# 3.1 Innovative Drugs Research and Development

**2024 R&D Achievements/Highlights**


Microbio's fermentation liquid has obtained the independent/self-affirmed GRAS certification, which is advantageous for entering the U.S. market.


The pharmacology paper on MS-20 combination immunotherapy has been published in the international journal Gut Microbes.


The exploratory clinical trial on MS-20 immune checkpoint combination therapy for lung cancer was unblinded, with the results indicating that MS-20 helps to increase the anti-PD1 antibody response rate from 25% to 75%.


The mass production process of MB828 nasal spray has been optimized, and the 510(k) application will be submitted next year.

"From Micro to Macro" has been the core of Microbio's technology in new drug development. We developed our proprietary "Chemo Young" Oral Solution (Renamed as "MICRSOY oral solution" in 2024 following official approval, hereinafter referred to as "MICRSOY oral solution" or "MS-20") by applying our patented technology - "innovative in-vitro cultivation of anaerobic symbiotic bacteria" on "intestinal ecosystem recreation" and "postbiotics". In 2011, we were awarded the first new oral adjuvant license for cancer in Taiwan. By regenerating the gastrointestinal ecosystem and immune system in humans, the drug alleviates fatigue and loss of appetite in patients who undergo chemotherapy and thereby improves patients' quality of life.

### Introduction to the intestinal microenvironment

The gut microbiota is known as the "second brain" and "second immune system" of the body. It has co-evolved and coexisted with human beings until now. After the NIH's Human Microbiome Project (HMP) was launched in 2007, the European Union also launched the MetaHIT (Metagenomics of the Human Intestinal Tract) project in 2008. Since then, many countries have joined the HMP, ushered into a new era of microbiome, of which the exploration of intestinal microecology is still one of the most popular fields. NIH describes this project as another milestone in the history of science after the Human Genome Project. Key international journals have also reported that the gut microbiota is closely related to metabolites, metabolic diseases, and the response rate to cancer immunotherapy. Studies have shown that the gut microbiota regulates the immune response of the whole body through the gut-body network. Therefore, intestinal imbalance may lead to related diseases, and as a result, major pharmaceutical companies and biotech companies have entered this emerging market one after another, making the field of intestinal microbiota therapy to flourish.

### MCM Library Introduction

With our patented technology platform, the Company focuses on the in-depth research on intestinal bacteria in cancer, immune and metabolic-related diseases. We engage in the mass culture of a variety of microorganisms and design different fermentation processes based on different plant medicines. So far, we have successfully developed over 1,500 types of fermentation products. In the future, we will continue to explore the most suitable fermentation processes for different botanical medicinal materials and food ingredients through the diversified combinations of various probiotic strains, and to combine with the rapid drug screening technology to continuously develop new drugs for different indications.

# 》Research and Develop Key Technologies and Patents

## • Technology Platform Introduction

The human intestine contains hundreds of symbiotic beneficial and harmful bacteria. The beneficial bacteria can inhibit the growth of harmful bacteria, enhance immunity, and have the effect of decomposing carcinogens. Harmful bacteria will spoil amino acids, produce carcinogens, and suppress the immune system, causing diseases and promoting aging. The intestinal tract maintains a balance between beneficial and harmful bacteria, which is called "bacterial balance." Once harmful bacteria dominate, humans begin to get sick. Take cancer as an example, the occurrence of cancer has a good correlation with it. When harmful bacteria in the intestine are dominant, the protein and fat ingested in food can be easily converted into factors such as nitrosamines, phenols, and secondary bile acids that promote the growth of cancer cells. The increase in beneficial bacteria can inhibit the production of carcinogens and achieve the effect of preventing and inhibiting cancer. Therefore, maintaining the balance of intestinal flora and the activation of beneficial bacteria are closely related to human health.

Beneficial strains from the human intestinal tract are purified, acclimated, and symbiotically cultured, and then inoculated into a medium rich in botanical drug extracts to complete fermentation under optimal conditions; the fermentation broth underwent sterilization, centrifugation, filtration, concentration and maturation processes, producing the fermented botanical extracts. The biological activity of these diverse plant fermentation broths will be tested through proteosome rapid screening technology and receptor binding analysis. Animal pathological models will be used to confirm their biological activity. After pharmacology and toxicology tests and purification of active composition, they will be considered new drugs if clinical trial shows that they are effective and safe; products are formulated into various dosage forms by the application of compounding technology.

## • Introduction to Next-Generation Sequencing Technology

Amplify a small amount of DNA by a factor of 10 to 100 billion after a large amount of chain replication reaction. Then, the DNA is sequenced with a fast and accurate sequencer, and the huge amounts of DNA sequencing data are converted into gene changes and expression levels through information analysis, so that the important information in DNA can be accurately and specifically understood and used.

