KRIBB *focus*

14th ISSUE | 2023

Development of gene and cell therapy for humanity

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Gene and Cell Therapy Overcoming the Limitations of Humanity with Disease Treatment and Life Prolongation

Special Interview
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KRIBB Special
Possibility of One-Shot Targeted Therapy for Intractable and Chronic Diseases

KRIBB *focus*

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.

MISSION, FUNCTION, VISION & GOALS

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

GOALS

Global Research Institute Leading the New Waves of K-BIO

- **W** — World-class R&D
- **A** — Accelerating Open Innovation
- **V** — Vitalizind Bio-industry
- **E** — Enhancing sustainability

HISTORY OF KRIBB

SINCE 1985 THE PATH OF KRIBB

1985. 2. Established the Genetic Engineering Center (Seoul and Hong Kong)

1990. 7. Relocated to a new building in Daedeok Innopolis in Daejeon

1995. 3. Renamed as "Biotechnology Research Center"

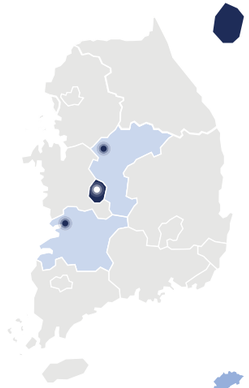
1999. 5. Became an independent legal entity under the Korea Research Council of Fundamental Science & Technology(KRCF)

2001. 1. Renamed as "Korea Research Institute of Bioscience and Biotechnology(KRIBB)"

2005. 9. Established the Ochang Branch (Ochang, Chungbuk)

2006. 11. Established the Jeonbuk Branch (Jeong-eup, Jeonbuk)

ORGANIZATION



DAEJEON HQ BIO CONVERGENCE & SOURCE TECHNOLOGY

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

- Aging Convergence Research Center
- Critical Diseases Diagnostics Convergence Research Center
- Korea Bioinformation Center
- Digital Biotech Innovation Center

SYNTHETIC BIOLOGY AND BIOENGINEERING RESEARCH INSTITUTE
- Synthetic Biology Research Center
- Genome Editing Research Center
- Cell Factory Research Center

DIVISION OF BIOMEDICAL RESEARCH
- Personalized Genomic Medicine Research Center
- Microbiome Convergence Research Center
- Rare Disease Research Center
- Biotherapeutics Translational Research Center
- Immunotherapy Research Center
- Disease Target Structure Research Center
- Metabolic Regulation Research Center

DIVISION OF RESEARCH ON NATIONAL CHALLENGES
- Infectious Disease Research Center
- Environmental Diseases Research Center
- Biodefense Research Center
- Stem Cell Convergence Research Center
- Bionanotechnology Research Center
- Plant Systems Engineering Research

DIVISION OF BIOTECHNOLOGY INNOVATION
- Technology Transfer Center
- SME Support Center
- BioProcess Engineering Center
- Bio-Evaluation Center
- Core Research Facility & Analysis Center

DIVISION OF RESEARCH STRATEGY
- Biotech Policy Research Center
- Korea Biosafety Clearing House
- National Research Safety Headquarters

OCHANG BRANCH INSTITUTE BIOMEDICAL SCIENCE

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

- Natural Product Research Center
- Chemical Biology Research Center
- Nucleic Acid Therapeutics Research Center

DIVISION OF NATIONAL BIO-INFRASTRUCTURE
- Laboratory Animal Resource & Research Center
- National Primate Research Center
- Futuristic Animal Resource & Research Center
- Bio-Resource Central Bank
- International Biological Material Research Center
- Korea Preclinical Evaluation Center
- Bio-Infrastructure Policy Support 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
- Biological Resource Center
- Primate Resources Center

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, University of Pennsylvania
Research Fellowship

USA
Korean-American Scientist and Engineers Association(KSEA)

