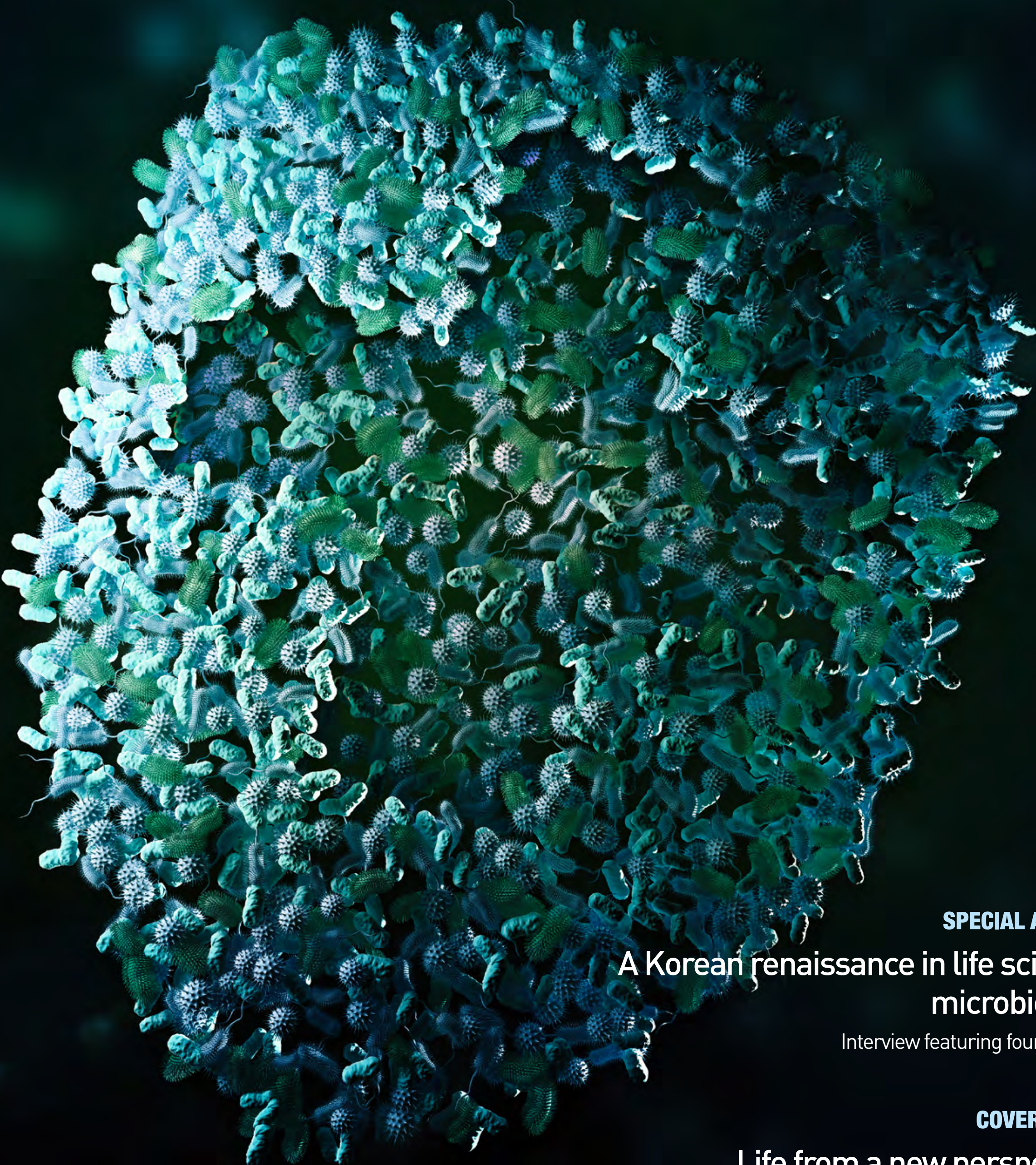
KRIBB *focus*

12th ISSUE | 2022

Microbiome & Medicine



SPECIAL ARTICLE

A Korean renaissance in life science, microbiomes

Interview featuring four experts

COVER STORY

Life from a new perspective

The body becomes a new ecosystem

Korea Research Institute of Bioscience and Biotechnology(KRIBB) is
research institute that specializes in bioscience and biotechnology.
It is the hub of national bioindustry research based on global standard research
on the origin of life and the establishment and dissemination of public infrastructures.

01

MISSION, FUNCTION & VISION

KRIBB conducts research on the fundamental principles of biological phenomena that contributes to the safe and healthy life of people and the advancement of the national bioeconomy.

MISSION

To carry out R&D activities and related projects in the field of bioscience and biotechnology in joint effort with other research institutes, academia, and industries at home and abroad

FUNCTION

Develop and disseminate sophisticated core technology in bioengineering and bioeconomy

- Innovative bio-convergence, creation of future growth engine, resolutions for the national bio-agenda

Support public infrastructures bioengineering R&D both at home and abroad

- Supporting for public infrastructure, think tank for national policy, institute that foster professionals, support for small to medium businesses towards commercialization

VISION

A Global Leader for Healthy Life and Bioeconomy

L Life-oriented · **I** Innovation · **F** Future · **E** Excellence

02

HISTORY OF KRIBB

1985. 2. Established as Genetic Engineering Research Center (Seoul)

1990. 7. Moved to Daejeon

1995. 3. Changed the name to Korea Research Institute of Bioscience and Biotechnology

1999. 5. Became an independent legal entity under Korea Research Council of Fundamental Science and Technology

2005. 9. Established Ochang branch Institute

2006. 11. Established Jeonbuk Branch Institute

SINCE 1985

THE PATH OF KRIBB

03

ORGANIZATION

DAEJEON HQ

BIO-CONVERGENCE & BASIC TECHNOLOGY

- Bio Convergence Research
- Basic Source Technologies for National Agenda
- Bio Infrastructure Hub
- Center for Domestic/Global Cooperation

DIVISION OF BIOMEDICAL RESEARCH

Personalized Genomic Medicine Research Center
Rare Disease Research Center
Biotherapeutics Translational Research Center
Immunotheraphy Research Center
Disease Target Structure Research Center
Metabolic Regulation Research Center
Genome Editing Research Center

DIVISION OF BIOMATERIALS RESEARCH

Synthetic Biology and Bioengineering Research Center
Bionanotechnology Research Center
Cell Factory Research Center
Plant Systems Engineering Research Center
Industrial Bio-materials Research Center

DIVISION OF RESEARCH ON NATIONAL CHALLENGES

Aging Research Center
Infectious Disease Research Center
Environmental Disease Research Center
Biodefence Research Center
Stem Cell Convergenece Research Center

DIVISION OF BIO TECHNOLOGY INNOVATION

Technology Transfer Center
SME Support Center
BioProcess Engineering Center
Core Facility Management Center

DIVISION OF RESEARCH STRATEGY

Korea Bioinformation Center
Biotech Policy Research Center
Korea Biosafety Clearing House
National Research Safety Headquaters

OCHANG BRANCH INSTITUTE

BIOMEDICAL RESEARCH

- Natural Pharmaceuticals Research &Industrialization
- Infrastructure Hub for Biological Resources
- Linked Development with Local Bio Cluster Cooperation

DIVISION OF BIOINFRASTRUCTURE

Laboratory Animal Resource Center
Bio-Evaluation Center
National Primate Research Center
Futuristic Animal Resource & Research Center
International Biolgical Material Research Center
ABS Research Support Center
Natural Medicine Research Center
Anticancer Agent Research Center

JEONBUK BRANCH INSTITUTE

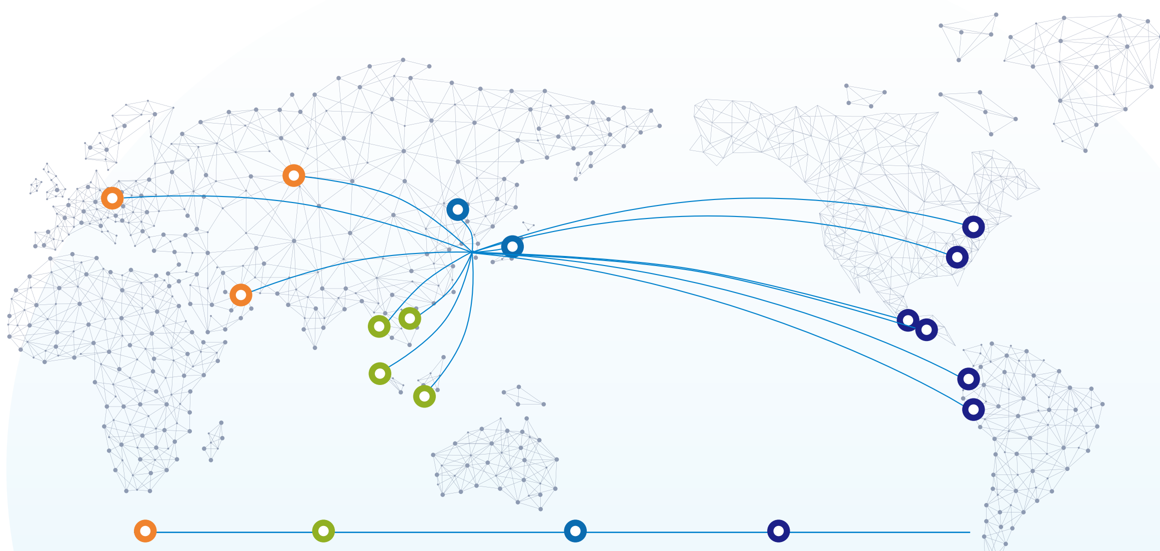
BIO MATERIALS

- Functional Bio Material Research & Commercialization
- Infrastructure Hub for Microorganisms & Cell Line
- Linked Development with Local Bio Agriculture Convergence Research

Functional Biomaterial Research Center
Microbial Biotechnology Research Center
Immunoregulartory Materials Research Center
Biological Resource Center
Primate Resources Center

04

INTERNATIONAL NETWORK



OECD
Working Party on Bio Nano and Converging Tech(BNCT)

KAZAKHSTAN
NCB

IRAN
Univ. of Tehran

THAILAND
NANOTEC

MALAYSIA
InterAcademy Panel in Biology(IAP)

INDONESIA / BPPT
Korea-Indonesia Biological Material Research Center

VIETNAM / IEBR
Korea-Vietnam Biological Material Research Center

CHINA / ISWC, YAAS
Korea -China Biological Material Research Center

JAPAN / RIKEN
Chemical Biology Joint Research Center

USA / NIH
Research Fellowship

USA
Korean-American Scientist and Engineers Association(KSEA)

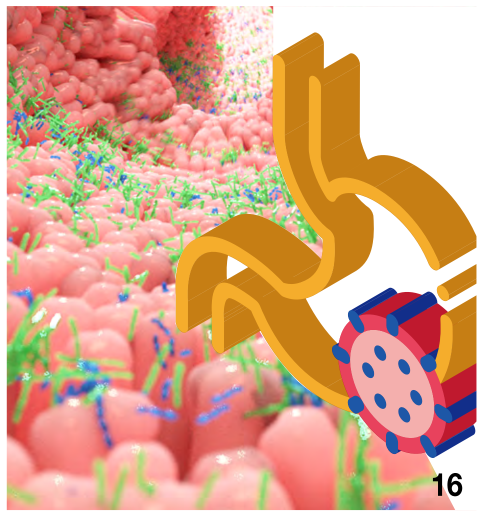
COSTA RICA / INBIO
Korea-Costa Rica Biodiversity Material Research Center

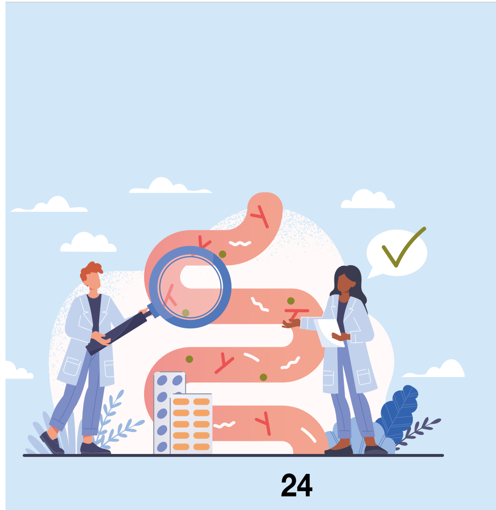
NICARAGUA / UNAN-LEON

PERU / UNALM

ECUADOR / INABIO

CONTENTS





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Public research must look to the future, not the present

Jang-Seong Kim, President of the Korea Research Institute of Bioscience and Biotechnology, nearing his second term.

"It is KRIBB's philosophy that research institutes in the public sector should not work only behind the scenes. We need to create results that make people feel imporving their lives. Therefore, KRIBB has been focusing on practicality-oriented research in the past. However, with the response to COVID-19, KRIBB's role has changed from developing the technology we need in the present to the discovery and development of the technology we need in the future."

Strictly speaking, government-funded research institutes are 'service organizations.' The starting point of Korea's government-funded research institutes was to provide necessary research services to the private and public sectors that would aid in industry growth. So, naturally, KRIBB focused on providing the knowledge and technology aligned with this policy and the industry demands. However, the emergency caused by the COVID-19 pandemic required KRIBB to take a much more active role than before to come up with a 'prepared response' to an unprecedented situation. And KRIBB did an excellent job in executing this role. Preparing for the future has been a key role that KRIBB has worked on over the years.

As the bio-industry has grown rapidly in the past two years since COVID-19, the status of government-funded research institutes, including KRIBB, has changed. In the past, the role of government-funded research institutes was 'concentration.' The strategy was to rapidly accumulate capital and grow the industrial ecosystem, with the public sector responsible for research with high prospects and uncertainties and the private sector responsible for commercialization and profit realization. In this division of labor structure, the public research and private industry played their respective roles, and the exchange of only the 'fruits of their labor' was sufficient at the time.

However, with COVID-19, it became clear that research and industry can no longer remain separate in the modern industrial environment. All fields of industry, including bio-industry, have become incomparably more complex and gigantic than their respective predecessors. However, each field was designed differently and limitations have arisen with the newly defined roles. Companies can quickly apply technology to the field, but the necessary facilities and equipment are not affordable. While for research institutes it is difficult to support essential research promptly because they cannot grasp the market's complex requirements with the limited human resources available to them. After all, research and industry must move together. Director Kim explains that these changes were a great help to KRIBB.

"I think the past two years have been a time to reflect on why government-funded research institutes are needed and what role they should play. In the past, many researchers pointed out that KRIBB should provide infrastructure services to the industry. However, since these services are burdensome, our research institute could not step forward. However, as of 2020, a consensus has been formed about KRIBB's new role."

The COVID-19 pandemic is just a starting point. From the environment to materials and energy, numerous challenges await. The 'Bio-transformation' currently in full swing is part of the preparation necessary to solve these difficult problems. Bio-transformation is not just a policy slogan but a huge change that is currently happening in the research community and industry in the biology field.

President Kim singled out three key factors for the great transformation of biotechnology: digitalization, strategic technologization, and platformization. Both biological information and research information should be digitized and accumulated as big data on the ICT platform. Numerous researchers, entrepreneurs, and policymakers should be connected and collaborate to produce the final product with the help of artificial intelligence (AI). Consequently, the field of biology will develop rapidly.

However, there are challenges that need to be addressed before this transition can take place. Korea's big biological data is of high-quality, thanks to the unique systems employed, such as e-government and national health insurance. However, more platforms are needed for the integration and utilization of such scattered data. President Kim emphasized that going forward, KRIBB, in addition to supporting the physical research infrastructure, needs to build such a platform.

"We need to effectively collect national biological data and deliver it to where it is needed. A part of such an effort is the 'National biological data Station' project. An institutional device has been prepared, and a path has been laid for KRIBB to integrate and manage domestic biological data."

Quantitative data is also a key issue. As seen in the recent trend of AI based technology, the volume of data present is directly linked to the competitiveness of knowledge. From this point of view, Korea is at a disadvantage compared to its competitors. We lack rich data from massive populations and aggressive deregulation unlike countries such as China, or quality data from extensive research networks unlike countries such as the United States. Korea's biological data strategy is to overcome these quantitative weaknesses with qualitative strengths.

"I believe that the competitiveness of data today lies in quality, not quantity. If we design and manage an efficient and sophisticated data platform, we can wisely overcome the limitations arising from the lack of quantitative data as compared to our competitors. But, of course, it will take a lot of experience to carefully analyze and apply which data is good for research. The significance of KRIBB's existence lies right here, taking the role of exploring and testing new technologies and building the foundation before rooting the system in earnest. It is difficult for companies and universities to do this, but someone must do it. I think the identity of public sector research lies here."

Recent rapid developments in science also show new possibilities. The more data are shared, the more impossible things of the past become possible in the present and future. For example, a "digital twin" of the human body can be constructed, if enough life-related information such as genetic, physiological activity, protein function, intracellular transport material, phenotype, and medical records are gathered. If we can build a digital life in this way, experiments that would have taken a long time or were difficult to conduct due to ethical and practical issues in the past could be conducted much faster and more efficiently. Moreover, what is needed here is the convergence of vertically and horizontally connected information in the digital environment.

"I once read an article that compared the game of Go to research. It is said that interest in Go has rapidly cooled after AlphaGo. No matter how hard people try, they cannot surpass AI skills. Under this situation, Shin Jin-seo, the professional Korean Go player previously ranked 9th, recently rose to the world's No. 1, it can be seen that Korean Go players are making rapid progress. I looked into how such a player could emerge despite the stagnation of the Go world and learned that he developed his skills by playing Go against an AI machine.

After reading this article, I thought this was it. Digitization changed the rules of the game. Until the beginning of the 21st century, the centers of world science and technology research were the United States, Europe, and Japan, which was because of the experience, know-how, and culture accumulated over a long period. Compared to the countries, Korea's experience in science and technology is shorter. However, digital-based data networks can significantly reduce this gap. As we are living in the era of data science, Korea can compete on an equal footing with traditional leaders, despite the obstacles."

The future of biology in Korea, as seen by President Kim, is by no means bleak. Quantity of data is important, but data-handling strategy is even more important. KRIBB set up the Digital Bio-transformation Center under the direct control of the Vice President to devise a data strategy for the development of the biology field.

Of course, exploring unexplored land is hard work and is rarely hailed. In some cases, there is criticism that the budget is invested without yielding any result. Nevertheless, despite these difficulties, KRIBB takes the lead in building a biological data platform to carry out its mission as a public research institute.

The answer lies within our bodies

HGP is a huge achievement in life science research. The human genome is too simple to explain the complexity of life through genetic determinism alone. Instead, it was clear that other factors intervened in expressing traits from genetic information. This perspective has led to various omics studies, one of the pinnacles of which is microbiome research.

Since their discovery in the 17th century, microorganisms have been an 'external factor' to humankind. Most microorganisms have been studied as pathogens or ingredients to be used in the food industry. Microorganisms are creatures completely independent of the human body and are considered foreign and physiologically harmful if they invade the human body. However, the more we understand microbes, the more apparent it is that individual microbes are not independent entities like mammals. Microorganisms constantly exchange signals and interact with each other or with other organisms. Therefore, the object of microbial research is not a single individual but a massive ecosystem in which they are gathered.

With the rapid accumulation of life science data in the 21st century, the horizon of microbial research has expanded once again. The relationship between the human body and microbes, revealed by the analysis of these data, was so close that interaction alone was insufficient to explain it. Microorganisms living in the human body exchange signals with its cells and consequently with tissues ,while also acting as a window through which the human body interacts with environmental factors. From this point of view, microbes are no longer considered foreigners and external entities to the human body. Instead, microbes and the human body are close to each other in a complex ecosystem.