## • Patent Technology Introduction

Since 1997, we have established the "Innovative commensal bacteria metabolite fermentation technology" and "SymbiotaImmuRestore Platform", which are world-leading in the application of simulated human intestinal bacteria, and established a large-scale fermentation production base in 2001. It is expected to expedite the screening of new candidate drugs with "gut micro-environment modulation", and the goal is to develop the world's only gut microbiome drug that can regulate the intestinal microenvironment. To date, we have obtained 30 domestic and international patents in this field and received the National Innovation Enhancement Award in 2023.

## 》5 Major Innovation Laboratories

### • Cellular Metabolism Lab (CML)

Combine cell culture and molecular biotechnology to construct various cellular physiological function platforms, and is responsible for preclinical pharmacological activity and pharmacological mechanism research.

### • Immune Barrier Lab (IBL)

Explore how drugs affect the immune response of various parts of the body, such as the skin, nose, and intestines. Blood cells isolated from animals or humans are used as the research material to simulate the occurrence of various immune responses in the body.

### • Bacterial Culture Lab (BCL)

With the ex vivo symbiotic anaerobic culture technology, we can reproduce the intact gut microbiomes in the test tube environment, and develop a high-throughput intestinal bacteria drug screening platform with this technology, which greatly improves the efficiency of drug screening.

### • Analytical Chemistry Lab (ACL)

Its main duties include the extraction, separation, identification, and synthesis of active pharmaceutical ingredients, as well as dosage form formula design and process development, as well as product physicochemical property analysis and stability.

### • Next Generation Sequencing Lab (NGS)

The next-generation sequencing platform is used to analyze the differences in the microbiome of the intestines, skin, and nose between healthy people and patients to identify key beneficial or pathogenic bacteria, which can also be used as indicators for drug development to shorten the time schedule of drug development.

## 》New Drug Development

As of December 31, 2024, a total of 2 new drugs have obtained drug licenses:

| Drugs | MICRSOY Oral Solution (MS-20) | Herbiron Oral Solution |
|---|---|---|
| Taiwan FDA Drug Permit License No. | DOH-OM-015926 | DOH-PM-057846 |
| Image |  |  |
| Indications | Improvement of fatigue and loss of appetite in chemotherapy patients. | Alleviation of iron deficiency anemia and menstrual discomfort. |
| Description | After 14 years and an investment of more than NTD 1 billion in R&D, MS-20 obtained Taiwan's first new drug license for oral cancer treatment in December 2011 (Microbio's MICRSOY Oral Solution). In compliance with international regulations on new drug research and development, Microbio Co., Ltd.'s " MICRSOY Oral Solution underwent rigorous preclinical toxicology, pharmacology, production, and manufacturing control drug research and development, and completed Phase III clinical trials in Taipei and Shin Kong Hospital Cancer Center. It has been proven to significantly improve cancer patients' fatigue (p-value<0.0001) and anorexia (p-value=0.0005) caused by chemotherapy, and enhance their ability to maintain family and social activities (p-value=0.0226). | In December 2013, a new drug license was obtained in Taiwan. This is the second autonomously developed new drug that successfully passed the registration process in Taiwan. "Herbiron" significantly improves menstrual discomfort and iron deficiency anemia. It won the Bronze Award 2015 in the category of OTC drugs manufactured by domestic pharmaceutical companies of the National Biotechnology and Medical Care Quality Awards. |

Note: On August 16, 2024, Microbio received a notification from the Ministry of Health and Welfare regarding the name change of the oral liquid " Chemo Young Oral Solution" to " MICRSOY Oral Solution". " MICRSOY Oral Solution" oral liquid is a product developed by Microbio using a unique anaerobic co-fermentation platform of gut microbiota, branded as Symbiota. It is approved for the indication of "improving fatigue and loss of appetite in cancer patients undergoing chemotherapy." Due to its potential for ongoing research into new indications based on its post-market efficacy in other diseases, the name change to " MICRSOY Oral Solution".

# 》Research and Development Focus

After 14 years of development and an investment exceeding one billion NTD, our company has achieved a significant milestone with the MS-20. In December 2011, we obtained Taiwan's first new drug license for an oral cancer treatment, under the brand name "Chemo Young". However, due to the novelty and particularity of postbiotic products, there are no clear regulations for such products in international drug laws and regulations. The Company actively promotes medical devices and new medical foods (FSMPs) that comply with international laws and regulations to accelerate product development and launch. For our non-invasive skin/nasal microecology products, we will submit a 510(k) premarket notification to the FDA as Class I/II medical devices, and will be placed on the market only after obtaining the FDA's approval. Products for oral intestinal microbiome (such as TB90010) will enter the market as medical food, and their safety must meet the FDA GRAS (Generally Recognized as Safe) standard. In July 2024, independent experts reviewed and approved the qualification of independent GRAS. US market strategy evaluation will be subsequently performed and business cooperation will also be engaged with potential international partners