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

NICARAGUA / UNAN-LEON

PERU / UNALM

ECUADOR / INABIO

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Gene & Cell Therapy

A Breakthrough in Disease Treatment with **Cell and Gene Therapy**

In November 2015, a shocking piece of news was delivered. One-year-old Layla from London, England, who was diagnosed with leukemia when she was just three months old, was given months to live after several rounds of chemotherapy failed, but her parents refused to give up and asked for a new treatment that was under development at the time, and within just two months, a miracle happened: the cancer cells disappeared. It was a cutting-edge therapy that involved creating "customized cells" by editing the genes of immune cells so that they would kill blood cancer cells. The treatment used was a type of cell and gene therapy (CGT), which uses genes to improve the cell function or to treat a disease. The hope that CGT will free humanity from disease, coupled with the expectation that it will bring immense economic benefits in the future, has led governments and pharmaceutical companies to invest heavily in developing related technologies. As of January 2023, there were reportedly a whopping 2,220 cellular gene therapies being studied in clinical trials, with 202 of those trials currently in Phase III, so it appears to be likely that we will see them on the market quite soon. There are also over 100 clinical trials on CRISPR genome editing technology. Currently, there are 1,457 companies developing CGT around the world, based on which we can infer the growth potential of the market. Korea is also making world-class achievements in CGT technology research, with KRIBB playing a leading role. KRIBB was the first in the world to successfully develop an immune cell therapy using natural killer (NK) cells, which automatically recognize and eliminate cancerous or virus-infected cells in the body. We are currently developing CAR-NK cell therapy that introduce specific receptors on the surface of NK cells as well as a technology to mass-produce NK cells using stem cells. Moreover, we have identified the mechanism by which enzymes that remove RNA modifications control the anti-cancer efficacy of NK cells, and this is expected to enable the development of effective treatment for intractable cancers and viral infections. We have also developed miniature base-correcting genetic scissors technology. "Genetic scissors" is a tool used to cut or modify DNA, and our researchers have created miniature genetic scissors with significantly improved correction efficiency that can be delivered to various organs in the body. This technology is expected to increase the applications and safety of gene therapy. We have also succeeded in culturing human liver and intestinal stem cells to build a three-dimensional model of the human liver which will help researchers study the mechanisms and treatments of liver disease. However, there are a number of challenges that need to be overcome in the field of cell and gene therapy. CGT is still in the experimental stage, and large amounts of clinical data need to be accumulated to prove its safety and efficacy. It is also a very complex and expensive treatment. The development of appropriate vectors, the isolation and modification of cells, and the reinjection or transplantation of the cells all require highly advanced technology and facilities. In addition, CGT can even lead to ethical issues. In the process of modifying genes, accidental errors may occur, modified genes may spread to other organisms, or modified cells may become malignant or mutate. There may even be attempts to use CGT to improve human abilities or appearance, which can lead to controversies about the essence and dignity of human beings. This is why we are working to strengthen legal regulations, such as the Bioethics and Safety Act, as well as supervision and to reach a consensus and promote dialogue among stakeholders from industry, academia, and the government to utilize CGT in an equitable and responsible manner. By doing so, we expect CGT to move away from ethical debates and gain the support from the public as technology "for people," bringing us closer to an era of healthy humanity that is free from disease.

Jang-Seong Kim
President of Korea Research Institute of Bioscience and Biotechnology (KRIBB)

Gene & Cell Therapy

Gene and Cell Therapy

Overcoming the Limitations of Humanity with Disease Treatment and Life Prolongation

Advances in biotechnology are driving a paradigm shift in healthcare and medical treatment. Gene therapy and cell therapy are fast-emerging as the therapies of the future. In fact, biopharmaceuticals are undergoing a paradigm shift from biologics and protein therapies (the first generation) to antibody drugs (the second generation) to cell and gene therapy (the third generation), with the development of related technologies. Cell and gene therapy (CGT), which has recently emerged as the next generation of therapeutics, has become the core part of the biotech field. Cellular therapeutics are medicines manufactured by manipulating human or living animal cells (stem cells, somatic cells, immune cells) *in vitro* by physical, chemical, and biological methods. Living cells are mainly used to induce regeneration to restore damaged or diseased cells and tissues. Gene therapy agents are medicines that treat genetic defects by injecting therapeutic genes into the patient's cells using genetic manipulation. They are intended to treat the disease by correcting defective genes using genetic material or cells with modified or introduced genetic material. According to the Global Cell and Gene Therapy (CGT) Market Forecast, a report released by the National Biotech Policy Research Center this past June, the global CGT market is expected to grow from USD 4.67 billion in 2021 to USD 41.77 billion in 2027, at a compound annual growth rate of more than 44%. To be more specific, the cell therapy market is projected to expand from USD 540 million in 2021 to USD 7.98 billion in 2027 (CAGR of 56.7%) and the gene therapy market from USD 2.03 billion in 2021 to USD 18.41 billion in 2027 (CAGR of 44.6%). The reason CGT is expected to change the paradigm of biotech R&D and drive the growth of the related markets is that they will enable personalized treatment. In particular, they appear especially promising in the treatment of intractable diseases such as cancer, neurodegenerative diseases, and genetic diseases thanks to their high targeting accuracy compared to conventional cancer therapies. The rising incidence of cancer worldwide is also raising expectations for the development of CGT. Another important factor is that the number of chronic diseases such as diabetes is steadily increasing due to the growing elderly population. KRIBB Focus sheds light on cell and gene therapy, which will become the core part of biotech R&D with expectations that it will change people's lives.