The microbiome and the new medicine

Microbiome & Medicine

A Korean renaissance in life science, **microbiomes**

Interview featuring four experts

Let us be realistic. Before the microbiome market emerges, there may still be a long way to go. For over ten years, genes and stem cell therapies have attracted attention, but no "hit product" has appeared. The number of companies and researchers has increased, but contrary to traditional chemical treatments, these drugs have yet to be easily recognizable just by hearing their name. Given these precedents, the microbiome market will likely take some time to develop. Forming a proper value chain takes years, regardless of how well-established a field is. To establish a profitable microbiome value chain, it is necessary to establish adequate human resources and systems in the field. Therefore, it is essential to prepare in advance, even if the future of the microbiome market is uncertain. With experts from medicine, industry, and universities, KRIBB discussed how to prepare for the future of microbiome research.


Byung-Yong Kim Research Director, R&D Center of ChongKunDang Healthcare


Jihyun F. Kim, Professor/Director, Microbiome Initiative at Yonsei University


Ji Won Park Associate Professor/Director of Planning and Budget, Seoul National University Hospital


Jung-Sook Lee Principal Research Scientist, Korean Collection for Type Cultures at KRIBB

The microbiome changed the life science research landscape.

The discovery of microorganisms is, without a doubt, the beginning of modern life science. Nevertheless, only recently have microorganisms and their role been revealed. Microbiomes are changing the landscape of life science by establishing themselves as a field within it, just as Koch's and Pasteur's research did. What changes did the microbiome bring about in research, universities, medicine, and industry?

J. Kim _ "As someone who studies microbes, I believe we are in the middle of a renaissance in microbe research. It has not been that long since microbes were properly studied. Only a tiny fraction of microbes has been proven harmful since we started understanding the microbiome rather than treating microbes as pathogens. Most microbes are indeed harmless or even beneficial to humans. Above all, the way we view disease and health has changed. In the past, we focused on how genes and the environment affected humans. Now, we see the human body as a huge ecosystem where various living things interact."

J. Lee _ "I think it has great implications from the biodiversity perspective. Despite rationally understanding that humans are part of an ecosystem and are only one species among many, we still consider the human species special. The human body, however, is an ecosystem in which many microorganisms live, and their activities affect human health and even the brain. So, in the end, microbes are a part of us."

B. Kim _ "A change in perspective can be seen even in the budget for 2022. In the recent years, we have seen a surge in interest in the microbiome, particularly as local governments have become more involved. Pohang City is an excellent example. The late professor Charles Suh built an aseptic mouse facility and created an immune animal testing infrastructure when he began working at POSTECH. By leveraging the facility as a starting point, we are fostering research and industry related to microbiomes. Jeongeup in Jeollabuk-do, where KRIBB Jeonbuk Branch is located, is actively promoting the bio sector by utilizing the infrastructure of the Korean Collection for Type Cultures Center. In Jeongeup, Jeollabuk-do, where KRIBB Jeonbuk Branch is located, the infrastructure of the Korean Collection for Type Cultures Center is actively utilized to foster the bio sector. In addition, several local governments are taking initiatives in microbiome research, including Asan in Chungcheongnam-do, Bucheon in Gyeonggi-do, Chuncheon in Gangwon-do, and Yeongju in Gyeongsangbuk-do. They are interested in developing microbiome-related biomedical and food-related industries as profitable local industries."

J. Kim _ "There are also significant changes at school. Similar to that in Yonsei University, there is a growing trend in many universities to operate labs with a small number of elite students. In the meantime, many schools are maintaining or expanding the microbiome field. The number of researchers in this field at universities has also increased significantly. What is encouraging is that as the microbiome field grows, the collaboration between fields has also become more active. As you know, microbiome research cannot be done alone. Researchers dealing with basic life sciences and clinical studies, actual microorganisms, or resources and information, and experts in animal experiments must all come together to make microbiome research possible. Naturally, there would be many collaborations and exchanges between various departments centered on microbiome research in universities. Almost all science and engineering departments can participate in microbiome research."

J. Park _ "The horizon of clinical research has also expanded in the medical field. Microbiome research goes beyond classifying patients and identifying risk groups, as it provides reliable information for finding the root cause of disease and advising on healthy lifestyles. As a result, many people in the medical field are also attempting microbiome-related research. In the past, I also looked at patients as hosts and microbes as pathogens. But these days, I think what constitutes our body is ultimately microbes."

B. Kim _ "Perhaps because of this possibility, more than ten related companies have been established in Korea alone. The field is also diverse, from developing treatments with the microbiome, providing diagnostic tools, and personalized analysis services, and developing cosmetics. As of last year, over 200 microbiome companies launched their websites. A new market has opened up."

J. Park _ "The medical community is actively trying to apply the microbiome to developing treatment approaches, including research for psychiatric disease treatment. In particular, it has been said for a long time that the microbiome is very important in immunotherapy. The new markets that CEO Kim mentioned are intertwined with each other, broadening the horizons in the clinical field."

Microorganisms do not grow on their own.

Research on the microbiome and microbes has grown rapidly in the recent years. Industrial use and related patent applications are also active. As the subject of research and patents is microorganisms, the number of places directly managing microorganisms is increasing. However, culturing microorganisms is more challenging than one might think. Many researchers and companies are experiencing difficulties in cultivating them. Therefore, it is necessary to first prepare the infrastructure for culturing microorganisms.

"As someone who studies microbes, I believe we are in the middle of a renaissance in microbe research."

J. Lee _ "Since I work with actual microorganisms, I am pleased with what I see in the current status quo, but I also see many limitations. The Korean collection for type cultures offers microorganisms to researchers across a wide range of disciplines. The recipients, however, find it challenging to grow microorganisms in their labs. The environment must be carefully managed to keep microorganisms alive for research. In particular, among the microorganisms used in microbiome research, there are many anaerobic ones. Because anaerobic microorganisms should not be exposed to oxygen, it is not easy to distribute them due to the requirement for specialized facilities. Therefore, it is necessary to supply an infrastructure capable of cultivating various microorganisms."

J.Kim _ "The more active research is, the more attention must be paid to safety issues. Research should be conducted, at the very least, in a BSL level 2 facility to handle microbes safely. We often think that microorganisms obtained from the human body are safe because they come from us. But we do not know how or when microbes can harm us, depending on the environment."

J.Lee _ "As a depository institution, the KRIBB Korean Collection of Type Cultures Center pays particular attention to this matter. Human microorganisms are often anaerobic, making them difficult to cultivate without dedicated facilities. Additionally, when making a deposit, we check a wide range of information related to livestock infectious diseases, high-risk pathogens, and quarantine before making the deposit. Receivers are warned of the potential dangers of the deposited microorganisms."

B. Kim _ "Industry has a different set of challenges compared to research. No matter how beneficial the isolated microorganism is, it needs to be a 'product' to be used in the field. Moreover, it is industrially meaningful only when it can be obtained in sufficient quantity at a reasonable cost. Therefore, efforts such as finding a medium with a similar culture environment and low cost are required before moving to the industrialization stage."

"It is important to maintain the ratio of species or genotypes of various strains in commercializing the microbiome."

A new system must be established to suit the newly formed market.

The biggest feature that distinguishes life science from other sciences is its anomaly. As one of the essences of life is diversity, it is not easy to predict it. The same goes for the microbiome, which deals with life in terms of organisms and microflora rather than breaking it down into chemical unit elements. So naturally, a different approach from the existing medical R&D system based on chemical analysis needs to be developed.

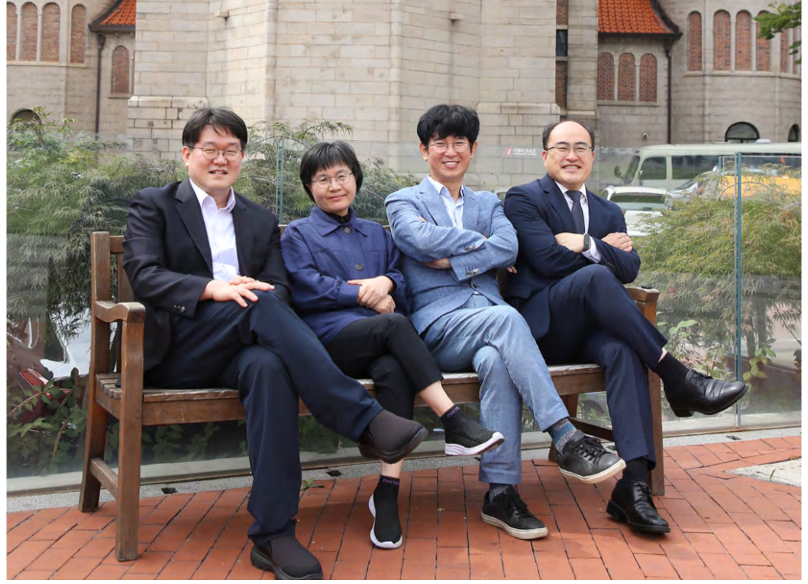
J. Lee _ "Given that the microbiome deals with living strains, the presence or absence of antibiotic-resistance genes is a new issue. In addition, when the microbiome is commercialized, several strains will be used in a mixed form, and it is also essential to maintain the ratio by species or genotype. Besides, dealing with microbial resources is a very difficult problem, even in the research field. When receiving microorganisms from the Korean Collection of Type Cultures Center, there are many things to consider when 20–30 microorganisms are mixed. Should each microorganism be stored separately for each species, or should they be cultured and stored as deposits? If preserved together, what are the dominant species, and in what proportion should they co-exist? These points must be checked one by one. In particular, when several species of microorganisms are mixed, the standards for safely managing them separately, now need to be revised. To establish itself in the medical market, the microbiome-related industry must resolve this issue."

"With institutional and legal support, we can take a leading position in the microbiome market."

B. Kim _ "The Food and Drug Administration is responding to this issue. In April 2022, the 1st microbiome guidelines were released. Guidelines for multiple genes are still incomplete, but judging from the situation, the Ministry of Food and Drug Safety is in a hurry to generate as many safety rules as possible. This is excellent news for the industry. However, since the microbiome field is developing very rapidly, it is crucial to maintain its operation flexibly so that even once established, systems or standards can promptly reflect the latest trends. As new strains continue to be discovered and classification systems change frequently, it is difficult for laws and systems to keep up with technological advances. Since Korean researchers and companies do not lag in development capabilities, they can take a leading position in the microbiome market as long as there is institutional and legal support."

J. Kim _ "Researchers also need to suggest what can be done with the microbiome. I think that researchers should identify and define what is needed in the clinical field and what is of interest to the medical community. Integrating microbiomes into cosmetics or health-functional food is close to expanding the existing area, but developing treatments is like creating a new market. The way in which products under development are approved will have a significant impact on the overall market. The field of microbiome utilization also needs to be viewed from a different perspective than existing drug development. The current drug development process assumes the development of drugs based on existing compounds. Naturally, developing biopharmaceuticals or microbiome-based pharmaceuticals as new drugs brings about many challenges. First, to develop a new drug, it is necessary to specify the active

"For exploratory work to be effective, we need a platform where clinical practice, research, and industry can effectively collaborate."



ingredient. Still, it is difficult to specify the ingredient for a drug based on living organisms. Second, microorganisms often show different characteristics even if they come from the same species depending on the culture conditions. In the case of complex strains, the problem becomes much more complicated because several species must be considered simultaneously. However, similar to stem cell or gene therapy, I believe that microbiome applications can eventually be applied clinically as a treatment method specific to the individual patient. Currently, stem cells and genetic products cannot be made into mass-produced drugs. Because controlling the activity of cells or genes perfectly is impossible, so is securing a level of safety acceptable for market sale. However, significant clinical effects can be observed depending on the patient or disease. The same goes for the microbiome. New drug development may be complex due to safety issues. However, that will not make microbiome research difficult. There are few life-threatening problems if only the pathogenicity of microorganisms is confirmed. Therefore, in my opinion, microbiome therapy has some advantages over stem cell and gene therapy."

Public research institutes must establish a 'standard' for a new industry.

Infrastructure and systems alone are not enough to develop a new industrial group. An industry's basis hinges on its ability to predict output based on input factors and structure its value chain accordingly. Therefore, standard information that anyone participating in the market can trust and follow is necessary. Standardization is the primary component of industrialization. But how do we standardize life? Who can set the standard for life?

B. Kim _ "I think what you just said is related to standardization. For a new technology to be used industrially, it must always produce the same result when the same elements are used. Therefore, using it in the industry must be simple and clear, above all else. However, as the microbiome field directly deals with living organisms, it is difficult to set specific criteria and make them standard. Therefore, it is necessary to objectify the microbiome somehow. Data is essential here. We need to create a microbiome bank to compile genetic information. Based on this information, we should be able to discover usefulness and verify safety. The product we developed this time was also born from a data-based methodology. Of course, to do so, biological resources and research data must be systematically accumulated and shared. Meanwhile, the industry should quickly absorb the findings established in academia and reflect them in practice."

J. Park _ "As a medical community member, I think we are still in the 'process' of finding our way. In the clinical field, which strain is effective for which treatment is not yet known. Effective exploration requires a platform on which clinical practice, research, and industry can effectively collaborate. When researching colorectal cancer this time, there were many difficulties in obtaining related data here and there. If something like a national data bank existed, I think we can make a synergy in earnest. The same applies to proving effectiveness or testing strains in the preclinical process."

B. Kim _ "That is why the role of the public sector research institutes is essential. For convergence between fields to succeed, an institution that places publicity as a core value should serve as a hub, avoiding complicated conflicts of interest. The fact that KRIBB is building basic infrastructure is encouraging in that regard."

J. Lee _ "As a public sector infrastructure service provider, I fully agree. The microbiome is a highly convergent field. A complex area like this needs a solid pipeline to run smoothly. Finding beneficial strains, analyzing them through bioinformatics to evaluate their usefulness, collecting evidence through animal experiments, and assessing the safety of candidates with proven efficacy are all different areas. Still, they must be linked in one chain and interlocked. Ultimately, a system that encompasses the whole process is essential for efficient cooperation between institutions and researchers in different fields. The role of KRIBB is right there."

B. Kim _ "However, we should not miss the time to nurture the private ecosystem by emphasizing publicity too much. In the end, small and medium-sized companies in the private sector should be in charge of services provided by the public sector and be able to generate profits. Only then will the industrial ecosystem be firmly established. A clear blueprint is needed to achieve this."

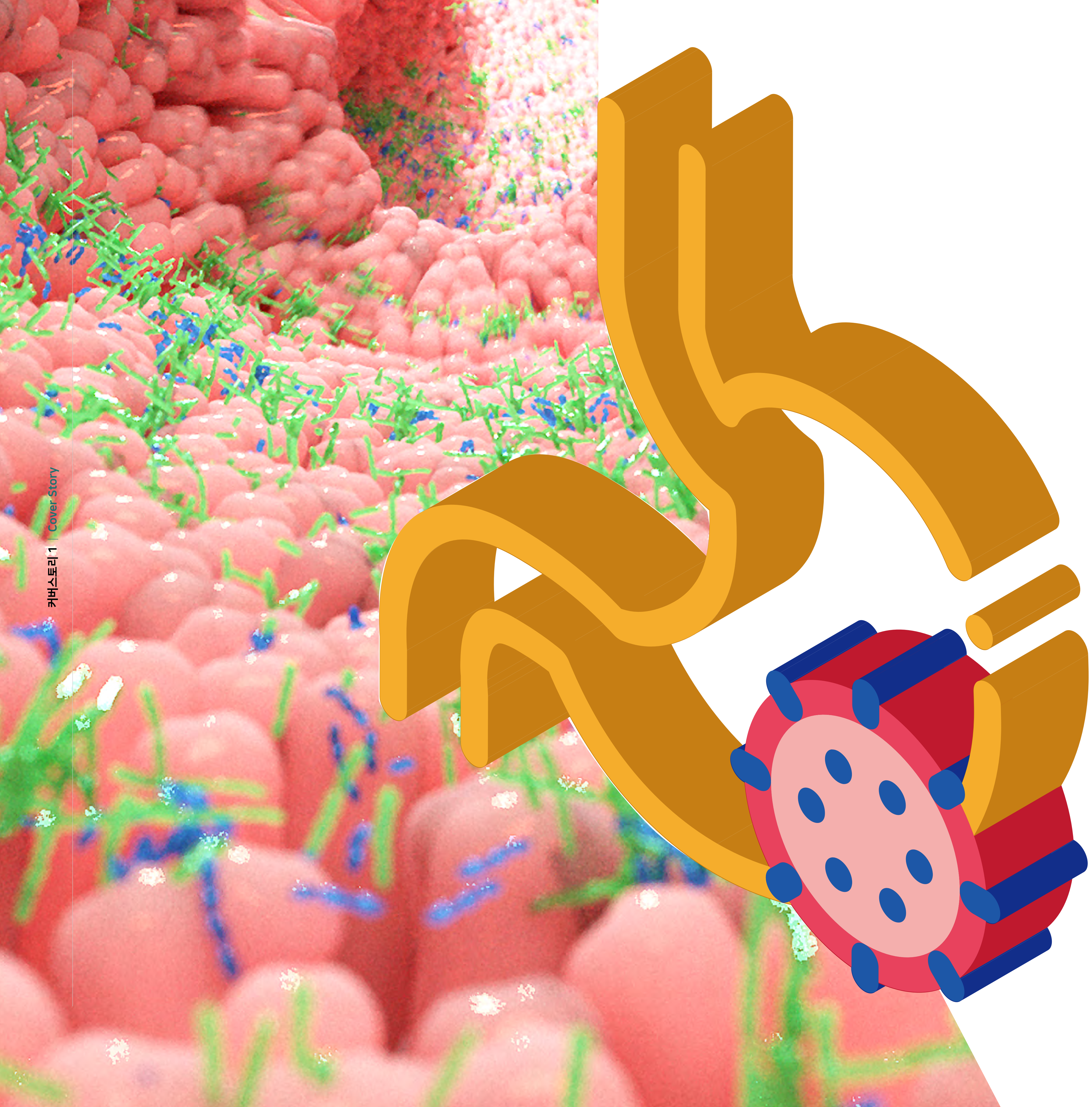
J. Lee _ "A public support service like an open lab could be a good solution. Equipment or facilities for analysis services are still needed. It would be good to provide an open laboratory in the public sector, even temporarily, and share it with private companies. With a clear goal and strategy of creating a microbiome industrial ecosystem as the premise, we need to consider what is needed at each stage and what kind of system will be efficient."

Jihyun Kim _ "Regarding the role of public sector research, I heard a story while studying in the United States. At that time, cancer research was in full swing, and there was talk in the United States about supporting cancer research at the federal government level. The most persuasive explanation was that 'it is still difficult to do in the private sector.' In a situation where it is unknown whether cancer research can actually create profits, the logic is that a private industry market will be formed only when the government provides an incentive. Conversely, it also means that there is no need for the government or public sector to step into areas where the private sector can generate profits. I think the same can be applied to the microbiome research."

J. Lee _ "In the same context, education support cannot be left out. The Korean Collection of Type Cultures Center distributes microorganisms at the request of companies. However, there are often cases where the company that received it cannot grow microorganisms properly. This is because small-scale companies lack specialized personnel dedicated to microbial culture and the infrastructure to finely control the culture environment. Even if an open lab is used, it is difficult to solve the lack of professional human resources. Therefore, I would like a system in which public infrastructure institutions such as the Korean Collection of Type Cultures Center can provide detailed instructions on cultivating microorganisms and precautions to professional personnel in companies. We would like to support companies as much as possible, but it is challenging to respond to each request with limited human resources and budget in the public sector."

