. A pregnant woman treated with FMT via colonoscopy for a *C. difficile* infection, transmitted FMT-originating strains to her child, 26 weeks after the FMT treatment. Although the full spectrum of microbes transferred with FMT tends not to stick for longer than a few weeks, individual species have been detected up to two years in recipients.

This has not been the only intriguing discovery around trans-generational microbiome implications, as in December authors described large-scale, mother-to-infant microbiome interspecies transfer of mobile genetic elements, frequently involving genes associated with diet-related adaptations, and with potential impacts on infant's health and development.

10. Unexpected microbiome players: Mining the microbial and biochemical dark matter of microbiomes is proving attractive not only to drug developers but for key players from other industries too, representing a potential source of solutions to many economic sectors. Demonstrating the capacity their AI tools, Meta AI (part of the former Facebook) published the ESM Metagenomic Atlas, the first large-scale structural characterization of metagenomic proteins, with more than 617 M structures, which gave an unprecedented view into the breadth and diversity of protein structures.

What should we expect in 2023?

Making predictions is difficult, especially with current market volatility and uncertainty. However, it is probable that 2023 will be a challenging year for the entire biotherapeutics sector again.

More **layoffs**, **company closures** and **industry consolidation** / **M&A activity** is to be expected. However, confidence in the field may be boosted by recent regulatory approvals, plus Seres' SER-109 **market authorization** is expected in April.

It is possible that capital originally intended for drug development could end up being invested in alternate applications of microbiome (and microbiology) technologies in lower-risk, faster-return sectors, such as **enabling technologies**, **biomanufacturing**, **biomaterials**, **agriculture** and **climate and food tech**.

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Sandwalk BioVentures is a specialty strategy, innovation, regulatory and management consulting firm focused on microbiome technologies servicing companies in the food and pharma sectors, as well as financial and strategic investors exploring to enter this field. The company has created the **Microbiome Drug Database™**, an online repository containing the most extensive and thorough analysis of biotechnology companies developing pharmaceuticals from or through the microbiome.