GENE&CELL

Close Collaboration and Division of Roles Essential for **Winning the Race for Supremacy in Cell and Gene Therapy**

Interview with experts on strengthening competitiveness in cell and gene therapy R&D

Professor of Ophthalmology, Seoul National University Hospital (SNUH)
Jeong-Hun Kim

Lead Researcher, Stem Cell Convergence Research Center, KRIBB
Jang-Hwan Kim

Director of the Center for Genome Engineering, IBS
Bon-Kyoung Koo

Division of Research on National Challenges, Korea Biotechnology Institute
Kyung-Sook Chung

Cell and gene therapy (CGT) is changing the paradigm of research and development (R&D) in the bio and medical fields and the landscape of related industries. It is considered a fundamental therapeutic technology that can help humanity overcome intractable diseases such as cancer, degenerative diseases, and congenital genetic disorders that threaten people's health and lives. With the CGT market exhibiting exponential growth each year, there has been a heated race to gain dominance over the global market. Korea has also jumped in, concentrating all its capabilities on R&D in the field of CGT, which is rapidly becoming one of the new growth engines of the future, based on the excellent bio-medical technologies secured by research institutes, universities, and enterprises. To learn about the global status of CGT and the current situation in Korea and determine what we must do to get ahead of the game, we sought valuable insight from experts, including Jeong-Hun Kim, Professor of Ophthalmology at Seoul National University (SNU), Bon-Kyoung Koo, Director of the Center for Genome Engineering at the Institute for Basic Science (IBS), Jang-Hwan Kim, Lead Researcher of the Stem Cell Convergence Research Center at the Korea Research Institute of Bioscience and Biotechnology (KRIBB), and Kyung-Sook Chung, Head of the Division of Research on National Challenges.

:: Korea's position in the global cell and gene therapy market

Korea has been striving to become a global biotech powerhouse, so what's its current position in the field of cell and gene therapy? What issues must we resolve first to gain an edge in the competition that's becoming increasingly heated? We diagnosed the current situation and challenges based on the voices of experts working in research and clinical fields.

Bon-Kyoung Koo —— New technologies are constantly being developed in the field of cell and gene therapy around the world, so securing patents for original technologies is of the utmost importance and Korea is gaining competitiveness in some of the areas. In the field of gene therapy, for example, IBS has patents related to "genetic scissors (CRISPR)," and KRIBB has also accumulated basic assets, including patented technologies. Efforts are also being made in the field of cell therapy, so I expect that excellent results will be derived one after another. Given that we have outstanding human resources and rich experience, I believe we'll become sufficiently competitive if young scientists take on challenging research.

Jeong-Hun Kim —— Antibody therapies such as small molecule drugs are not developed in-house*. Researchers are involved in the R&D phase, but multinational pharmaceutical companies further develop the results obtained from the R&D, conduct clinical trials, and then launch the products. Ultimately, it is difficult to develop drugs without multinational companies with an enormous amount of capital and infrastructure. However, cell and gene therapy is different. You don't necessarily need a large corporation or a global multinational company to develop it, as it can be developed sufficiently in-house, so I think it's a field that we can venture into, and there's even a possibility that we may even have an edge in the global race for supremacy.