J. Kim _ "We have only discussed a rosy future so far. However, it is necessary to recognize the limitations. In reality, the microbiome is by no means a panacea. Existing chemotherapy or surgical procedures may show much better efficacy. So, it has to be acknowledged that the microbiome is not a unicorn replacing the existing medical market but rather one of several avenues that go hand-in-hand with existing therapies. Furthermore, while the microbiome may be more likely to treat the cause and symptoms of a disease, that does not mean symptomatic treatment is not necessary."

In this hour-long conversation, the attendees agreed that the microbiome is by no means a universal key to solving everything. Still, it can potentially change the direction of the life sciences and bio industries. At the same time, they agreed that priming a newly emerging market like the microbiome could not be carried out solely by universities, the field of medicine, or industry. Therefore, it was also agreed that public research institutes such as KRIBB are most important in laying the groundwork according to the industry's blueprint. KRIBB has led in building core infrastructures such as the Korean Collection of Type Cultures, The Korean Bioinformation, and the Digital Bio Innovation Centers. Therefore, KRIBB is adequately equipped with all the elements necessary to establish a solid foundation for the microbiome market. The interviews with experts in each field have confirmed that KRIBB has chosen the right path.



Life from a new perspective

The body becomes a new ecosystem

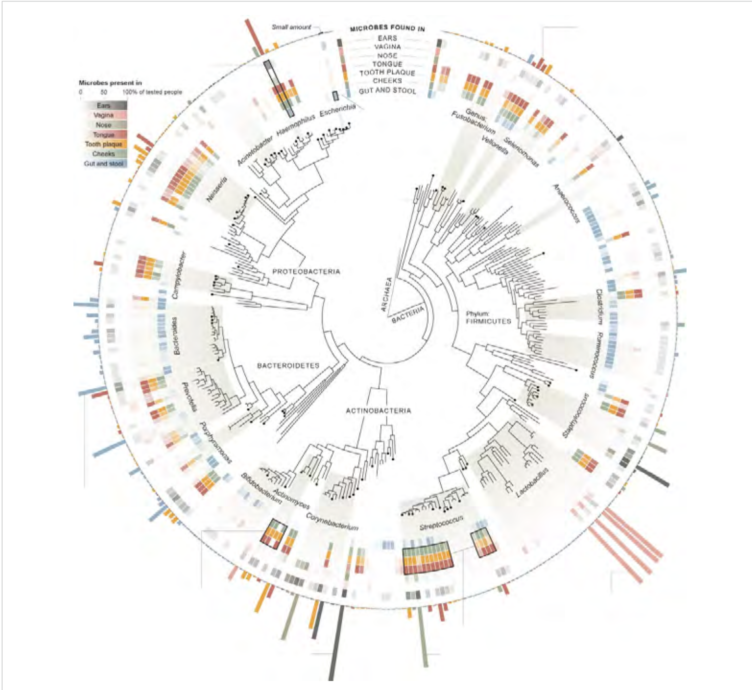
What word can replace the 'health' of the body? There is no better expression than 'balance,' which, in English, means a state of being unbiased. However, 'symbiosis' is another terminology that describes the state of balance for living organisms like the human body. As seen from the combination of the prefix 'syn-' meaning 'together' and 'bios' meaning 'living thing,' symbiosis means 'two or more different things live in harmony by benefiting each other.' Conversely, an unhealthy imbalance is called 'dysbiosis' where 'dys-' means 'bad.' So, what does it mean for a 'symbiotic body,' not just 'my body,' to be healthy?

When I look at pictures of the Earth taken from space, I am humbled by the fact that all life is contained in one blue dot. Now, let us increase the magnification of the lens and look into 'ourselves'. Interestingly, when I look through the lens, the universe unfolds inside me again, and I see a landscape where numerous living organisms, in this small universe, whose existence I have not been aware of. There are a variety of microbes here, from bacteria to archaea, and some protozoa and viruses, 500 times more in number than the stars in our galaxy.

To these small beings, the human body is a vast universe and ecosystem. They inhabit many body parts, including the skin, mouth, teeth, genitals, and the gastrointestinal and respiratory tracts. The first fact revealed through the 'Human Microbiome Project (HMP)' led by the US National Institutes of Health (NIH) for ten years since 2007 is that the number of bacteria living in the human body is greater than the total number of human cells. According to a study published in 2016, about 30 trillion somatic cells make up the human body in adult males. In contrast, bacteria, which account for the most significant proportion of microorganisms in the human body, are estimated to be more than 39 trillion. In particular, approximately 500~1,000 types of bacteria inhabit the gastrointestinal tract, which has the highest number of microorganisms with various species co-habiting. Their weight reaches to approximately 0.5~1.5 kg.

Discovery of the human microbiome

The human microbiome is a field that aims to identify the correlation between the microbial ecosystem



The Human Microbiome Project has identified microorganisms that live symbiotically in the human body. The inner line represents the taxa of commensal microbes, and the bars facing outward represent the population. As you can see from the graph, the human body forms a very complex microbial ecosystem. ⓒ Curtis Huttenhower and Nicola Segata, Harvard School of Public Health; National Institutes of Health Human Microbiome Project

inhabiting the human body and human disease and health. As the types and roles of microorganisms in the human body are known through research in this field, it has recently been revealed that these microorganisms have an important effect on maintaining homeostasis and biological and metabolic functions. However, it is relatively recent that humankind has come to view microorganisms as 'human symbionts' rather than as 'the main culprits of disease.'

The history of the microbiome can be said to have begun with the father of microbiology, Antonie van Leeuwenhoek. In 1681, he left a record that he observed 'more than 1,000 live small animals (animalcules)' while observing his stool under a microscope. Then, two years later, he described creatures on the surface of teeth. However, until the middle of the 19th century, there was no meaningful progress in studying the life he discovered.

In 1842, Scottish surgeon John Goodsir was the first to describe gastric bacteria. While examining the gastric juice of a 19-year-old patient, he discovered Sarcina, which he thought was the cause of the patient's symptoms, and tried to remove it. But the insight of German pathologist Friedrich T. von Frerichs was different. He speculated that the fungus might be a harmless symbiont that does not affect digestion.

In fact, by the end of the 1880s, the Germ Theory of Disease, which held that certain bacteria caused certain diseases, was widely accepted among doctors. This was because the causal relationship between microorganisms and diseases was being discovered at the time. For example, in 1874, Armauer Hansen of Norway found a bacillus that causes leprosy (also known as Hansen's bacillus and Hansen's disease, respectively). Subsequently, in 1879, Albert Neisser of Germany discovered gonorrhea-causing gonococci. In 1880, Karl Joseph Eberth of Germany discovered typhoid bacillus, which causes typhoid fever, and in 1881, Louis Pasteur of France discovered pneumococcus, which causes pneumonia. The theory of microbial pathogens was the representative work of the German microbiologist Robert Koch, who also successively discovered tuberculosis and cholera bacilli.

Although it became clear that fermentation, spoilage, and infection were linked to microbes, the presence of bacteria in the intestines and other body parts of healthy people was not demonstrated until the late 19th century. Austrian pediatrician Theodor Escherich first wrote about the Escherichia coli population in 1885 in the article 'Bacterium Coli Commune.' This bacterium was later named after him, the famous 'E. coli.' He detected many microorganisms in the feces of breastfed babies and adult men and studied the role and clinical significance of these intestinal florae. In addition, Henry Tissier conducted a follow-up study. He found that E. coli is anaerobic. He also extracted 'beneficial bacteria' and induced recovery of intestinal function by administering pure cultures to people with gastrointestinal diseases.

Meanwhile, in the late 19th century, the so-called "autointoxication" theory that the metabolites of the gut microbes had adverse health effects was prevalent. In response, Ilya Mechnikov (Илья Ильич Мечников) argued that as a preventive measure against self-poisoning, the intestinal microflora should be changed from harmful bacteria to beneficial bacteria. He created a new method for treating lactic acid bacteria using fermented dairy products, focusing on how healthy Bulgarian older people consume a lot of fermented milk.

Thanks to the remarkable development of biotechnology, scientists in the 20th century succeeded in isolating and detecting numerous microorganisms not only in the gastrointestinal tract but also in the nasal and oral cavities, skin, and genital organs and analyzed their genomes to conceptualize and classify microbial groups by their characteristics.

The 'microbiome' vs. "Microbiota"

Increasing knowledge about microbes in the human body has increased the awareness of the importance of the interaction between microbes and their host rather than just microbes themselves. Therefore, it makes sense that the term 'microbiome' was developed in microbial ecology during the 20th century.

In an ecological literature on plant diseases and fungi in 1988, John M. Whipps and colleagues first introduced the term 'microbiome,' a compound word of 'micro,' meaning microorganism, and 'biome,' meaning group system of living organisms. They defined this word as 'a group of microorganisms living in a unique environment with distinct physical and chemical characteristics' as 'an ecological concept established for convenience to investigate the microbial community.' In addition, they further explained that it is a term that 'comprehensively refers not only to microorganisms but also to the area in which microorganisms are active.

More than a decade later, this word started to become famous when Joshua Lederberg, known for his Nobel Prize in Physiology and Medicine, used it to suggest that the microbes living in the human body should be looked from a different perspective than before. Lederberg's definition did not contextually stray far from the usage in 1988 but primarily used the term to mean 'communities of pathogenic microorganisms that coexist in a particular

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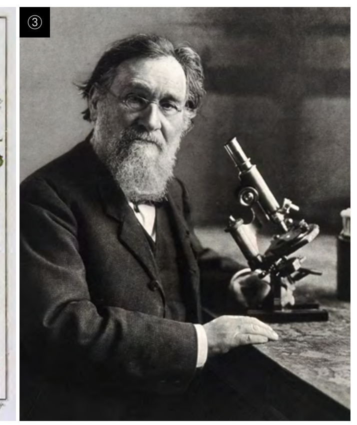

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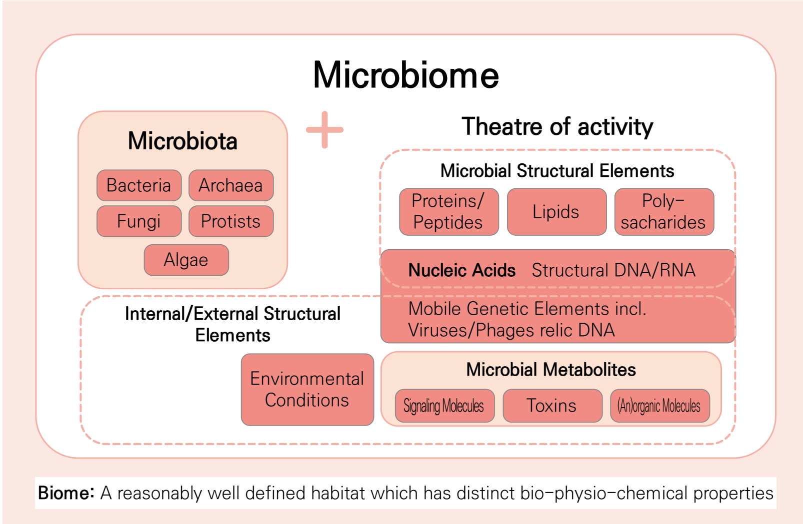
① 'Small animals' observed by Leeuwenhoek. It includes a variety of taxa, from multicellular organisms such as daphnia to protists.

② Koch established that microbes are the cause of disease. While this was certainly an accurate insight, the perception that "microorganisms are harmful" spread, creating barriers to viewing microorganisms as symbionts of the human body. A German postage stamp depicting Koch and his discovery of Mycobacterium tuberculosis. ⓒ spatuletail/Shutterstock.com

③ Metchnikoff contributed to the concept of beneficial bacteria. His research showed that microbes could be used for treatment



Metchnikoff contributed to the concept of beneficial bacteria. His research showed that microbes could be used for treatment.

environment, including the body.' At this time, he emphasized the relationship between the host and the microbes symbiotic with the host and their genomes.

Since then, the term microbiome has been mentioned more frequently, as people's interest in the human gut microbiome increased. However, this word was often misunderstood as a term derived from 'omics,' which means genome. It was also misunderstood as a 'set of microorganism genomes' and was mixed with 'microbiota,' which means only 'microorganism'.

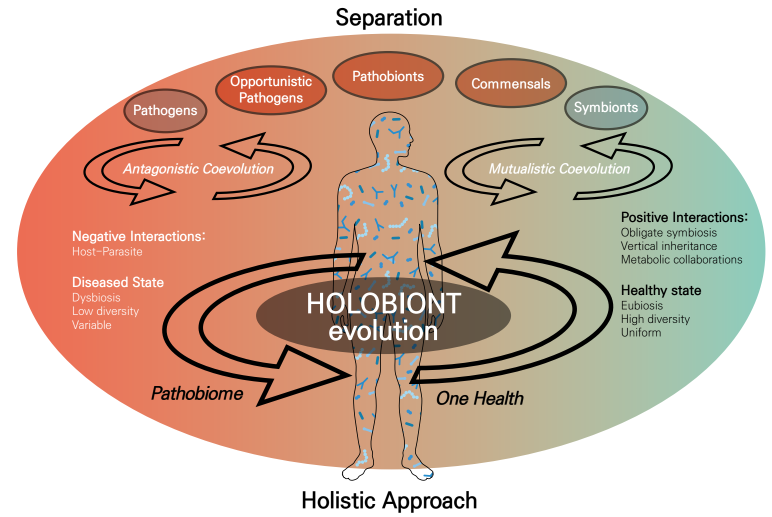
And finally, in 2020, microbiome researchers pointed out the limitations of the existing definition. As a result, they agreed to define the term more precisely and elaborately, considering the rapid development of technology related to this field over the past few decades. In the new definition, the microbiome adds several features to the original meaning by Whips and his colleagues.

Among them, the main points are that 'members of the microbiome actively interact with each other and form a spatiotemporally dynamic micro-ecosystem' and that 'they are simultaneously integrated into the surrounding ecosystem (such as a eukaryotic host) (macro-ecosystem). In doing so, they play an important role in the health and function of the organisms that serve the surrounding ecosystem.' These supplementary definitions reflect newly discovered knowledge about microbial structures and metabolites. It has also been recognized that mobile genetic elements such as transposons, phages, viruses, and other DNA components present in the environment can also interact with the microbiome. Microbiome research today focuses on the co-evolution of host and microbial communities. As a result, based on the advanced knowledge accumulated, we are taking a holistic approach to this yet unknown world.

The human body as a symbiotic ecosystem

The early achievements of microbiome research taught us that the taxonomic classification of microbes is needed to fully understand their effects on host health. Therefore, subsequent studies have been conducted using an integrated approach to the microbiome and the human host. In addition, efforts were focused on accumulating genome analysis data in a deeper and broader approach.

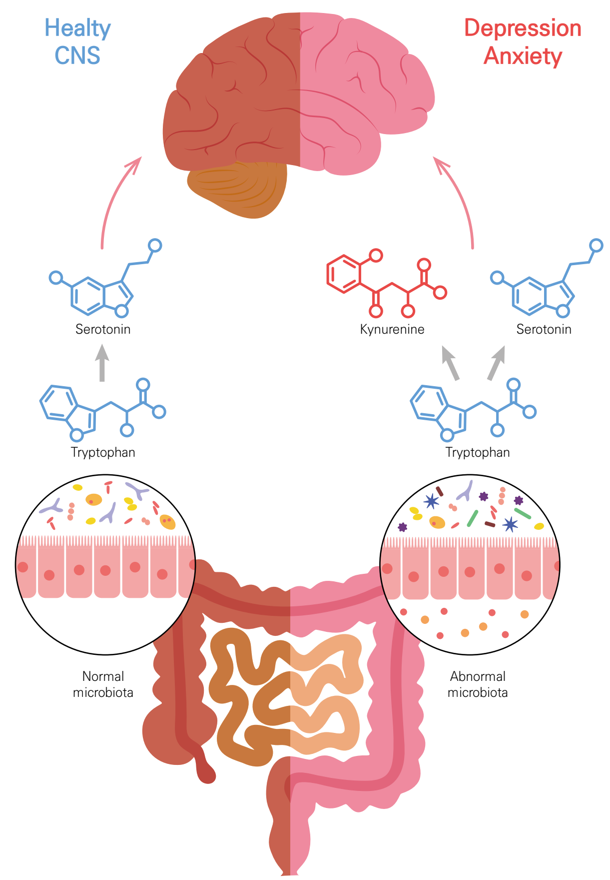
Thanks to human microbiome studies, the existence of an association between the microbiome imbalances and an increased risk of several diseases is now known. For example, it is now known that the normal intestinal microbiome is deeply involved in the development and maturation of the intestinal mucosal immune system. In particular, a specific group of microorganisms regulates the balance achieving a stable immune response by inducing differentiation and activation of immune cells. Studies related to this have shown that allergic diseases are more likely to occur if the



From a modern point of view, microorganisms residing in the human body are considered to co-evolve with humans beyond just parasitic and symbiotic levels. This includes both positive and negative effects, which means that it is not reasonable to classify human microorganisms into beneficial and harmful bacteria. Gabriele Berg, Daria Rybakova et al./Microbiome (2020)

intestinal microbiome is not formed during the neonatal period. In addition, immune disorders result if the intestinal microbiome balance is destroyed by external factors such as taking antibiotics. The diversity of microorganisms in the intestines of people with inflammatory bowel disease is reported to be lower than that of healthy people and certain bacteria dominate. In addition, associations have been found between the gut microbiome and obesity, cardiovascular disease, and type 2 diabetes. There was also a study that analyzed the vaginal microbiome of pregnant women and used it as a risk marker for premature birth.

Human microbiome research looks at the human body as an ecosystem. It seeks to improve human health by transplanting a specific microbial community into the body or restoring balance by controlling the metabolites or environment of microorganisms. To achieve these goals, a fundamental understanding of the complex interactions between microorganisms, hosts, and the environment must be grounded above all else, and an integrated and systematic approach is required. What if we expand this view further? Suppose we get away from the foolishness of seeing the world as being centered on humans and seek a balance with a holistic view by looking at the connection between humans and the surroundings as a whole. In that case, we might become better beings than before, trying to protect the coexistence of the world's large and small ecosystems.

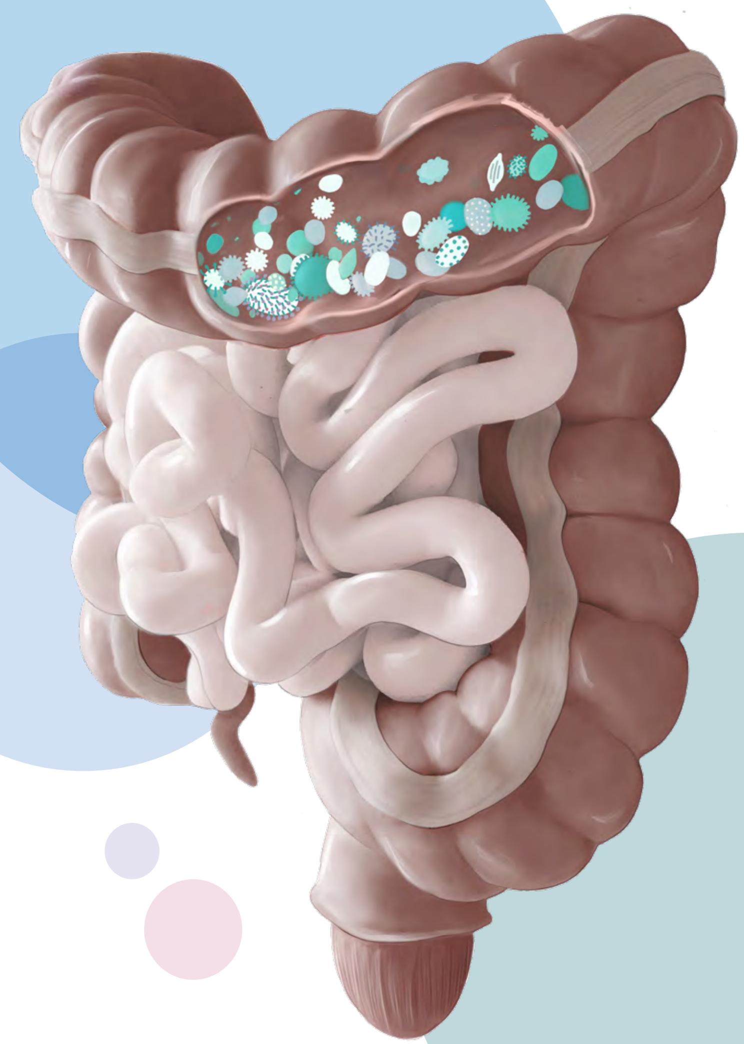


Recently, specific signaling mechanisms have been identified, along with the fact that the gut microbiome can also affect the brain through various pathways. This discovery gave rise to the concept of the 'gut-brain axis' and shows that the influence of microbes is far more comprehensive than commonly assumed.