## • Development of new indications for MS-20

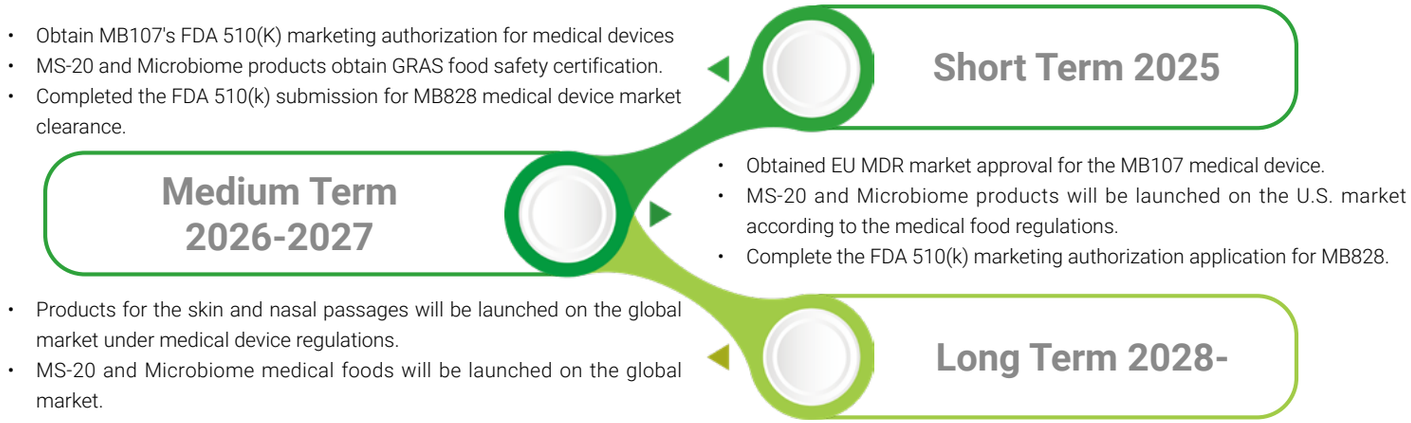
MS-20 has collaborated with a number of major medical centers and conducted multiple clinical trials, actively conducting efficacy verification or new drug development of new dosage forms or new routes. The field of new microbiome drugs has become a new direction of drug development that international pharmaceutical companies and venture capital companies are paying attention to. Therefore, the Company will actively align with international standards and continuously accelerate collaboration with internationally renowned teams. The Company will advance through clinical evidence, new drug development and international cooperation.

| Category | Immune Checkpoint Combination Therapy | Treatment of Inflammatory Bowel Disease (IBD) |
|---|---|---|
| R&D Results | • The fecal microbiota platform confirmed that MS-20 regulates the interaction of bacteria in cancer patients and increases the bacteria that respond to immunotherapy.<br>• Animal experiments have confirmed that MS-20 microbiota combined with immunotherapy inhibits tumor growth and increases CD8+ T cells in the tumor microenvironment.<br>• The exploratory clinical trial, with a plan to enroll 30 patients, will be held in 7 experimental hospitals in Taiwan to verify the safety and efficacy of the drug. The clinical results were unblinded in December 2024, and the analysis indicated that MS-20 significantly improved the immunotherapy response rate. | • The Fecal microbiota platform has proven that MS-20 can inhibit the increase of bad bacteria in IBD patients and increase the good bacteria that promote intestinal health.<br>• Animal experiments have confirmed that MS-20 effectively reduces the severity of DSS-induced colitis and restores the normal villus structure of the intestinal wall.<br>• The exploratory clinical trial, with a plan to enroll 40 patients, will be held in 4 experimental hospitals in Taiwan to verify the safety and efficacy of the drug. Unblinding is scheduled for January 2025. |