The future of bio-healthcare lies in microbes

Standardization of Korean gut microbiome banking

There are ten times more microorganisms living in our body than human cells. The microbiome, the sum of the genes of these microbes amounts to 100 times more than that of human genes. A growing body of research suggests that the intestinal microbiome, widely distributed throughout the intestine, is closely related not only to the intestine but also to the health and disease of other parts of our body, such as skin, metabolism, mental health, and aging. Accordingly, the Korea Research Institute of Bioscience and Biotechnology (KRIBB) established an integrated database for the first time to optimize and standardize the technology for isolating, culturing, and preserving the intestinal microbiome of Korean citizens. As a result, we have built the infrastructure of a world-class gut microbiome bank system.



The gut microbiome varies from country to country, depending on the environment and culture. Therefore, it is important to secure real resources by establishing a standardized Korean-specific gut microbiome bank to study the microbiome for each disease unique to Koreans. Many studies have proven that gut microbes affect the human mind and behavior, including obesity, diabetes, cancer, other diseases, growth, development, and aging. Therefore, the impact of gut microbiome research on national health is significant. However, most of the microorganisms in the intestines live in an anaerobic environment, so it is challenging to isolate them outside the body.

Building a Korean-specific microbiome information database

Korean Collection for Type Cultures (KCTC) conducted R&D under the recognition that a new approach was needed for the environment suitable for the gut microbiome isolated from Koreans. Research and development were carried out in three stages. In the first stage, we optimized the technology to isolate and culture intestinal microorganisms from the feces of healthy adults and established an integrated database. In the second stage, we conducted a genome analysis of the isolated gut microbes, and a standardized method was developed. In the third stage, based on the integrated system established in the first and second stages, we established a bank system to preserve intestinal microorganisms beneficial for commercialization candidates. These steps will support commercialization, including clinical, industrial, and original technology development.

KCTC is Korea's best biological resources management infrastructure institution. It manages more than 32,000 microorganisms, 1,105 of which are absolute anaerobic microorganisms, and as a research institute, possesses the extensive knowledge of the practices related to symbiotic microorganisms in the human body. In this standardization of Korean intestinal microbiome banking, the institute cooperated with the Korea Bioinformation Center (KOBIC), Seoul National University, and Seoul National University Bundang Hospital.

KCTC received feces from healthy adults at Seoul National University Bundang Hospital under anaerobic conditions, isolated a total of 6065 strains, and confirmed that 323 strains were isolated through genetic analysis. In the process, we established protocols for isolating and culturing the obligate anaerobic microbiome in the intestine, and the real resources isolated through a resource rights program were databased. Accordingly, the information on each strain can be managed and tracked, and all strains are barcoded. Consequently, we have established a bank that preserves the real resources of gut microbes.

We continued and created a database that can utilize the domestic resources of the gut microbiome in an integrated manner. At Seoul National University Bundang Hospital, clinical information and fecal sample information on healthy adults were obtained together, and multi-omics analysis, such as cluster analysis, metagenome, and metatranscriptomic analysis, was conducted on the microbiome in the intestine together with ChunLab of Seoul National University. This information was incorporated into the Gut Microbiome Database (KGMB) to standardize all data on the gut microbiome. Thus, stored data can be easily retrieved in the future, and high-quality data can be used for various research and development purposes.

Set out to preoccupy the microbiome market with a solid infrastructure

The Korean-specific human gut microbial genome database constructed this way can be used in various fields including for research and industrial purposes. KRIBB has created the optimal standard for studying intestinal microorganisms for each disease. In the future, Korean-specific gut microbiome data will be the key to research on the effects of the environment and aging on diseases.

The development of bioinformatics and the standardization of Korean-specific intestinal microbial banking will increase the possibility of personalized diagnosis and medical treatment. This means that patients suffering from a specific disease can receive a diagnosis that matches their genome and gut microbiome and can advance the era in which medical prescriptions and medications can be administered accordingly.

The high correlation between the gut microbiome and human disease has become common knowledge. Still, studies comparing differences in microbial composition between healthy people and patients are in the early stages. However, it is known that the microbiome in the human intestine influences and regulates intestinal permeability, the mucosal layer, epithelial cell function, innate and acquired immune responses, and neurotransmitter secretion by forming a mutually functional network. Therefore, more advanced research on the interaction between the human body's immune and metabolic systems and the microbiome is now possible using the Korean Intestinal Microbiome Bank of KRIBB.

From an economic point of view also, this R&D is significant. The R&D protocol established through this task facilitates technology transfer and support for clinical use and industrialization. In addition, it can be used as a proprietary technology to discover new valuable microorganisms from the yet unknown intestinal microflora.

At present, the standardization of Korean intestinal microbiome banking by KRIBB, which researches and preserves the unique intestinal bacteria of Koreans, will help initiate the research in next-generation lactic acid bacteria or new drug substances. In the future, if long-term and systematic human microbiome research investments are made in line with the international trend, there will be a whirlwind of various research results on a solid infrastructure, leading to market preemption.

The emergence of new microbiome drugs

A new regulatory approach and the creation of an ecosystem for related industries must be accelerated.

Proposal for securing competitiveness in the microbiome industry

Written by_Byung-Yong Kim, Research Director, R&D Center of ChongKunDang Healthcare

The first microbiome drug was approved.

Since the launch of the Human Microbiome Project (HMP) in the United States in 2007, microbiome treatments are expected to emerge finally. In September 2022, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) under the U.S. Food and Drug Administration (FDA) made a recommendation for the approval of Rebyota (RBX2660), a candidate for the treatment of recurrent Clostridioides difficile infection (CDIs) developed by Rebiotix. Rebiotixs is a venture company established in the United States in 2011. In 2018, while conducting phase three clinical trials, it was acquired by Ferring Pharmaceuticals, a multinational pharmaceutical company in Switzerland. RBX2660 was approved ten years after it was applied to the FDA, in 2012, for the first clinical trial plan (IND).

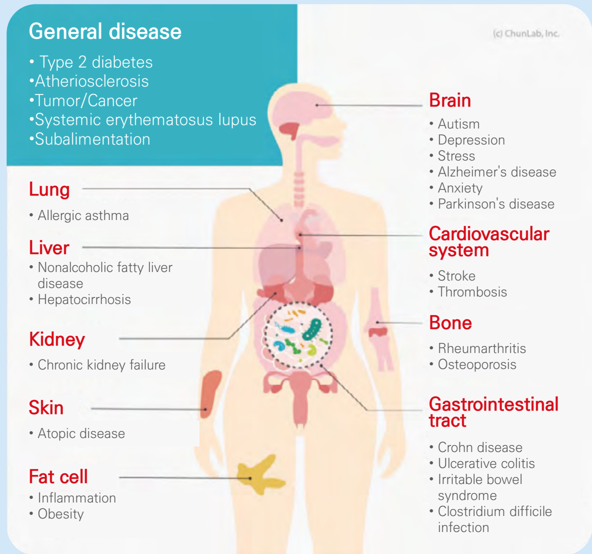
CDI occurs when long-term antibiotics are administered, beneficial microorganisms in the intestine are killed, and toxin-producing C. difficile bacteria proliferate in the intestine. Symptoms such as fever, abdominal pain, and diarrhea usually appear, and in severe cases, symptoms such as intestinal perforation or osteomyelitis accompany. Usually, it is treated with metronidazole, vancomycin, or fidaxomicin, which are used against bacterial infections. Still, if the drug is ineffective due to antibiotic resistance, it may lead to death. Recently, a novel procedure (fecal transplant, FMT), which consists of transplanting a microbial community isolated from the large intestine of a healthy person has been applied as an alternative treatment. However, since FMT is an in-hospital surgical therapy, it is challenging to manage scientific quality like pharmaceuticals, and safety concerns persist. One patient who underwent this procedure in the United States died from being infected with pathogenic Escherichia coli in 2020. RBX2660, which has been recommended for approval, has shown efficacy in improving the imbalance of the intestinal microbiome caused by long-term use of antibiotics and reducing the infection cycle of recurrent CDIs in clinical studies. Therefore, it can be an effective alternative to overcome the risks of the FMT procedure applied to recurrent CDI patients. Seres Therapeutics in the United States, is competing with its counterparts to develop a new microbiome drug, and in September, submitted to the FDA application data for a new drug product approval (BLA) for 'SER-109', a CDI treatment candidate under development. This substance has already completed phase three clinical trials at the end of last year, and has now entered administrative procedures for official marketing. The product is expected to be released soon after the final permission is approved.

Definition and use of the microbiome

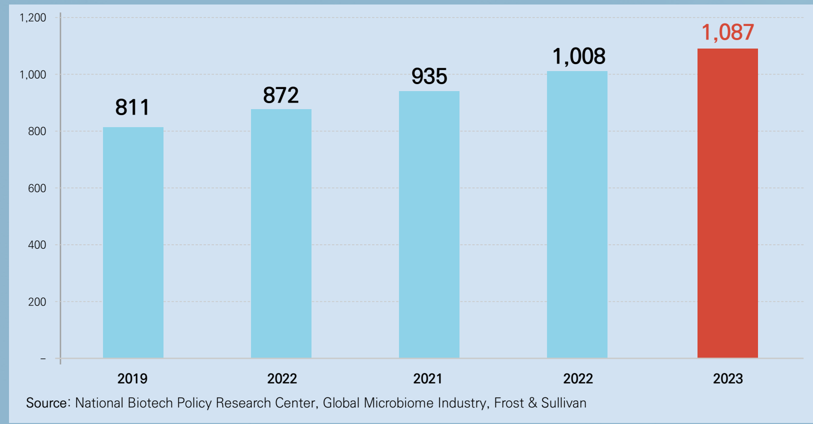
The microbiome is the sum of all microorganisms and their genomes in a particular environment. It is a compound word for microbiota, a microbial community in a specific environment, and genome, which means an individual's complete genetic information. The human microbiome is an ecosystem composed of all microorganisms in the body, including the intestinal, skin, and oral cavity microorganisms. In the case of intestinal microorganisms, the number of individual strains is about 38 trillion, and their metabolic activities and physiological functions are known to affect human health and disease. Since more than a decade ago, several global pharmaceutical companies have been studying the use of these intestinal microbes as therapeutic agents. Such research became possible after the next generation sequencing (NGS) technology was introduced. With this technology, it was possible to analyze complex microbial communities in large quantities and create big data, and the technology was used in earnest for disease diagnosis and treatment development.

Trends in the microbiome Industry

As microbiome treatments are about to be commercialized, the



The association between the microbiome and human disease



Global microbiome market forecast by Frost & Sullivan

related market is expected to expand rapidly. Since the microbiome market has been formed, securing leading technologies will enable us to gain a competitive edge in preoccupying the market in the future. The global microbiome market is growing rapidly, with an average annual growth rate of 7.6%. According to Frost & Sullivan, a global market research firm, the global microbiome market is expected to grow from approximately $80 billion (approximately KRW 100 trillion) in 2019 to approximately $110 billion (approximately KRW 130 trillion) in 2023. In terms of market size by region, the North American market is the largest and is expected to reach 50 billion dollars (approximately KRW 60 trillion) in 2023. The European market is expected to grow by 33.6 billion dollars (approximately KRW 40 trillion) in 2023. Asia is the fastest-growing market and is expected to grow at an average annual rate of 10.2% to 24 billion dollars (approximately KRW 30 trillion) in 2023.

In preparation for the rapidly developing microbiome industry, large-scale projects have been carried out in the United States and Europe for several decades. The United States started microbiome research in earnest by conducting the Human Microbiome Project (HMP), investing more than 1 billion dollars for ten years starting from 2007. Europe launched the International Human Microbiome Consortium (IHMC) in 2008 to share data with the global scientific community. Since then, academic conferences have been held regularly, and this year, the 9th conference is scheduled to be held in November in Kobe, Japan.

The Korean government has also invested in and supported microbiome research for several years. Since 2016, with funding from the Ministry of Science and ICT, the National Research Foundation of Korea's bio and medical technology development project, "Establishment, utilization, and development of a public-based Korean intestinal microbiome infrastructure system" has been carried out for eight years. Korea Research Institute of Bioscience and Biotechnology (KRIBB), the host organization of this project, analyzed the metagenome of the Korean gut microbiome and established a database by isolating real resources from medically healthy people. Identified real resources derived from the gut microbiome are distributed to domestic researchers through the Korean Gut Microbiome Bank (KGMB) website to actively support domestic microbiome research and commercialization. The Ministry of Food and Drug Safety formed a consultative body to support microbiome commercialization in April and established guidelines for developing live biotherapeutic products (LBPs) as novel drugs. Other ministries also established their R&D tasks tailored to each industry sector.

In line with this trend, domestic pharmaceutical bio companies are also making great efforts to develop microbiome treatments. In September, Chong Kun Dang Bio (CKD bio) established a joint clinical research center with the Yonsei University Medical Center's Industry-University Cooperation Foundation. It started clinical research to develop a microbiome treatment and plans to focus on research on diseases with a high demand for treatments, such as inflammatory bowel disease (IBD), Alzheimer's disease, and respiratory infections. In addition, Yuhan Corporation has invested in several companies in the field of microbiomes and probiotics. It made strategic investments in Mediogen and GI Biome, and in September, it secured a stake in AtoGEN and became the largest shareholder. Based on this, research on functional lactic acid bacteria will be expected to be conducted in parallel with research on microbiome treatments.

Genome & Company is conducting phase two clinical trials for gastric cancer with its microbiome treatment 'GEN-001." In March, it signed a joint development contract with Merck (MSD) of the United States and is preparing for phase two clinical trials for bile duct cancer, in which GEN-001 is administered in combination with MSD's immune anti-cancer drug 'Keytruda (ingredient name: pembrolizumab).' Last year, the company acquired List Biological Laboratory (List Labs), a US microbiome consignment development, and manufacturing (CDMO) company, and entered the microbiome drug CDMO business. KoBioLabs is conducting phase two clinical trials for its candidate substance 'KBL697' as a treatment for psoriasis and IBD and has also completed phase 1 clinical trials for atopic dermatitis and asthma. In March, it signed a joint research and partnership agreement with Celltrion for microbiome-based treatments.

Earlier this year, CJ Bioscience was launched by acquiring ChunLab, a microbiome company listed on the stock exchange. The company also focuses on microbiome treatments. They develop drugs for intestinal and liver diseases and combination treatments with immuno-oncology drugs using intestinal microbes. CJ Bioscience is evaluating the efficacy and safety of strains based on its big genomic data, which is globally recognized for its excellence and is also securing immunological data from related clinical trials. It plans to apply for an Investigational New Drug (IND) to the US FDA within the year. In addition, companies such as Kolmar Korea and Ahn-Gook Pharmaceutical are actively investing in the microbiome field.

Challenges in developing microbiome drugs and overcoming them

Approval and launch of new microbiome drugs, which seemed opaque just a few years ago, have become visible. Therefore, it is expected that competition for products from domestic and foreign companies specializing in microbiome will intensify. However, it is true that there are still negative concerns regarding treatment using intestinal microbes. Although microbiome therapeutics have the advantages of low toxicity to the human body and high potential efficacy for the prevention, diagnosis, and treatment of chronic diseases, there are still many difficulties in developing them as pharmaceuticals. For example, regulations on microbiome-based medicines have yet to be fully established internationally. The terms are even interchangeable with other terms, such as LBPs and pharmabiotics. Even at the stages of development, production, permit acquisition, and approval, there are many complicated hurdles. For example, 'difficulty in identifying the mechanism of action (MOA)' and 'standardization of production for multistrain-based drugs' are major obstacles during the development stage. In particular, since most intestinal microorganisms are anaerobic strains, mass culture is complex, so chemistry, manufacturing, and control (CMC) are challenging while increasing productivity.

Addressing these challenges requires a regulatory approach that is different from that for the existing pharmaceutical industry. Research capabilities on the efficacy and safety of materials are essential, but efforts in the development stage to strengthen product quality, including production facilities, will also be critical. In addition, we should support related industries, such as the CDMO project, to activate relevant ecosystems at the same time. Currently, most microbiome companies in Korea produce and procure samples needed for clinical trials from abroad. Therefore, the pace of clinical trials by Korean companies is delayed compared to that by foreign pharmaceutical companies. As such, securing microbiome-specialized culture facilities by the government or private sector will be an alternative solution. It is believed that international competitiveness will be enhanced only when actively coping with newly emerged industrial fields through this close cooperative relationship between the public and the private sector.

Researching microbiome-based **metabolic disease**

Myung Hee Kim, Associate Director, Microbiome Convergence Research Center

The microbiome field has become a blockbuster in biotechnology. It is a young field that is still getting a lot of attention, but the world is coming to the same conclusion. It is clear that gut microbes have specific effects on human health and disease, and understanding the mechanism of this interaction will be a breakthrough in treating chronic diseases and developing new drugs. The United States has already developed a new drug using the information on microbiome and is waiting for review by the US Food and Drug Administration. Korea, which has the best talent and technology in the biotechnology field, is also accelerating research and development. The government will promote the 'National Microbiome Initiative' and invest a total of 1.1506 trillion won by 2032. How will microbes change our lives? We met Dr. Myung Hee Kim of the Microbiome Convergence Research Center at the Korea Research Institute of Bioscience and Biotechnology, who studies the interaction between humans and microorganisms, and diagnosed the future.

Started with fun, thinking about what it means to be a scientist

While infection, microbiota, and microbiome are key words that describe the career of Dr. Myung Hee Kim, she graduated from Chungnam National University with a degree in Food and Nutrition. Dr. Kim's firm stance about her graduation period was "I did not really like the study." She was introduced to microbiology when she entered a master's program in the early 1990s. It was at this time that she finally found the fun.

What made research fun according to her was the academic research program in association with Chungnam National University and the Korea Research Institute of Bioscience and Biotechnology. "I took the lecture at school and learned the latest research techniques in molecular biology, microbiology, and enzyme engineering by designing studies and conducting experiments at the Life Research Institute. I guess I was lucky. Because the research complex is located in Daejeon, I, as a student at Chungnam National University, benefited from it. During this time, I focused especially on studying enzymes produced by microorganisms."

Dr. Kim studied lipase, a fat hydrolase while researching enzyme engineering. After her doctorate, she naturally turned to the field of structural biology, which explores the three-dimensional structure of proteins, and knocked on the door of a laboratory analyzing the structure of lipolytic enzymes. This was another turning point for Dr. Kim. "A professor at the University of Virginia who explained the lipase structure gave me a letter. He mentioned in his letter that his laboratory no longer studies lipase but analyzes the structure of proteins related to brain diseases. He told me that I was essential for his lab because my background was specialized training in protein purification. It was a very kind letter. So, I started researching brain diseases without applying anywhere else."

Until then, she had only looked at microorganisms, but studying the human body and the interaction between the human body and microorganisms had never been so much fun for her. Dr. Kim studied the brain, cell, and structural biology in Virginia, which later lead to microbiome research. Dr. Kim says that her years in Virginia were not only a turning point for her in terms of her studies but also gave her a chance to reflect on who she was as a scientist and what 'her science' was. The inspiration for such thinking came from Prof. Zygmunt Derewenda.

"Prof. Derewenda made me think about the ultimate purpose of my research. He said that identifying the structure of a protein is important, but it is just a technology in itself, not academic research. He emphasized why the structure is important, which site of the structure is associated with which disease, from the viewpoint of cell biology and immunology, and verification through animal models. In short, I learned about science as a convergence activity that can solve human problems."

That was one of many things she learned from Prof. Derewenda. She was even taught the details of scientific work, including how to write cover letters to editors when submitting her papers to journals. Her experience helped her establish herself as a serious and credible scientist who communicates and appeals to her fellow scientists about her research. She was the first Korean female postdoctoral fellow at the University of Virginia, Charlottesville, USA.

At the University of Virginia, Dr. Kim studied the brain's 'neuron migration protein.' Nerve cell migration protein is a protein that moves nerve cells to their designated positions. Mutations in this protein can cause problems setting neurons in place during the fetal period, preventing the normal development of brain structures. As a result, it can cause diseases such as mental disorders and epilepsy. The paper dealing with the neuronal migration protein was published in Nature Structural Biology in May 2003.

Since 2004, she has been assigned to the Korea Life Research Institute, where she studied interactions and infections between the human body and microorganisms, in earnest. Her representative research investigates the survival mechanism of Vibrio sepsis bacteria in the human body. Among patients with Vibrio septicemia, patients with chronic diseases are more likely to convert to sepsis, and the mortality rate at the time of conversion is ≥50%. Dr. Myung Hee Kim and her co-research team uncovered the mechanism by which Vibrio bacteria enter the human body and how they survive, grow, and become pathogenic.

When Vibrio vulnificus infects the human body, the bacteria require an energy source for its own survival and growth. At this time, metabolism begins to use N-acetylneuraminic acid present in the human intestine as an energy source. Therefore, metabolic intermediates are produced when Vibrio bacteria metabolize in the human body. The research team found that an intermediate metabolite called N-acetylmannosamine 6-phosphate (ManNAc-6P) modifies the structure of the NanR protein by binding to the NanR protein of septic bacteria. When the NanR protein structure is modified, the expression of metabolic genes in Vibrio bacteria, which metabolizes N-acetylneuraminic acid in the intestine and uses it as an energy source, increases, which exerts pathogenicity.

Microorganism, the endpoint of the quest for health

Dr. Kim realized through her research that the microbiome is closely related to the human body and diseases. The microbiome is a compound word of microbiota, which means a microbial community as a collection of all microbial genomes existing in a specific environment, and genome, which means all genetic information of an individual. Of particular note, is the gut microbiome.

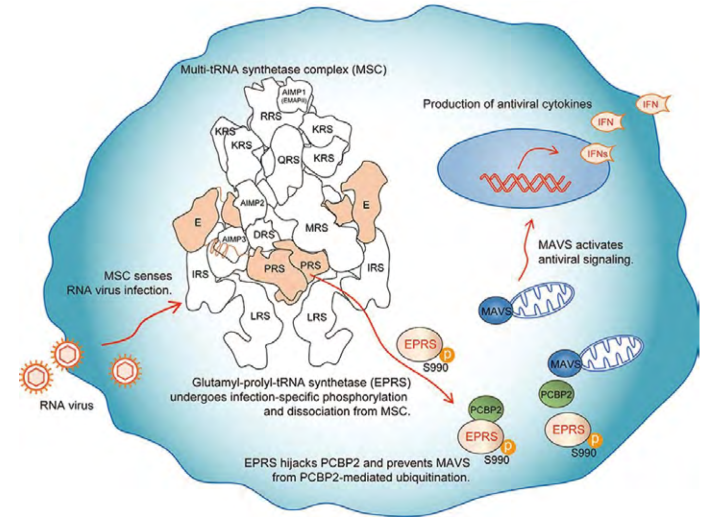
“After studying the interaction between pathogenic microorganisms and the human body, I realized that the microbiome cannot be overlooked. Because the microbiome coexists with the human body, it interacts in a very complex way. Therefore, I initially did a research project on the relationship between the microbiome and metabolic diseases. From 2014 to 2015, we conducted a study to compare the genomes of the feces from healthy individuals by analyzing the genomes of microorganisms in the intestine isolated from fecal samples.”

Myung Hee Kim examining the presentation materials. Dr. Kim has pursued to identify the relationship between the human body and microorganisms.

And since then, microbiome research has developed at a breathtaking pace. In the United States, metagenome research projects such as the Human Microbiome Project, similar to the Human Genome Project, which analyzes the entire human genome, revealed about 3.3 million unique genes in the human colon alone, 150 times the total number of genes. The human microbiome performs various functions, such as immune system development, pathogen defense, and energy metabolism.

In addition, over the past decade, innumerable studies have shown that the microbiome is involved in various diseases. For example, in the brain, autism spectrum disorders, Alzheimer's, and Parkinson's diseases; in the lungs, allergic asthma, cardiovascular disease, rheumatoid arthritis; in the gastrointestinal tract, Crohn's disease and ulcerative colitis; in the liver, non-alcoholic steatohepatitis, liver cirrhosis, etc. There are too many to list them all.

“The fact that there is a causal relationship between the intestinal microbiome and disease has been strongly proven through clinical treatment analysis for many patients in a short period. Now, the important thing is to identify the mechanism by which this microbiome causes disease or, on the contrary, makes the human body healthy. If this is done, innovations will occur in the entire process of diagnosing, treating, and prognosing diseases and developing new drugs.”



The antiviral immunomodulatory function of protein synthase complex (MSC). Upon recognizing the virus infection, MSC releases EPRS, a component protein, and binds to PCBP2 protein, which carries out MAVS degradation. This protects the MAVS protein, induces activation of MAVS-mediated antiviral immune signal transduction, and promotes antiviral cytokine secretion, in turn suppressing viral proliferation. Dr. Myung Hee Kim, recognized for this research, was awarded the Science and Technology Award of the Month in November 2018.

The beginning and the end of the microbiome, big data

Microbiome research is basic research that uncovers life phenomena and is essentially a convergence science in which many fields come together. How microbes and their associated proteins form and function at multiple levels, including the molecular level, requires collaboration among omics, immunology, and cell and structural biology. The precision medicine and customized treatment we hope for in future healthcare can only be achieved when convergence scientific research on the microbiome is conducted.

“Even if you take the same medicine, the effect is different for each individual. The reason is obviously the gut microbiome. Microorganisms are responsible for metabolizing drugs in the intestine. Therefore, depending on how healthy my microbiome is, the same medical intervention can have different effects on me. When developing personalized medical diagnosis and treatment in the future, the microbiome cannot be left out, and Korea is preparing various policies and support for this scenario.”

However, even so, there are still challenges to be addressed to promote microbiome research in Korea. Since the microbiome is classified as a clinical sample, it must undergo a rigorous review by the Research Ethics Review Board. Despite the need for this process, it is so complicated that it takes months for the research to begin.

In addition, microbiome research is fundamentally a big data study that requires systematic handling of numerous biological information. To conduct big data research, we must accumulate a lot of information. However, Korea's microbiome clinical big data is still small compared to that of overseas. “For example, we do not collect and analyze feces from cancer patients in medical settings. Data on what kind of microbiome composition cancer patients have must be accumulated so that we can extract truly meaningful information from it.” Therefore, what Dr. Kim wants from the Korean government, which supports microbiome research, is not much. One is to reform the research approval process to be efficient, and the other is to build a nationwide system that can accumulate valuable data.

“In the future, microbiome data will be a tremendous asset that can improve public health. Creating a social structure that allows such information to be collected and analyzed well is not difficult.

According to Dr. Kim, communication is the most crucial skill for a modern researcher since research cannot be done alone in this age. Dr. Kim's laboratory is also home to researchers from various fields, so mutual conversation and discussion are crucial.

The first new microbiome drug will be released soon. Taking over the market for the first time will be significant and have great ripple effects. It also indicates that Korea may fall behind if we do not hurry. There is no system for microbiome clinical trials in Korea yet, and I hope the government will hurry to solve this problem."

Scientists must be able to communicate.

As a scientist who has made significant achievements in convergent research, Dr. Myung Hee Kim emphasizes convergence research and communication between scientists above all else. "Our laboratory is based on structural biology and biochemistry, but experts from various fields participate and collaborate. Lab members include PhDs in Immunology, Cell Biology, and even Veterinary Medicine. Such experts can benefit from discussing and researching a topic in multiple layers. At daily lab meetings, I always think, 'Oh, why did I not think of this?' This means that it prevents me from falling into the risk of being locked in my resume and asking narrow questions about the research topic."

Dr. Kim applies this philosophy to education as well. When a student gives a presentation in Dr. Kim's laboratory, they are asked questions from various aspects, such as immunology, structural biology, and zoology. After one year like that, they will be equipped with the qualities of a convergence scientist who can draw a big picture. "When a student first comes to my lab, I emphasize communication first. Discussing with other experts is more important than conducting my own experiments. For example, suppose you have identified the structure of a protein. From a structural biology point of view, the fact that the structure is important is not very meaningful. You need to be able to convince what the structure means from an immunological point of view, from a cellular point of view, and on an animal model. You must present evidence from a convergence point of view, and communication makes that possible."

If you feel a sense of déjà vu, you saw it right. Yes. This is precisely the way Dr. Kim was trained as a postdoctoral researcher. There is no single cause for the painful diseases that humans suffer from. How can one principle explain the incredibly complex life phenomenon of the interaction between the human body and the microbiome? There may be no such principle. Nevertheless, scientists are trying to figure out this complexity somehow. This is the scientist's attitude. Dr. Kim's career as a scientist was also the process of forging this attitude. Until the day the microbiome dramatically improves human health, people in various fields will inevitably undertake the difficult task of finding clues in this incredibly complex research.

From an advisor and a student to a colleague **who makes artificial proteins together**

Euijeon Woo Principal Researcher, Disease Target Structure Research Center
| **Kwang Hyun Park** Senior Researcher, Critical Diseases Diagnostics Convergence Research Center

When you teach someone, you are drawing their future. If you are a teacher, you will feel strange when you see the future next to you—simultaneously feeling proud that your disciple has finally grown up enough to share his thoughts with you and the feeling of wanting him to surpass you. Therefore, the relationship between teachers and students who meet again as colleagues may be unique. Dr. Euijeon Woo and Dr. Kwang Hyun Park met as an advisor and a student, respectively, at the University of Science and Technology (UST) and have now become colleagues at the same Research Institute. Hear about their 10-year special relationship with the Life Research Institute.

UST and Life Research Institute forged their relationship

The relationship between the two began in 2010 when senior research scientist Park graduated from university and interned in the laboratory of principal investigator Woo.

“Originally, I applied elsewhere, but the atmosphere was very depressing. However, Dr. Woo welcomed me warmly right from the beginning. I had a bit of a fear of animal testing, where I had to kill mice or draw blood. Because I wanted to continue my biological research and also because Dr. Woo's laboratory does not conduct animal testing, I was attracted to his group.”

Dr. Woo's laboratory researches on revealing the structure of proteins. He has mainly used X-rays to identify proteins' three-dimensional structure and function.

Not unexpectedly, Dr. Park went on to graduate school at the University of Science and Technology (UST) after doing an internship and continuing his laboratory life. UST is a graduate school of national research institutes jointly established by government-funded research institutes to foster professional researchers. Unlike graduate schools of most universities, it is characterized by appointing excellent researchers from government-funded research institutes as faculty members to focus on research field-oriented education and fostering talents who can be immediately utilized in industry and research fields. The Korea Research Institute of Bioscience and Biotechnology has worked hard to establish an education system and major courses since the establishment of UST.

Dr. Woo has guided students since 2004 as an adjunct professor at UST. Dr. Park has also become a UST faculty member and guides students. This time he took on two students for the first time.

“UST is more focused on research than most graduate schools. So there are advantages and disadvantages. First of all, since the place is a research institute, experimental equipment is well prepared. Unfortunately, the classes are not as diverse as those in regular graduate schools. Because there is no idyllic atmosphere here commonly associated with universities, some students may find their lives difficult. Unlike most graduate schools where you can recharge even when you are having trouble in the lab, there are only research institutes here, so you have no choice but to focus on research."

“From the perspective of a fresh graduate, life at UST can be both an advantage and a disadvantage, depending on which professor you meet. If you meet a competent advisor, you will write many good papers and learn much before graduation. But there are many cases of the opposite. General graduate schools are similar, but there is something average there. However, it seems that there are many polar opposites in UST. So this time, my first goal is to develop the thinking power of the students I supervise for the first time. I do not have a teaching philosophy as of yet because my experience is still short. However, I am teaching while considering what is more important than a good thesis or research performance in graduate school.”

The supervisor-student relationship evolved into the colleague-colleague relationship in the

institute.

Even after graduating from UST, Dr. Park continued research as a postdoctoral researcher in the laboratory of Dr. Woo. In the meantime, the Life Research Institute needed a protein structural biologist, and Dr. Park was hired because he was the right person. Of course, it is not uncommon for a researcher to remain in a laboratory for such a long time and continue his career, but what particular reason made him make that choice? Dr. Park laughed, saying, "It seems to be the will of heaven."

"The subject of research has changed every time. life are all well-balanced. I have seen many researchers, but at the Life Research Institute, I respect Dr. Woo the most."

Formerly an advising professor and a supervising student, the two are now colleagues at the same research institute. Dr. Woo expressed, "It is reassuring that he became a colleague with whom I can share difficult tasks."

Dr. Park laughed, saying, "Dr. Park is such a gentle person. Even as a student, I never had a tough time with him, so nothing has changed." He added, "He is the only person at the research institute I can confide my heart to."

Euijeon Woo, Principal investigator at Disease Target Structure Research Center (left), and Kwang Hyun Park, senior researcher, Critical Diseases Diagnostics Convergence Research Center (right).

Whenever I thought about where to do my best research, I always concluded that this is the best environment."

Dr. Woo is very grateful to Dr. Park, who has made those decisions.

"The pride of our lab is that no students quit midway, and everyone is friendly. Not only do we meet often, but we also have family gatherings, so all members are close. Dr. Park is the one who created this atmosphere, so I am very grateful."

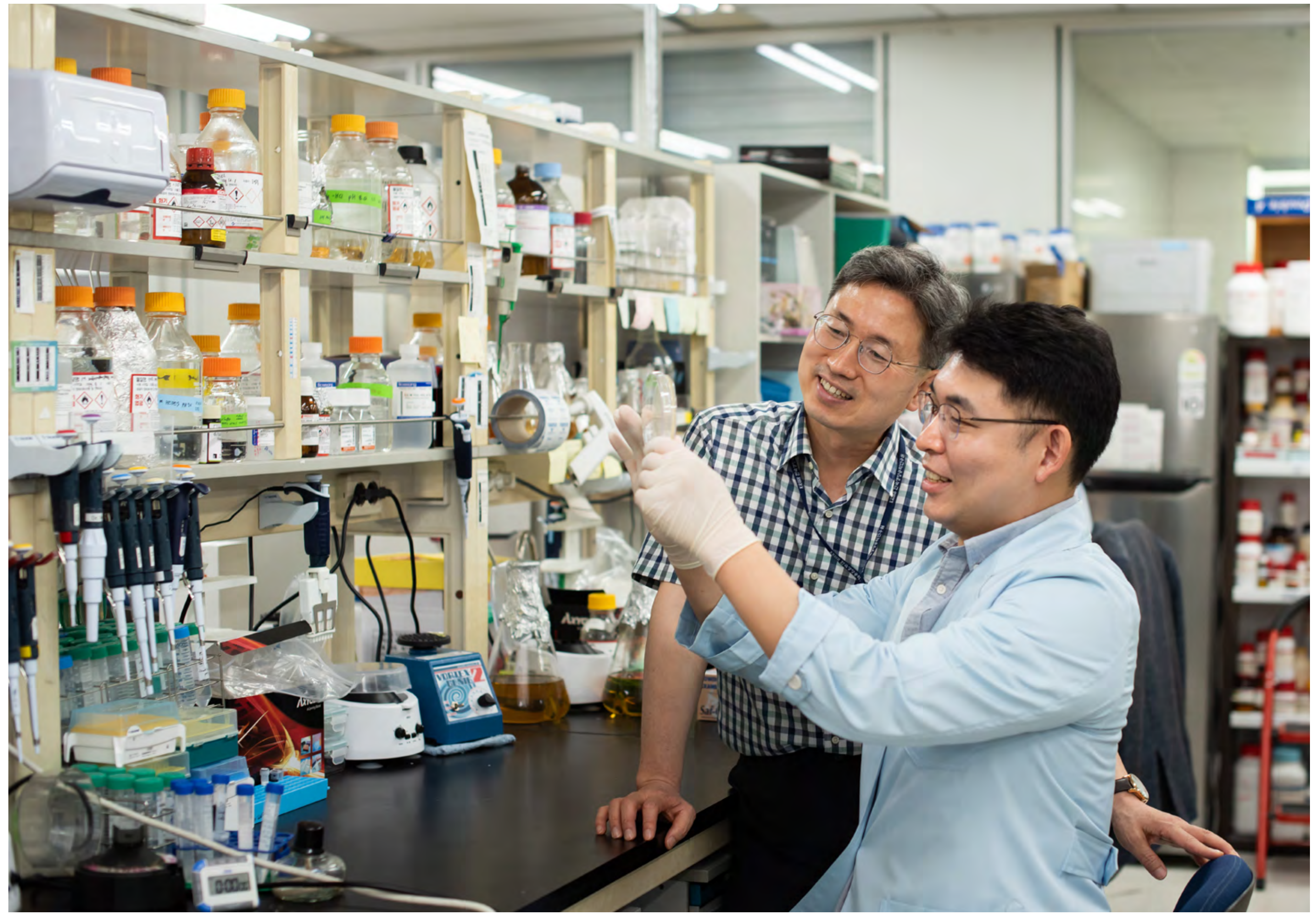
Dr. Park also started a 'storm of praise' for Dr. Woo, as much as Dr. Woo did.

"Because I had a lot to see and learn, I stayed by Dr. Wu's side for so long. I have watched him for ten years, and Dr. Woo is my role model. His research, society, and family

They are now challenging the design of artificial proteins.

Due to their long relationship, Dr. Woo and Dr. Park did a lot of research together. They revealed the enzyme's crystal structure and discovered a new CRISPR protein to reveal its function. In 2020, along with a research team led by Lee Seung-gu, director of the Synthetic Biology Institute of Life Research Institute, they found a protein that decomposes phenol in purified microorganisms, revealed its structure and function, and published it in Nature Communications. Recently, they are working on designing artificial proteins.

"Until now, the structure or function of proteins has been revealed through experiments, such as intentionally



The two have been together for a long time. Now they have become 'academic' companions.

creating mutations. Now, with the development of artificial intelligence (AI) technologies such as AlphaFold, it has become easier to predict protein structures with computers. It has also become easier to create new proteins that did not exist before through computing. So, using computers, we are researching making proteins that do not exist in nature which can perform specific functions."

In particular, Dr. Park is researching creating artificial proteins capable of gene editing.

"I wrote my doctoral dissertation on revealing the CRISPR protein function. However, since CRISPR is a microbial system, its use in humans still has many limitations. By overcoming this shortcoming with protein design technology, we aim to create artificial proteins suitable for humans."

Dr. Woo is also building an AlphaFold server for researchers.

"Since researchers in the protein field are scrambling to use AlphaFold, we have to wait several days before we can research using AlphaFold. So, we are working on building an AlphaFold server within the Life Research Institute for domestic researchers. First, the goal is to run it as a pilot, and if it goes well, make it usable by more people, from researchers to general graduate students."