## • Innovative micro-ecological technologies and products

| Category | Micro-ecological Medical Foods | Micro-ecological Medical Devices for the Skin | Nasal Cavity Micro-ecological Medical Devices |
|---|---|---|---|
| Item | TB90010<br>Type 2 diabetes microbiome | MB107<br>AhR Booster, New Drug for Skin microbiome | MB828<br>Novel multi-functional micro-ecological nasal spray<br>Allergic Rhinitis and Chronic Sinusitis |
| R&D Results | • The results of the meta-analysis published in the top 5% journals in the field of pharmacology show that microorganisms can stabilize blood sugar and have the potential to be used as an adjuvant therapy.<br>• The clinical trial in collaboration with Taipei Medical University has been completed. Both human and animal results have shown that TB90010 has the effect of regulating blood sugar and good safety.<br>• It is equivalent to the clinical efficacy of the best-selling medical probiotics product in the United States. | • Completed the preclinical efficacy study and two clinical trials for psoriasis and atopic dermatitis.<br>• Has the effect of inhibiting Staphylococcus aureus and improving skin bacterial flora.<br>• Approved for FDA 510(K) pre-sub medical device application.<br>• Initiate a strategic assessment of the U.S. market and negotiate with international partners. | • Suppresses the Th2 immune response, with an effect equivalent to steroids.<br>• Effectively inhibits the growth of opportunistic pathogens and inhibits the formation of biofilms of pathogens.<br>• The integrity of the abdominal and nasal epithelium is repaired.<br>• Completed product efficacy confirmation and commissioned manufacturer evaluation.<br>• Initial trial mass production testing has been initiated.<br>• Prepare 510(k) medical device application documents. |

## 》Development Strategies and Goals




## 》R&D Personnel training

The new drug development industry is characterized by prolonged R&D periods, enormous funding needs, highly demand for R&D personnel with professional competence, strict legal control of R&D processes, and the need for extensive risk control. It is therefore essential to provide annual training for R&D personnel to constantly enhance their professional expertise. The following training programs have already been completed in 2024:

| Category | Name of education and training | Key content |
|---|---|---|
| New Technology Introduction | Big Data-oriented precision medicine in kidney research | Importance of data-oriented and multi-omics research on research direction and translational medicine. |
| Regulations and Quality System | MDSAP training | 1. Medical Device Single Audit Program (MDSAP)<br>2. Medical device compliance requirements of different countries<br>3. Medical device product application and certificate acquisition<br>4. Medical device risk management |
| | MDSAP Canada Reg. Training | |
| | MDSAP Training (Australia Reg.) | |
| | MDSAP Brazil Reg. Training | |
| | ISO14971 risk management education and training | |
| | Internal training workshops: 1. Internal audit regulatory requirements<br>2. Internal audit skills | |

## 》R&D Pipeline

| Drug | Category | Indication | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|---|---|---|---|---|---|---|---|
| MS-20 | Microbiome | Immuno-oncology | V | V | V | V | V ((Drug license has been obtained) |
| Herbiron | Botanical | Dysmenorrhea, Anemia | V | V | V | V | V (Drug license has been obtained) |
| MBS-COV | Nucleic acid | COVID-19 | V | V | V | | |

| Medical Food/Device | Category | Indication | Pre-clinical | FDA 510(K) Medical Device Application |
|---|---|---|---|---|
| TB90010 | Microbiome | Diabetes | V (exploratory clinical trials completed) | |
| MB107 | Microbiome | Atopic dermatitis, Psoriasis | V (exploratory clinical trials completed)) | V (USFDA 510(k) medical device application pending) |
| MB828 | Microbiome | Allergic rhinitis, Chronic sinusitis | V (exploratory clinical trials completed) | |

Microbio (Shanghai), a subsidiary of Microbio Co., Ltd., is composed of a GMP-certified manufacturing plant and a corporate HQ. This subsidiary assists Microbio Group in ongoing R&D and licensing initiatives, acquisition of drug permits, medical insurance, and marketing authorizations, expansion of marketing channels, and the search for strategic investment partners in China to ensure the availability of sufficient funding for R&D projects and sales channel expansion. Microbio (Shanghai) has obtained licensing rights for several new drugs in Mainland China as well as Hong Kong and Macao, including ON101 for the treatment of diabetic foot ulcer, FB825 for the treatment of allergic asthma, and FB704A for the treatment of neutrophilic asthma. In addition, we are also actively developing the next generation of innovative nucleic acid drugs. Among them, the new broad-acting small nucleic acid drug MBS-COV (SNS812) has obtained the results of the Phase II clinical trial, and the meeting with the US FDA has been completed. Subsequent development will be carried out according to FDA recommendations, and the Company will also actively seek commercial partners to promote international market expansion. The new drug MBS-MA01 (SNS851), a mall nucleic acid candidate drug for the treatment of obesity and metabolic diseases, has completed several pre-clinical trials, and the IND application is planned to be submitted in Q4 2025. A clinical trial will also be started. Microbio (Shanghai) accelerates the market launch of existing new drugs in China. The ultimate goal is to transform the Company into a heavyweight biopharma enterprise in China through the establishment of an international joint drug development mechanism based on out-licensing.

| Consolidated R&D expenditures and manpower | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|
| R&D expenditures (in NTD thousand) | 861,536 | 264,914 | 404,491 | 388,658 |
| R&D manpower (number of employees) | 58 | 56 | 57 | 58 |
| R&D expenditures/Operating revenue | 48.35% | 15.39% | 25.42% | 22.56% |

Refer to Microbio 2024 Annual Report p. 4.