Researched sugar metabolism of corynebacteria, an industrial strain, and suppression of inter-bacterial signaling

Achievements in two microorganism research fields have marked his career

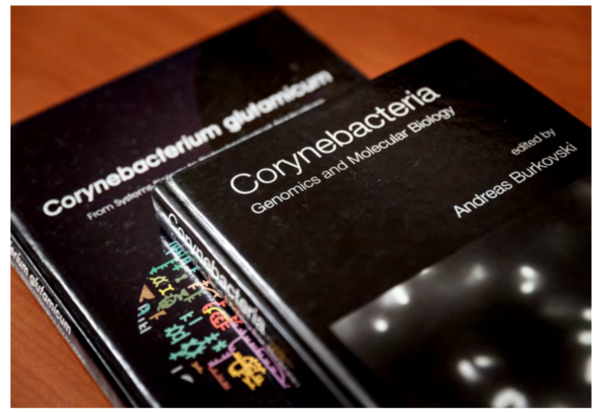
Jung-Kee Lee,
Professor, Department of Biomedicinal Science and Biotechnology, Pai Chai University

Dr. Jung-Kee Lee, currently a professor at the Department of Biomedicinal Science and Biotechnology at Pai Chai University, is an alumnus of the Korea Research Institute of Bioscience and Biotechnology. For 19 years, he worked at the Life Research Institute, contributing significantly to microbiological research in Korea. Since moving to Pai Chai University, he has been conducting research and teaching. In his research career, so far, Prof. Lee has made significant achievements by researching two themes: the metabolism of corynebacteria and the inhibition of cross-bacterial signal transduction. We met the expert in the field of microorganisms, a KRIBB alumnus, in the laboratory of Pai Chai University.

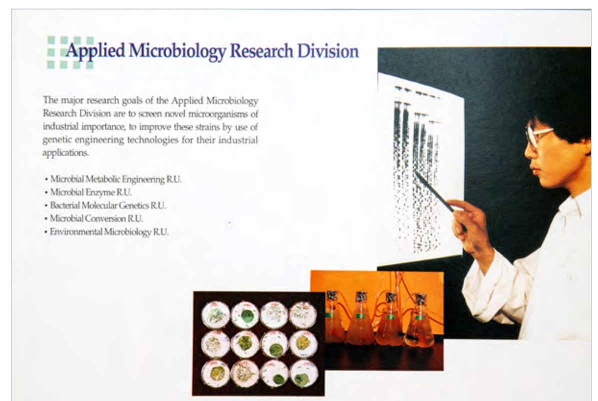
A newly recruited KIST researcher takes on corynebacteria research

"Think of how you would lay a brick to build a big house when you experiment!"

Prof. Jung-Kee Lee of Pai Chai University's Department of Biomedicinal Science and Biotechnology completed his master's degree in 1987 and joined the Korea Institute of Science and Technology (KIST) Genetic Engineering Center, the predecessor of Korea Research Institute of Bioscience and Biotechnology, as a researcher. The phrase quoted earlier was what Kim Byeong-hong, head of the research lab at the time, asked him to keep in mind when he first started to work. Prof. Lee said, "Chief Byung-Hong Kim was a scholar who majored in microbial physiology and wrote excellent books. He was such a great teacher, and I aspired to become a researcher like him." The Genetic Engineering Center moved to a new building in the Daedeok Research Complex in 1990, and the name was changed to the Biotechnology Research Center in 1995. After that, it became an independent corporation under the Basic Technology Research Society. In 2001, the name was changed to the Korea Research Institute of Bioscience and Biotechnology.



Since Prof. Lee first met Prof. Andreas Burkovski of Cologne University in Germany at a foreign conference in 1998, he has been related to corynebacteria research. Prof. Lee went to the University of Cologne in Germany as a visiting researcher, and Prof. Berkowski sent his book. The pictures are of the books written by Prof. Berkowski.



Prof. Jung-Kee Lee appeared in a booklet introducing his department (Applied Microbiology Research Division) while working at the Life Research Institute.

Prof. Lee, who joined KIST through open recruitment, said, "The researchers at KIST's Genetic Engineering Center at the time were very proud. I entered the Ph.D. program in 1990, when KIST moved to the Daedeok Research Complex, and wrote a doctoral thesis in association with a project at the Life Research Institute project." The subject of his doctoral research was corynebacteria. Corynebacteria is an industrially important bacterium used in the fermentation process of producing glutamic acid, an umami component, that eats waste molasses remaining after sugar is extracted from sugarcane. Prof. Lee said, "I devoted myself to finding the gene for the transporter protein needed to absorb glucose in corynebacteria. I found a glucose transport gene that was unknown until then by constructing a genome library of corynebacteria using the mutant strain." He received his doctorate in 1995 by identifying corynebacteria's glucose transport protein gene and then also researched fructose and sucrose transport protein genes. Prof. Lee said, "CJ CheilJedang showed interest in his research. I went to the CJ CheilJedang Bio Research Center to hold a seminar on corynebacteria research and was appointed as a technical advisor." The relationship with CJ CheilJedang that began in this way continued for about 15 years. They obtained international patents for research results, including for redesigning fructose metabolism to improve lysine productivity. The relationship became closer in 2002 when the Microbial Genome Utilization Technology Development Project, one of the 21st Century Frontier Projects under the Ministry of Science and Technology, was launched. CJ CheilJedang was interested in corynebacteria, which produce lysine, an essential amino acid (feed additive), through fermentation for raising pigs at an industrial scale. So, CJ CheilJedang joined the Life Research Institute as the leading institution, and Prof. Lee continued the relationship for ten years until the end of the project group by conducting joint research with CJ CheilJedang at the Life Research Institute.

While working with CJ CheilJedang, Prof. Lee succeeded in identifying genes that regulate sugar transport proteins in corynebacteria and constructing deletion mutants for these genes. Prof. Lee said, “Despite the great worldwide interest at the time, none of them were able to construct mutants related to sugar metabolism regulation. Dr. Moon Min-woo (currently a senior researcher at Daesang Materials Research Institute), a doctoral student at that time, also continued performing experiments to create mutations in this gene but failed several times. Then, after the experiment, Dr. Moon inspected the culture plate that had been abandoned on the bench for more than a week. He accidentally discovered that tiny colonies had formed.” “It was serendipity,” he said. “Because it is an essential transcriptional regulatory protein gene, it hardly grew during mutation experiments, so it could not be obtained through normal observation. Thanks to the first acquisition of this mutation, it was possible to study the sugar metabolism control-related function of a key master regulatory gene in corynebacteria and to publish a series of related papers," he explained.

After visiting Germany, he emphasized the necessity of forming the ‘Coryne Research Society.’

In 1999, basic research on corynebacteria was conducted by Life Research Institute, and CJ CheilJedang conducted research to improve lysine productivity by applying related basic research to the field. According to Prof. Lee's explanation, Germany, Korea, Japan, and China are the four major powerhouses in the Corynebacterium-related industry. This is because it is a device industry that requires a considerable investment. Ajinomoto in Japan began to produce glutamic acid, a raw material for seasonings, using corynebacteria mutant strains. CJ CheilJedang is also producing several amino acids, including nucleic acid, glutamic acid, and lysine, using its corynebacteria-producing strains, and their sales have recently reached trillions.

Prof. Lee said, “Corynebacteria is a GRAS strain certified by the FDA that it is safe to use for applications in various fields. Therefore, processes related to food, feed, environment, and pharmaceuticals are intended to be made with Corynebacteria. Currently, CJ CheilJedang has changed the production process of nine out of 20 amino acids that are marketable using corynebacteria.” He also added, "Four countries around the world are fiercely competing to lower the production cost," adding, "since it is industrially valuable, I felt proud to be at the forefront of this related research while researching with CJ CheilJedang." Prof. Lee studied corynebacteria while working with CJ CheilJedang for about 15 years at the Life Research Institute. As a result, he was awarded the CJ Special Academic Award in 2020 by the Korean Society for Microbiology and Biotechnology for his contribution.

In Jerusalem, Israel, in 1998, Prof. Lee presented his research results on corynebacteria as a poster. At that time, he had the opportunity to meet Prof. Andreas Berkowski of Cologne University, Germany, who also studies corynebacteria. Through that relationship, Prof. Lee, went to the University of Cologne in Germany as a visiting researcher. Although he only stayed in Germany for three months, he was able to take advantage of Germany's corynebacteria research system. After that, his relationship with Prof. Berkowski continued and to this day, they help each other. In particular, during his stay in Germany, the ‘powerhouse of coryne,’ Prof. Lee came across a model in which about ten universities and research institutes divided their roles in research on all fields related to a single strain of corynebacteria and gathered together to exchange information under the auspice of the relevant industry. He thought this model was ideal.

After returning from Germany, he persuaded CJ CheilJedang of the importance of forming a research group to gather domestic corynebacteria researchers for collaboration studies. This is how the “Coryne Research Society” was born. Prof. Lee, who also served as the chairman of the v Research Society in 2014, said, “The Coryne Research Society has been gathering at the CJ CheilJedang Research Center once a year to hold seminars and help provide employment counseling to graduate students.”

Four countries worldwide fiercely compete to lower the production cost, which is industrially very valuable.
While researching with CJ CheilJedang, I felt proud to always be at the forefront of related research.

Another subject of his research is the inhibition of bacterial communication

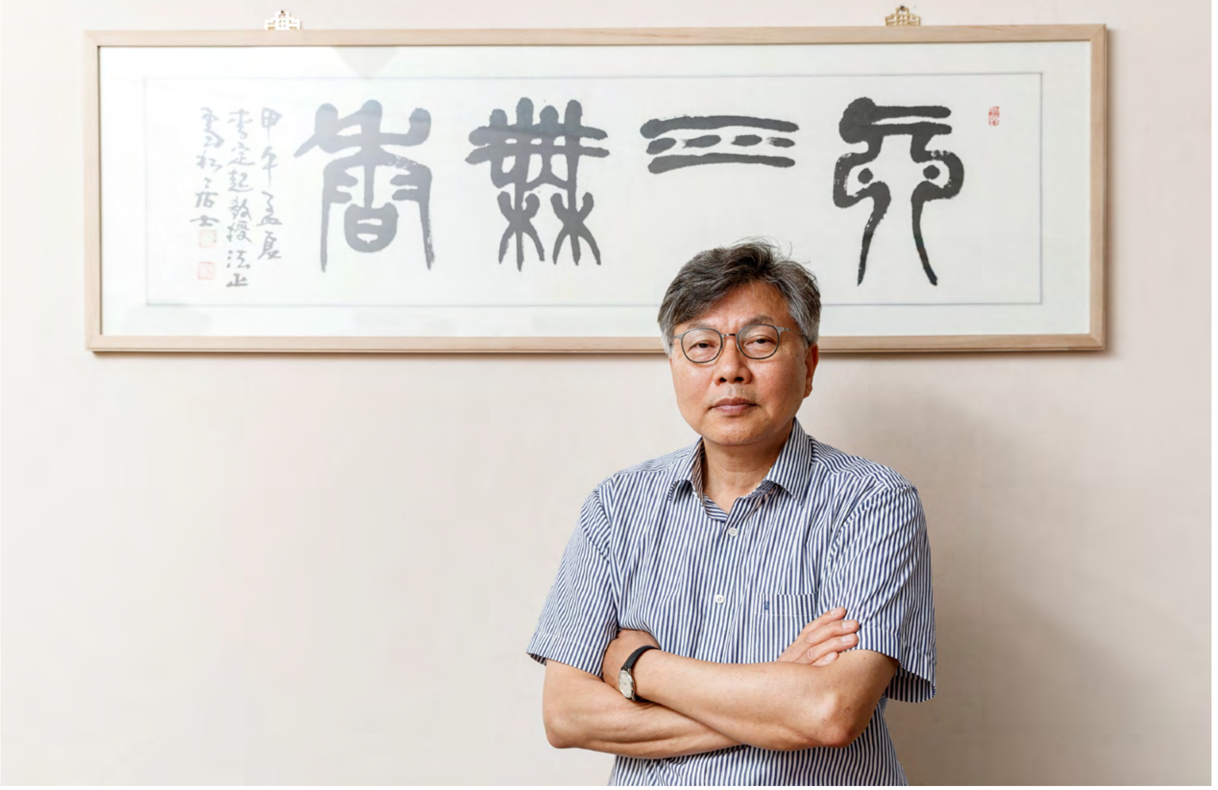
Throughout his career, Prof. Lee has been researching two major fields; corynebacteria and ‘quorum quenching study.’ The research on ‘inhibition of quorum sensing’ to block the signal transduction system between bacteria is a topic initiated by his attraction to the field of quorum sensing research presented at the 2000 American Society of Microbiology meeting in Chicago.

Humans communicate with language, and multicellular organisms communicate between cells through hormones or other signal molecules. Do single-celled bacteria also have a communication system with each other? Prof. Lee said, “Bacteria communicate with each other using chemicals. As some bacteria grow, they secrete a substance called acyl-homoserine lactones (AHL) outside the cell, so the extracellular concentration of this substance is proportional to the number of bacteria. In particular, in the case of pathogenic bacteria, in the early stage of infection, only the number of their species is quietly increased; however, when the number grows enough to overwhelm the host's immune system, that is, when the concentration of the signal substance secreted to the outside increases (when quorum is reached), the signal is transmitted to between the bacteria. They recognize each other’s signals and take collective action to produce virulence factors all at once, and the infection succeeds,” he explained. The phenomenon in which bacteria detect signals for colony behavior is called ‘quorum sensing,’ and blocking this signal transduction system to prevent pathogenicity is called ‘quorum quenching.’ After Prof. Lee joined Pai Chai University, he gave a public seminar on the subject of “Do bacteria need to talk?”

This research began with a study in which Prof. Lee discovered that Bacillus thuringiensis (BT), known as an insecticidal biological pesticide strain, also has a wide range of enzymes that degrade the signal transducers of pathogenic bacteria. At that time, Dr. Park Seung-han's team at the Life Research Institute collected BT bacteria to develop a biological pesticide. With Prof. Lee Sang-Joon, currently working at Chung-Ang University, he found out that all biopesticide strains have the gene for the enzyme isolated from these bacteria. This research was published as the first paper in Applied and Environmental Biology (AEM), a journal published by the American Society for Microbiology.

Afterward, Prof. Lee, in a collaboration with Dr. Myung-Hee Kim, studied the structure of an enzyme (AHL-lactonase) that decomposes the signal transducer isolated from the biopesticide bacterium BT. Dr. Kim was a postdoctoral researcher at the time, a structural researcher who came to the Life Research Institute from the United States. In 2005, Prof. Lee and Dr. Kim succeeded in analyzing the tertiary structure of this enzyme protein in six months and also identified its specific action mechanism. The study was published in the Proceedings of the National Academy of Sciences (PNAS) and has attracted attention, as it can be used to effectively control plant diseases and develop a new class of anti-infective agents that treat various bacterial diseases.

While presenting related research results at the Department of Chemical and Biological Engineering at Seoul National University, Prof. Jeong-hak Lee suggested collaborating on a study to eliminate biofilms by “suppression of quorum detection.” Biofilm is a viscous film produced by microorganisms. In particular, when using a membrane bioreactor (MBR) system for sewage treatment,

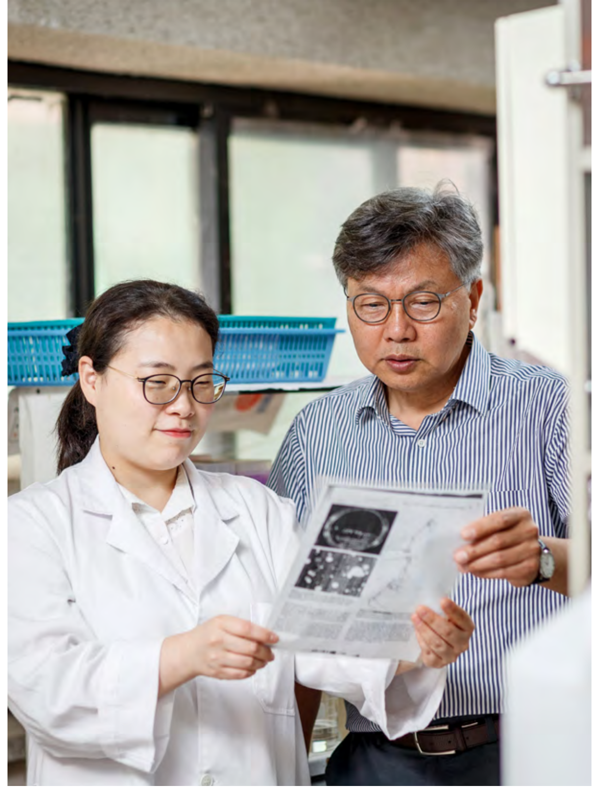


A framed picture with the phrase 'Real water has no fragrance' is hung in Prof. Lee's room. This phrase can be interpreted as genuine researchers doing their best in silence.

biofilm produced by microorganisms present in sewage causes a chronic problem of biofouling, which clogs the separator during operation. Prof. Jung-Kee Le, along with Ph.D. student Sun-yang Park (currently a staff scientist at Boston Children's Hospital, Harvard University), continued to search for bacteria that exhibit vigorous decomposition activity against signal transduction materials while working at the Life Research Institute. Afterward, Prof. Jung-Kee Lee said, "We searched for and selected bacteria with excellent quorum quenching activity at the Daejeon sewage treatment plant. By using this bacterium Prof. Jeong-hak Lee of Seoul National University has significantly reduced the biological contamination of the membrane, which is a problem in the MBR system." Prof. Jung-Kee Lee said, "We discovered bacteria that produce enzymes that break down signal transducer substances, that is, bacteria that can suppress quorum detection, and carried out the MBR wastewater treatment project of the Ministry of Environment for about ten years together with Prof. Jeong-hak Lee's team at Seoul National University. The results of this research have been published in a number of related papers in journals, including ‹Environmental Science and Technology (ES&T)›, an authoritative academic journal in the field of environment published by the American Chemical Society (ACS), and an international patent has been issued." Research related to this was also introduced in the 'Technical Trends' section of ‹Nature› on July 24, 2014. Regarding the successful research results achieved by introducing the method of inhibiting signal transduction into the MBR, Prof. Jeong-Hak Lee often told Prof. Jung-Kee Lee that "it is the result of meeting experts in completely different fields, such as chemical engineers and microbiologists."

The reward of teaching students, his expectations of young scientists

Prof. Jung-Kee Lee worked at the KRIBB for 19 years, from 1987 to 2007. Prof. Lee said, "The main job of researchers at the Life Research Institute is research, but university professors do 50% student education and 50% research. When I lectured as an adjunct professor, I felt the joy of teaching, so I wondered if being a professor would better fit my profession." Prof. Lee worked as an adjunct professor at Pai Chai University and the University of Science and Technology (UST). Prof. Lee moved to Pai Chai University as an associate professor at the age of 47, and he said, "I feel like a 'natural teacher' after teaching at Pai Chai University."



Prof. Lee, who says he feels that he is a 'born teacher,' emphasizes that teaching students at universities is rewarding.

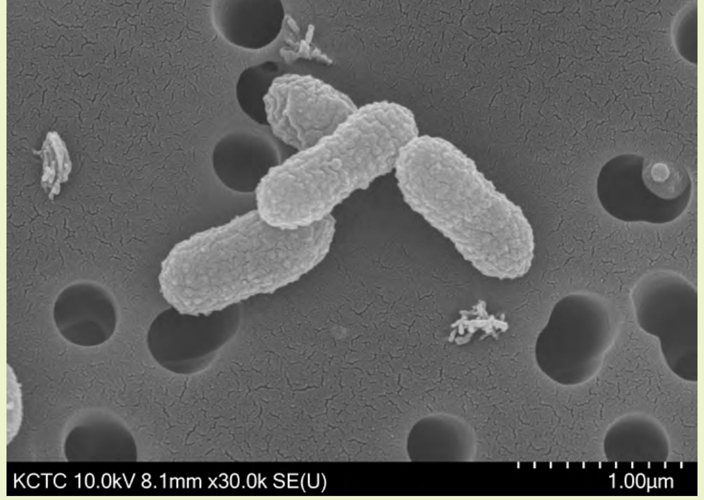
Prof. Lee was selected as a 'professor who gave excellent lectures' and was also selected as a 'master of online lectures' during the COVID-19 pandemic. He said, "I came up with many ideas so that online lectures would not be boring. I even wore a bow tie to liven up in front of the camera. Sometimes, for students who could not come to school, I put the photos I took while walking around the school in my spare time in the lecture materials." Prof. Lee is currently two years ahead of the retirement age at the school, and when he retires, he will finish his 17-year teaching career. He said, "When I started to give lectures at universities after only doing research at the Institute for Life Sciences, I felt that my window for looking at life had widened a little. It is also rewarding to teach students."

Prof. Lee has also played an important role in academia. Since 2013, he has served as the chairman of the microbial genome academic subcommittee, the secretary general, and the chairman of the academic promotion committee at the Korean Society for Microbiology and Biotechnology. In addition, he has served as the society's chairman since January of this year. Prof. Lee said, "Next year is the 50th anniversary year of the society. The regular academic conference, held in Gyeongju for two nights and three days in June this year, was a success with about 2,000 people registering and a total of 940 papers, including 710 poster papers, being presented." The society began as the Korean Industrial Microbiology Society in 1973 and changed its name to the more comprehensive Korean Society of Microbiology and Biotechnology in 2002. Prof. Lee said, "As seen in the recent examples of genetic scissors and mRNA vaccines, the distinction between basic and applied science is now ambiguous. The society has various experts from 15 academic divisions, ranging from basic research in the field of biotechnology, including microbiology, to various industrialization research related to food, medicine, and environmental biotechnology convergence technology." He also said, "Convergence research is possible by gathering various researchers, and I look forward to new convergence research connected to AI and big data in the future. In particular, the society believes that the most important role of the society is to enable young scientists to debut and present good research to maintain the continuity and development of the academic field."

As a senior researcher from Life Research Institute, what does he hope for Life Research Institute? Prof. Lee premised that "the reason for the existence of a researcher is 100% research." He continued, "I studied very hard at the Life Research Institute. However, as is frequently the case in this world, I was immediately put into the research field without any special training on the mindset and attitude of a true researcher and research methods and philosophy. I was an occupational researcher who worked hard while being chased by papers that came out every day." He added, "At the Life Research Institute, it seems that new researchers, in particular, need educational programs outside of their major fields as vocational researchers and true scientists. For example, for many fundamental discussions, including the history, philosophy, and ethics of science, and how to do science, biophilosophy, and bioethics, you should be able to access a somewhat humanistic program necessary as a life scientist. Through this, I believe they can cultivate their major knowledge and think more deeply as researchers and increase their self-esteem." He also expected, "Through such education, researchers will have a broader view of the entire field in their research." My eyes go to the words on the frame hanging in Prof. Lee's room that were, 'Real water has no fragrance.' It must mean many genuine researchers of each field doing their best research in silence in the laboratory.

Uncovering the evolution and competitive advantage of beneficial bacteria living in the intestines of Koreans

A research team from the Korean Collection for Type Cultures (KCTC) of the Korea Research Institute of Bioscience and Biotechnology identified the genetic differences and evolution of beneficial bacteria living in the intestines of healthy Koreans. These findings are expected to be used in developing next-generation probiotic strains and microbiome treatments tailored to Koreans.



Akkermansia muciniphila characterized by Dr. Jungsook Lee's research team

Next-generation probiotic candidate, *Akkermansia muciniphila*

There are 39 trillion microorganisms living in the human body. Among them, the largest number of highly diverse microorganisms live in the intestine. Intestinal microorganisms are responsible for the absorption and degradation of nutrients in the intestine and are also involved in the pathophysiology of various intestinal diseases. In addition, they secrete mediators involved in human gene expression regulation and inflammatory signaling systems. Through this mechanism, it is known that intestinal microbes affect the occurrence of allergic diseases, neurological diseases such as depression or dementia, and metabolic diseases such as obesity and diabetes, in addition to intestinal diseases.

Thus, probiotic products isolated and consuming beneficial intestinal bacteria have been widely developed and marketed. However, most probiotics known so far are lactic acid bacteria. As the next generation of probiotic strains is discovered, more and more are being developed.

Among them, the *Akkermansia muciniphila* strain is vital for maintaining intestinal health in the body. In particular, research results have been announced that *Akkermansia* strains are effective for various metabolic disorders such as obesity, metabolic syndrome, and type 2 diabetes and show excellent therapeutic effects when administered in combination with immuno-cancer drugs. Based on this, the *Akkermansia* strain is attracting attention from many domestic and foreign companies as a target for developing next-generation probiotics and treatments. However, the therapeutic efficacy of *Akkermansia* strains differs depending on their origin, making it challenging to develop new products.

Finding characteristics unique to *Akkermansia* strains derived from Koreans

The research team isolated *Akkermansia* strains from the feces of healthy Koreans and performed a comparative analysis of the whole genome with foreign strains. Whole genome analysis is a technique that comprehensively studies genetic factors for disease and drug responsiveness.

The phylogenetic diagram showed that *Akkermansia* strains were divided into two subspecies, group A, which included Korean-derived strains, and group B, which included standard strains and foreign-derived strains, even though they evolved from the same ancestor (MRCA) strain. The Korean-derived *Akkermansia* strains had very low genomic similarities with the strains in group B. This shows that functionally significant differences can be seen depending on the strain.

The research team also found a specific gene only found in *Akkermansia* strains derived from Koreans. This means that the Korean-derived *Akkermansia* strain has evolved to gain an advantage in competition with other intestinal microorganisms by inhibiting the growth of intestinal pathogens.

Principal investigator Jungsook Lee said, "The therapeutic efficacy of *Akkermansia*, which is in the limelight as a next-generation probiotic strain, is different for each strain, and it was regrettable that most of the research was conducted with foreign-derived strains."

"Based on the competitive advantage of the *Akkermansia* strain isolated from Koreans, it is expected that it can be used for the development of next-generation probiotics tailored to Koreans and microbiome treatments," she said. In addition, the research team plans to conduct a comparative study on the treatment effect between actual strains through specific experiments.

Embracing the history of life around the world

Korean Collection Center for Type Cultures (KCTC), KRIBB Jeonbuk Branch

Lee Jung-sook, head of the center, is examining dried microbial samples. According to Lee, speed is the key. After the entrustment is completed, the microorganism officially gives the number. It's important how quickly the consignment process is processed because the thesis can be submitted only if it is accepted.

The field of life sciences in the broad field of science is unique because of its diversity and anomalies. According to a 2016 survey, it is estimated that there are more than one trillion species of life on Earth. Of these, less than 20% are known to mankind. According to a 2009 study, less than 1% of the viruses and prokaryotes estimated to exist on Earth are known to humans. Even though the life we know is so diverse and complex, there are more things we do not know than we know. So life science begins with collecting and arranging numerous species. At the base of the dazzling life science technology covered brilliantly in the media, there is the arduous task of silently collecting, organizing, and preserving countless lives.

This is also why the history of the KCTC located in the KRIBB Jeonbuk branch dates back to when KRIBB was a genetic engineering center at the Korea Institute of Science and Technology (KIST) in Hongneung, Seoul. The current center director, Dr. Jung-Sook Lee, also worked with the KCTC even before KRIBB was separated from KIST. She is a living witness to the history of Korean biological resources.

Deposits are usually requested online. The application documents contain detailed information such as species and major genes. When the application is completed, the microorganisms are cultured in a liquid or solid medium, as shown in the picture, or made into a dry ampoule and sent to the entrusted institution. The conditions of the samples that arrive at the center are also different because numerous researchers cultivate and send them their way. The center does not keep deposited microorganisms as they are. Depending on the species, the composition of the culture medium or the suitable culture method is different depending on the genotypical trait of the same species. The composition of the culture medium and the culture medium is also different for each laboratory. Therefore, it should be subcultured to ensure that it can be stably managed and stored in the center and to confirm that it is the same microorganism described in the application.

The process of creating a medium for culturing microorganisms. Depending on the characteristics of microorganisms, solid or liquid media are used. Although there is a commonly used composition, there are many cases in which a specific composition needs to be adjusted depending on the microorganism. Especially in recent years, this trend has been getting stronger. The media composition information alone can reach two or three pages of A4 paper.

A gloveless anaerobic culture device which is connected to separate airlock.

The nitrogen injected into the anaerobic culture device is drawn from a large nitrogen tank 'installed in a separate safe place' through pipes in the building. Thanks to this, there is no need to carry a nitrogen cylinder. These plumbing facilities were also installed on the strong recommendation of the head of the center, Dr. Lee, who has know-how on what the research center needs.

When dealing with anaerobic microorganisms, it is performed in a 'glove box,' a chamber blocked from the outside air. It is also called an 'anaerobic culture device' because nitrogen is injected at high pressure inside to block contact with oxygen. Some devices are equipped with external gloves so that you can do other work at any time while working. There are also devices with only armholes; you cannot remove your hands while working.

A glove-type anaerobic culture device which has integrated airlock.

The work of culturing microorganisms is thoroughly an area of experience. The media to be used, the treatment to be followed, and the environmental conditions to be set are tweaked according to the competitiveness of the BRC. The photograph shows the process of collecting cultured microorganisms for testing. It runs inside the glovebox. The medium is red because it is mixed with animal blood.

The deposited microorganism is transferred to a culture medium and cultured. At this time, it is crucial to how well the composition of the medium or culture conditions are controlled. One of the difficulties for life science researchers is the 'know-how,' which is difficult to define clearly. The composition and conditions of the medium were all matched, and the culture environment was precisely controlled. Nevertheless, microorganisms that do not grow well often appear depending on the hands of the people who handle them. This is why standardization is difficult in the bio-industry using microorganisms.

Living organisms are not preserved in one way. This is because viability varies depending on conservation methods, and certain environments can be lethal for some species. So, at least three methods are applied per species. Here, microorganisms are frozen according to their characteristics and stored in a liquid nitrogen bath at -196 degrees Celsius. It is said that the center can store a total of 30,000 culture medium test tubes.

Microorganisms collected and cultured from deposited samples. Microorganisms cultured in the way described previously are analyzed and compared with the recorded documents, and when the traits are maintained stably by culturing several generations, preservation procedures are started.

There are many ways to preserve microorganisms. In the case of 'drying method', microorganisms are sealed in a sealed glass tube, called 'ample.' After dried microorganisms are placed in an ample, open end of glass tube is melted at high temperature with a Bunsen burner, sterilizing and sealing up the tube at the same time. Sealed amples should be stored immediately to ensure high survival rate during re-culture.

The core of the KCTC is the underground conservation facility. There are over 30,000 microorganisms stored here. Of course, the actual number of species is less, as different strains are stored differently. Microbes classified in a project that investigated and analyzed the microbiome of Koreans are also stored here.

The KCTC shows clearly what role KRIBB plays in the domestic bio field along with the bio-data station project. The KCTC collects and preserves biological resources from all over the world as well as Korea. In particular, it mainly manages plants and microorganisms. To publish a new microorganism, culturable organisms must be deposited with the biological resources management authorities of at least two countries. This is because, to be officially recognized as a new species, at least two research institutes must confirm that it is viable and that its characteristics are maintained constant. The same goes for organisms artificially synthesized for industrial purposes.

The role of the KCTC continues beyond simply verifying and preserving living things. It also serves to store actual organisms in a state that can be re-cultivated at any time and provide them to researchers who need them and acts like a bank. The KRIBB KCTC is an indispensable infrastructure for studying plants and microorganisms.

Living things are not preserved in one way. This is because viability varies depending on conservation methods, and certain environments can be lethal for some species. So, at least three methods are applied per species. Here, microorganisms are frozen according to their characteristics and stored in a liquid nitrogen bath at -196 °C. The center is said to be able to store 30,000 culture medium test tubes.

Microorganisms that have completed the preservation process are preserved for a long time under environmental conditions that maintain an inactive state. For example, freeze-dried microorganisms are sealed in ampoules in a dry state and stored in a cool place.

Frozen samples are preserved at minus 70 degrees Celsius. For maintaining the required temperaturem, conservation facilities of the Biological Resource Center have their own generators.

Start-up and growth of bio ventures and innovation in the ecosystem of the bio-industry

KRIBB SME Support Center

Forty-two bio venture startups, including Korea's No. 1 bio-venture company, 25 bio venture companies in business incubation, 74 bio venture center graduates, 15 KOSDAQ-listed companies, and 1 KONEX-listed company! This is one of the achievements of the Korea Research Institute of Bioscience and Biotechnology (from now on referred to as KRIBB), a government-funded research institute whose main mission is to develop and distribute source technology in the advanced life science technology field and lead the bioeconomy. In addition, KRIBB Small and Mid-size enterprises (SME) Support Center serves as a pillar for the start-up, growth of the national bio ventures, and innovation in the bio-industry ecosystem.

From the BT-specific business incubation center to step-by-step customized support

The SME Support Center is affiliated with the Bio Economic Innovation Division in partnership with the Technology Commercialization and Bio Commercialization Support Centers. The center supports the start-up of bio ventures, operates incubators, supports the technology and growth of SMEs, discovers and coordinates the needs of SMEs, and strives to create a bio innovation ecosystem. In addition, it is collaborating with the Technology Commercialization Support Center, which is in charge of technology discovery and commercialization, and the Bio Commercialization Support Center, which supports the use of commercialization technology and equipment. The SME Support Center comprises Center Director Kwon Oh-Seok, SME expert committee members, and business support team personnel. The expert committee member is a former researcher and is in charge of coordinating industry-research cooperation. The business support team mainly engages in the bio-industry ecosystem, innovative growth, technological cooperation, and start-up support and incubation.

Center Director Kwon Oh-Seok introduced the start-up support, business cooperation, and representative achievements of business support programs conducted by the center. First, a BT-specific start-up incubation center is being operated as part of the start-up support program. Daejeon headquarters has a ‘Bio Venture Center’ designated by the Ministry of SMEs and Startups. Launched in 2000, it includes 36 incubating rooms, and currently, 25 companies are located there. Director Kwon said, “Early-stage companies can move in and stay for up to 10 years.” “So far, 78 companies have graduated from the Bio Venture Center, most of them before the deadline, to expand their businesses as they grow.” Nine companies that graduated from the center and one that is still residing in the center entered the KOSDAQ. In addition, 28 companies have started research institutes from 1996 to the present. Regarding start-up support, there is a Bio Inno-Biz Center in the Jeonbuk

Branch of KRIBB. As a venture business cluster designated by Jeollabuk-do province in 2017, it aims to lead the growth of the bio-industry in Jeollabuk-do and become a base. The occupancy space has seven rooms; currently, six companies have moved in.

The center also operates a researcher start-up program as one of the start-up support programs. Most of the start-ups through this program are 'initiative' (a research staff (technical developer) starts a business using the technology developed at the research institute in which they worked). However, starting in 2020, 'commissioned' (a joint venture between a technology developer and non-technical research staff using a research institute's technology) and 'open' (co-founded by external experts and research staff) start-ups are increasing in number. Of the 31 companies founded by the researcher start-up program so far, seven companies, including Bioneer, the first 'initiative' start-up originating from KRIBB and the first bio venture in Korea, have been registered on KOSDAQ.

In addition, the KRIBB Bio Startup Booster Platform, which provides customized support for each stage, from the discovery of startup items to foundation and growth, is also in place. It is an accelerating platform that supports the entire cycle of start-up and growth, from the discovery of start-up items to initial R&D and attraction of Series A. The KRIBB Bio Entrepreneurship Camp supports the initial stage. Director Kwon said, "We are operating a practical start-up camp program by innovating/opening the existing seminar-type start-up school." "In the first half of the year, we held a bio boot camp to strengthen participants' venture business capabilities, and in the second half, we held a bio challenge camp to materialize a business model and establish a business plan," he explained. The Bio Boot Camp, run in May this year, was attended by 67 people from 28 institutions, and 44 completed it. The bio challenge camp was held on October 20 and 21.

Additionally, the SME Support Center operates a start-up support program with the Korea Innovation Foundation, the Ministry of Science and ICT, and the Ministry of SMEs and Startups. To begin with, the Korea Innovation Foundation supports researchers from government-funded research institutes to establish a collaborative team with private experts to foster star companies based on public technology. In 2019 and 2021~2022, three and five startups respectively, led by KRIBB researchers participated in this program. Genecore, Aventi, and Cupik Bio were launched as a result. Moreover, KRIBB is establishing a technology commercialization collaboration platform as part of the Ministry of Science and ICT's project that supports startups and strengthens investment attraction capabilities by finding ten preliminary startup teams and ten early-stage companies yearly. Korea Innovation Foundation is the exclusive agent, and Daejeon Techno Park is the leading agency on this project, which will run until the end of next year. Director Kwon said, "We plan to promote and increase the success rate of entrepreneurship by establishing an incubation and acceleration model specialized in the field of bio-health with 14 local industry-university research institutes participating." KRIBB has also participated in the Ministry of SMEs and Startups' Private Investment-Led Technology Start-Up Support Program (TIPS) since 2015. As cooperative partners, Blue Point (2015), Hugel (2016), Daily

The KRIBB SME Support Center has entered into a family business partnership with 205 companies in 2021 to provide customized support according to each company's key growth factors. The photo shows the 'KRIBB Family Company Networking Day' event on December 2, 2021.

The SME Support Center has held various support events such as Techbiz Partnering Technology Exchange Meeting, Bio Startup School Boot Camp and Challenge Camp, and Bio Core Facility Innovative Growth Workshop.

(2019), and Innopolis Partners (2020) helped select 13 TIPS and followed up with them. Examples include Plasmapp, Biorchestra, Revosketch, and HealthBiome.

Operated the KRIBB Bio Mentor Group and established the 'K-Bio Tech Biz Cluster.'

The SME Support Center carries out the 'Bio Core Facility Establishment Project' of the Ministry of Science and Technology as part of the corporate cooperation program. It nurtures future innovation leading companies in the bio industry. In addition, it operates the KRIBB Bio Mentor Group, a system that closely supports KRIBB family companies, and builds and operates the K-Bio Tech Biz Cluster. First, the Bio Core Facility construction project recruits bio venture companies that have been in business for less than three years. They are provided with lab space in the KRIBB's business incubation center, cutting-edge research equipment, R&D funds, investment attraction support, and customized growth support based on corporate management diagnosis. Five companies, including Plasmapp, participated in the first and second stages from June 2017 to December 2020, and five companies, including Organoid Science, participated in the third stage from January 2021 to June 2024. In addition, since 2019, it has supported demand-based technological innovation to nurture future bio-innovation-leading companies. In other words, market-leading bio small giants (hidden champion, new product development), technology innovation bio venture companies (tech in business, production process innovation), and regional innovation bio venture companies (regional innovation leading companies, technological innovation and problem-solving) are nurtured. Through this program, 50 companies were fostered between 2019 and 2021, and 14 new companies are being supported in 2022.

In addition, the SME Support Center operates the KRIBB Bio Mentor Group, which supports pinpoint mentoring in line with technology, investment, and growth, which are key factors for corporate growth. Specifically, the technical mentor group (100 internal experts in industrial materials, medicine, convergence, and infrastructure) provides coaching support for technical difficulties in the field. The investment mentor group (50 investment experts) strengthens investment attraction (IR) capabilities and supports investment attraction. The growth mentor group (50 field experts) supports patents, marketing, management consulting, certification and licensing, and overseas expansion. Director Kwon said, "The performance of investment attraction support for 22 resident companies through the mentor group from 2015 to 2021 amounts to KRW 193.6 billion." In addition, through partnerships with KRIBB family companies, it provides demand-based technology mentoring, short-term technical bottleneck solution support, and connection support with the KRIBB bio-mentor group. By signing partnerships with 205 companies in 2021, the mentor group is providing customized support according to the key growth factors of each company. In addition, KRIBB R&D experts have been dispatched to technologically innovative companies to support product and technology development. In addition, through the 4th talent development project (2018~2020) of the government-funded institute, the job skills of unemployed bio majors were cultivated, and job-related support was provided. Director Kwon explained, “We trained 244 people as part of the 4th talent development project, and more than 50% of them got a job at a related company during the six-month training period.” Furthermore, ‘Bio-Industry 4.0,’ a basic bioindustry course run by experts from the industry, academia, and research institutes, and ‘Spot Bio,’ a course on promising future biotechnology, are available. In the case of ‘Bioindustry 4.0,’ hundreds of people accessed it online.

This year, the ‘K-Bio Tech Biz Cluster’ has been established as a network-type win-win cooperation program. Technology-oriented tech biz clusters will be established in the Daejeon headquarters (bio convergence), the Ochang branch office in Chungcheongbuk-do (biopharmaceutical), the Jeongeup branch office in Jeonbuk (eco-friendly industrial materials), and Gyeonggi (diagnosis and medical devices). Centered on bio companies, the KRIBB, universities, hospitals, and local governments form a network to promote corporate growth and strengthen technological cooperation. Center Director Kwon said, “We support companies' demand discovery, hold bio-industry forums, provide bio-industry training, and dispatch researchers to companies. Through our support, corporate ideas are shared, technology is transferred, and joint ventures are established.”

Fostered a KOSDAQ-listed company, and “We will help any founder grow.”

Director Kwon also introduced cases of corporate support and the achievements of creating an initial public offering (IPO). Incospharm, founded in 2011 and graduated in 2016, is a venture company that develops peptides and resins, raw materials for functional cosmetics. The KRIBB supported prospective entrepreneur discovery, company establishment, production process development and prototype production, and investment attraction in connection with investment mentor groups. During the move-in period, Incospharm attracted a total of 7 billion won in investment and even exported 5.5 million dollars to Arista in Japan. As a result, Incospharm's sales in 2021 recorded 3.7 billion won. In addition, Plasmapp, which moved in in 2015 and received growth mentoring, TIPS selection, business incubation, and growth support, is a venture company that developed a low-temperature plasma sterilizer for medical use. Plasmapp attracted a total investment of 24.6 billion won, its sales reached 6.3 billion in 2021, and it recently entered the KOSDAQ.

So far, 15 companies have been listed on the KOSDAQ with the support of the SME Support Center, and one company has been listed on KONEX. Director Kwon explained, “Among these listed companies, Mico Biomed, Bioneer, and Sugentech recorded a growth in sales even during the COVID-19 pandemic.” In addition to Plasmapp, which recently entered the KOSDAQ, two companies (Y Biologics and Biorchestra) are preparing to be listed on the KOSDAQ.

In addition, Director Kwon mentioned the support provided in the field of microbiome, which is attracting attention these days. HealthBiome, started in 2017 by Dr. Kim Byung-Chan of the KRIBB as a research institute-supported start-up, is a representative example. Director Kwon said, “Regarding the HealthBiome, we have provided support for start-up incubation, strengthening Tech-in-biz investment attraction capacity, designation as a family company, technical support from the KRIBB, and support for joint research related to technologies facing difficulties.”

In addition, Director Kwon explained, “The KRIBB is currently promoting the ‘Korean-specific intestinal microbiome banking project’ at its branch office in Jeongeup, Jeollabuk-do, and is supporting real resources through national infrastructure to industry, academia, and research institutes. Activities to support

KRIBB operates a BT–specific business incubation center in the Daejeon main office and Jeonbuk branch office. The photo shows Center Director Kwon Oh–Seok looking around the laboratory at the Bio Venture Center in Daejeon.

Center Director Kwon Oh–Seok introduces the KRIBB Bio Startup Support Platform.

companies are being carried out in various ways, such as discussing the possibility of using KRIBB’s national infrastructure facilities in response to company-specific needs of and transferring useful strains from individual researchers to companies for further development.”

What future direction will the SME Support Center develop?

Regarding business incubation and support, Center Director Kwon said, “KRIBB is currently operating the Bio Venture Center, a BT-specific business incubation center, and providing step-by-step customized support for early-stage startups. In the future, the ‘K-Bio Startup Booster’ will be operated to support the start-up and growth of internal and external technologically innovative bio ventures. Through this, we plan to operate a program that provides step-by-step customized support from discovering bio venture entrepreneurship items to leading start-ups to present early growth nationwide.” He added, "Through this, I believe that the foundation for creating bio-startups with promising growth will be created through the advancement of the platform that supports start-ups and their growth in all phases."

In addition, regarding corporate support, Center Director Kwon said, “We are investing intensively in research capacity and support to nurture 50 future innovative companies in the bio-industry through the expansion of customized R&D based on demand. In the future, the KRIBB and companies will cooperate to invest in material and human resources. In addition, we plan to establish and operate the ‘KRIBB Industry-Research Joint Research Center’ to create R&D outcomes and promote technology transfer in the joint research space.” Furthermore, he said, “The ‘KRIBB Industry-Research Joint Research Center’ conducts joint strategic R&D between demand companies and researchers and enables support. This will increase the efficiency of corporate demand-based research, create a basis for generating promising large-scale results, and contribute to sharing these results,” he explained about the future direction of industry-research cooperation and corporate support.

Lastly, regarding the aspect of the ecosystem between companies, Center Director Kwon said, “We plan to establish and strengthen a network in which multilateral innovation entities participate in the 'K-Bio Tech Biz Cluster' to increase the effectiveness of corporate support and operate a program that strengthens technological cooperation.” In addition, he added, “Through this support, the SME Support Center of the KRIBB will enhance its role as a bio venture start-up hub by advancing the start-up support platform for the entire cycle. In addition, it will contribute to enhancing national competitiveness by strengthening various corporate support programs and networks. In strengthening this role of the KRIBB, if support such as space and infrastructure expansion of the Bio Venture Center is supported, it will be possible to respond more actively and proactively to the increasing demand for corporate support in the future.”

Taking the lead in developing **microbiome therapies**

Byungchan Kim, CEO of HealthBiome

Studies have demonstrated intestinal microbes are associated with our brain as well as many metabolic diseases, such as obesity and diabetes. Therefore, the value of the microbiome as a treatment approach has been rising rapidly. Various bio venture companies have been established domestically and abroad based on microbiome technology that is actively developing medicines and functional foods. Following the acquisition of superior microbiome technologies at the Korea Research Institute of Bioscience and Biotechnology, a researcher founded a start-up. Let us meet Byungchan Kim, CEO of 'HealthBiome.'

A company founded by the Research Institute based on obligate anaerobic strains

Lactic acid bacteria are the most studied and widely commercialized intestinal microorganism in the probiotics market. Lactic acid bacteria, however, are abundant in the intestines of infants and less than 0.1% in healthy adults. In addition, most intestinal microbes are obligate anaerobic bacteria since the human intestine provides an anaerobic environment. Thus, the strains attracting attention as next-generation probiotics are primarily obligate anaerobic bacteria.

HealthBiome is a bio venture company founded in 2017 by CEO Kim, then a principal investigator at the KRIBB, based on these obligate anaerobic strains.

"In the future, obligate anaerobic strains will occupy the microbiome market. However, since these bacteria die or become less effective when exposed to even very low levels of oxygen, it is difficult to isolate and culture the strain for mass production. As a microbiologist for over 20 years, I have been studying obligate anaerobic microorganisms at the KRIBB. We have the expertise and technology to grow and mass-produce obligate anaerobic strains by preventing oxygen exposure during the isolation process of about 3,000 strains. That is our competitive advantage."

CEO Kim started the business by chance.

"In the second half of 2015, as a national project of the KRIBB, we researched the effects of obesity and diabetes with obligate anaerobic strains. I isolated the strain and handed it over to the animal testing team. The head of the animal testing team was surprised by the research results and suggested starting a business. The animal experiments confirmed that the effects of representative treatments for metabolic diseases and obligate anaerobic bacteria were almost the same."

CEO Kim also received one year of entrepreneurship training supported by KRIBB thinking it will be beneficial for the business. However, after receiving his education, he said he decided it would be better not to start a business.

"Money, human resources, and timing are all important items of starting a business. Unfortunately, I was a researcher who had only done research and read papers all my life, so I was not familiar with business terminology or contracts. So, I gave up, but an acquaintance who worked in the investment side helped me to get started."

Development of functional health food and treatment with unique separation and culture

When dealing with anaerobic bacteria, the most important thing is to avoid exposure to oxygen. Therefore, HealthBiome has an optimal system for isolating and culturing strains, such as anaerobic chambers and microbial fermentation facilities (fermenters).

technology

Microbiome companies' most crucial success factor is technology or R&D performance. Currently, HealthBiome has secured the technology to isolate obligate anaerobic strains from feces or breast milk and mass-produce them on a factory scale. Through this, it is developing cancer, dementia, and metabolic disease treatments and health functional foods.

“We have secured several strains, and AKK (Akkermansia muciniphila) is a representative strain. This strain was first known to be effective in the treatment of obesity and diabetes and was actively studied, which led to the discovery that it is beneficial in many ways. This is the advantage of the microbiome. Because microbes make multiple metabolites, they are effective against more than one disease. We have confirmed that the AKK strain is particularly effective for dementia and anticancer therapy, and we are developing health functional foods and treatments in this field.”

First, they are accelerating the development of health functional foods using the AKK strain. The United States has invested a huge amount of capital since last year, aiming to preoccupy the market for the AKK strain. To this end, it is most important to possess original patents, and HealthBiome has considerable competitiveness.

“HealthBiome has original patents regarding the use of microbiome to improve muscle strength loss, skin aging, and cognitive decline due to aging. We are still in the process of obtaining a patent for their use in developing treatments for metabolic disease. We also aim to release a health functional food next year that effectively reduces loss of muscle strength due to aging. Human clinical trials are currently underway, and results are expected soon.”

Treatment development is also progressing steadily. Currently, there are not many treatments for Alzheimer's, and even if there are, severe side effects or low effectiveness has been observed. Side effects such as vomiting, depression, and behavioral aggression are common with donepezil, a representative Alzheimer's drug. Through experiments, CEO Kim confirmed that a synergistic effect occurs when a low concentration of donepezil is combined with an AKK strain. As a result of this research, they are developing a therapeutic approach together with a large domestic company and have successfully attracted Series A investment.

“Developing therapeutics takes a long time and requires a lot of investment, so it is not easy. Microbiome therapeutics are as effective as existing drugs and have the advantage of not being toxic. However, since the microbiome is a collection of living organisms, microbiome therapeutics have the disadvantage of unclear dose-dependent effects, unlike the existing treatments. Therefore, we are working on a realistic strategy for developing therapies. Along with existing treatments that cannot be used in high concentrations due to side effects and toxicity, microbiome treatments can be used as an adjuvant or in combination. When combined with lower doses of existing treatments, there are fewer side effects, and the treatment may be as or even more effective than when the drugs are administered at high concentrations. So, we believe that there are grounds for the development of a novel treatment approach.”

Institutional support for bio venture companies is needed

Five years have passed since the company was founded in 2017. CEO Kim said he is finally getting used to his job as a representative after working as a researcher for a long time. It was not easy to run a company, but he could take full advantage of a start-up supported by a research institute.

I received a lot of help from KRIBB when I started and ran the company. It was beneficial to have experimental equipment and infrastructure already in place. KRIBB also has a well-equipped animal experimentation laboratory, so I was greatly assisted. Research networks such as KAIST, Chungnam National University Hospital, Seoul National University Bundang Hospital, and fellow researchers at KRIBB, which I worked with before starting the business, were also very helpful."

Since CEO Kim continues to be a KRIBB member, this assistance was possible.

“I took a leave of absence after starting the business. However, there is a six-year limit on the leave of absence, so the time when I must choose whether to keep the representative position or come back as a researcher is approaching. I am a little worried because it will be difficult to use the available infrastructure if I quit the KRIBB. However, even if it is difficult to combine business and research, I hope there is a little more room until I get results.”

He also emphasized the need for more institutional support for biotech companies.

“It takes time for bio start-ups to generate profits early on. Growing a company involves more expenditures and investments based on trust and potential. Recently, however, the economic downturn has declined investment in biotechnology companies. I hope that an institutional foundation will be established to support startups founded by members of research institutes in the early stages and then pay royalties in exchange for the technology transfer as sales generate capital.”

HealthBiome is gradually growing although there are still lots of challenges. Recently, they signed an investment agreement of 20 billion KRW with Cheongju City, Chungcheongbuk-do that will secure them a 1500-pyeong site in Osong Medical Cluster and build a production plant.

“Our technology that enables strain separation and direct production has been recognized, and investment is going well. Our strength is that we can build multiple pipelines because of the many strains we have secured. The strength of microbiome companies stands in the technology they possess, which can allow them to expand not only to health functional foods and treatments but also to cosmetics and medical food. However, more capital is required to do so. I want to secure enough capital to launch a microbiome-based treatment for the first time in Korea.”

Now at KRIBB

KRIBB News

KRIBB's micro-genetic scissors technology was selected as one of the ten best research achievements by NST-sponsored research institutes

Dr. Kim Yong-Sam's 'CRISPR-Cas12f technology,' developed at the Genetic Editing Research Center of the Korea Research Institute of Bioscience and Biotechnology (hereinafter referred to as KRIBB), was selected as one of the top ten outstanding research achievements by the Ministry of Science, ICT, and NST. For this achievement, Dr. Kim Yong-Sam received the Ministry of Science and ICT Award.

The 2020 Nobel Prize in Chemistry was awarded to the discovery of genetic scissors, a promising future technology for science and medicine. However, CRISPR-Cas9, the representative gene-scissors technology, has limitations in commercialization due to the large size of the product.

Nevertheless, the research team of KRIBB has developed new gene-scissors that overcome these shortcomings.

The development of a base-correcting gene-scissors technology that can correct the DNA without causing breakage led to a high-efficiency gene-scissors technology involving CRISPR.

The CRISPR-Cas12f technology is expected to contribute toward resolving the patent problem in the commercialization of gene therapy products due to its high proofreading efficiency and stability.

This technology was published in 'Nature Biotechnology (IF 54.908),' a world-renowned journal in the field of biotechnology, and five patent applications have been filed.

KRIBB-GIST joint research team wins second place in the International Precision Medicine AI Contest

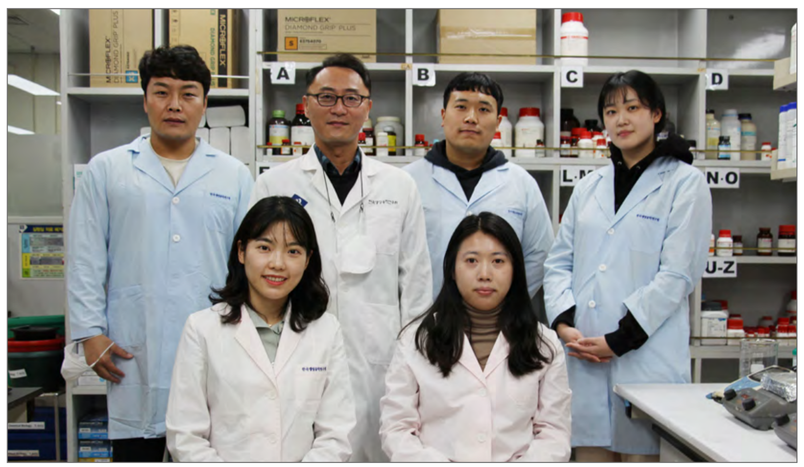
A Korean research team was the runner-up in the International Precision Medicine A.I. (Artificial Intelligence) Contest.

At the 'Microbiome DREAM Challenge,' Dr. Soo-Bok Cho and Jong-Beom Jeon from KRIBB were placed at the second position.

The project was a collaborative effort with Dr. Eun-Young Kim and Dae-Hoon Bae from the Gwangju Institute of Science and Technology Department of Electrical and Computer Engineering (Advisor Professor Ho-Jeong Nam). The DREAM Challenges, held every year since 2007, is a crowd-sourcing competition that seeks solutions to biomedical challenges using the ideas presented by participants.

In the 'Microbiome DREAM Challenge' category, a total of 42 teams and 318 participants from around the world engaged under the theme of 'Preterm Birth Prediction-Microbiome.' It was co-hosted by the National Institute of Child Health and Human Development (NICHD) under the National Institutes of Health, non-profit organization Sage Bionetworks, University of California, San Francisco, and IBM Research Institute.

Worldwide, approximately 11% (15 million) of newborns, each year, are born before completing 37 weeks of gestation (preterm). Despite the high mortality rate of infants due to premature birth and financial and emotional burden on the birthing family, there is a lack of technology that can effectively predict it. The research team built an optimal model based on machine learning using big data from more than 50,000 vaginal microbiomes presented in the contest. They ranked second in predicting early preterm birth. Along with this, they also ranked fourth in preterm birth prediction.



Microorganisms from Ulleungdo Island meet Antarctic micro-organisms to become new drug candidates

A research team in Korea has developed a new cancer metastasis inhibitor by combining microorganisms found in Korea with those abroad.

A research team led by Dr. Jaehyeok Jang of the KRIBB Center for Chemical and Biology discovered a new anti-cancer metastasis inhibitor by co-culturing native microorganisms living in the soil of Ulleungdo and fungi living in Antarctica. This discovery is expected to contribute to the development of cancer metastasis treatment based on native microorganisms and the development of new drug candidates derived from microorganisms.

The research team developed a new drug candidate, 'Ulleungdolin,' which possesses an inhibitory effect on cancer cell migration, by co-culturing a native actinomycete found in the soil of Ulleungdo and a fungus found in a lichen inhabiting King George Island in Antarctica. The research team confirmed these actinomycetes (Streptomyces sp. 13F051) produced Ulleungdorin with a novel chemical structure. However, the amount of the compound produced in a single culture was insufficient to elucidate its structure or function, but when mixed with the above-mentioned fungus (Leohumicola minima 15S071), the production of the compound increased more than tenfold. Using this method, researchers were able to reveal the structure of Ulleungdorin. This led to the discovery of a mechanism that lowered the motility of breast cancer cells, without being toxic to them, confirming the cancer metastasis-inhibiting properties of the novel drug.

Dr. Jang Jae-hyeok, head of research, said, "This is an achievement in increasing the production of new active pharmaceutical and target substances by inducing the expression of dormant biosynthetic genes through heterogeneous mixed culturing. The number of microorganisms used by humankind is only a small fraction. If we can identify the infinite potential of microorganisms, we can offer new alternatives to respond to various diseases, including rare and incurable ones such as cancer."

Meanwhile, the research team discovered new substances from actinomycetes obtained from Ulleungdo and Jeju Island soil, that can be used for novel drug development. They were named using local names, such as Ulleunganiline, Jejuketomycin, and Jejucarbazole, and were opened to the public to enhance the value of native microorganisms. The research team is conducting follow-up studies to secure these substances in large quantities and increase their utilization for various diseases, including cancer.

This research was published in the October issue of the Journal of Natural Products (IF 4.803), an international journal in natural product chemistry. The study was funded as a major project of the Ministry of Science and ICT's microbial central bank development project, Ministry of Education's protection research project, and KRIBB's main projects.

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