*In-house: The opposite concept of outsourcing that means the work is performed inside the organization itself

Jang-Hwan Kim —— I mostly agree that the field of cell and gene therapy will continue to grow, and I see this as a positive thing. Small molecule drugs continue to remain prominent not only in Korea but globally, but in terms of the overall proportion, it is shrinking in size, while the biologics and advanced biopharmaceuticals market is growing. The problem is that the research and development stages are not separated but combined together. People, for some reason, expect that good research will lead to good results, but when I participated in the establishment of a startup within the institute, I came to realize that research and development have such different differences and that we need to clearly separate research and development conceptually and support them separately for people working in the research stage to pursue more creative and challenging research and people in the development stage to speed up the process required for development.

Jeong-Hun Kim —— If you have a team of people who excel at research, you can actually get to the clinical phase and help patients. The reason why you need a multinational company is that clinical trials require a lot of time and money, but due to the nature of rare and intractable diseases where gene therapy or cell therapy is applied, there are only few patients, so it's impossible to do all three phases of clinical research, and there is no reason to. Another thing to note is that gene mutations have racial characteristics. For example, if you have a disease called A, the mutation may be common in the United States or Europe, but not as so in Korea or Asia. In other words, instead of aiming to export to the United States, Europe, and so on, cell and gene therapy needs to be developed based on a hub concept. That is, if we offer good treatment, patients with this disease will come to Korea to receive treatment. This is why I think this is an opportunity we must seize now.

Bon-Kyoung Koo —— Actually, I think both ends are in good contact. There is an excellent network of people who do basic research and people who can conduct clinical trials, like Professor Kim, and we even have the technology. It would be great to have more legal and ethical protection measures. People need to feel protected when they try something new because without such protection, they may be held accountable for the research later. Naturally, accidents can happen during testing, and from a researcher's perspective, being protected against liabilities is an important issue. In the case of cell and gene therapy, in particular, it must differ in many ways from previous new drug development methods and procedures. The patient pool is extremely small, so even large corporations cannot easily jump in. This is why we must approach it differently.

:: The global status cell and gene therapy

The competition for technological supremacy and global market dominance in the field of cell and gene therapy is growing increasingly fierce. This is because cell and gene therapy, which aims to protect human health and life from rare and incurable diseases, is fast-emerging as a new growth engine for the future with the expansion of related markets. Here, we examine the current global situation with cell and gene therapy.

Jeong-Hun Kim —— If you look at the main direction of cell and gene therapy today, the United States is focusing on common diseases because their first and foremost objective is to make profits. In other words, they're focusing on diseases that they can make a lot of money on by selling lots of drugs. On the other hand, Europe is investing in diseases that cannot be treated with conventional therapies, or what we call rare and intractable diseases, where cell and gene therapy is the only option because there really is no other treatment. There's only a small pool of patients, and it's costly, but they are using public funds toward it, and this is a great opportunity for researchers. It's a great opportunity for researchers because they can be proactive and try new things in R&D as long as they meet the prescribed regulations.

Kyung-Sook Chung —— I think we should first look at why many

global pharmaceutical companies have become interested in developing cell and gene therapy. First of all, it's been a long time since synthetic biology or synthetic drugs have not produced a blockbuster drug that boomed or dominated the market. So, naturally, global pharmaceutical companies began looking toward cell and gene therapy as a new growth engine. The reason behind this is that with the advancement of technologies such as next-generation sequencing and the gene mapping that Professor Kim Jeong-hun and Director Koo Bon-kyoung are doing, there have been technological innovations that allow us to target areas that were previously inaccessible. At the same time, patients are growing more and more aware of what genes or cells are causing their problems and are demanding that treatments be developed for them.

Jeong-Hun Kim —— To give you a better understanding of cell and gene therapy, I'd like to introduce the area of research that I'm working on, which is cell and gene therapy for the eye. At the stage where there is a gene mutation and the retinal cells are damaged, gene therapy or gene correction is necessary, and past that stage, cell therapy will become necessary. I'm basically a clinical researcher who studies and deals with both gene therapy and cell therapy, and the challenge I experience in the clinical setting is that even if there are patients who have the same disease and gene mutation, the treatment needs to be customized for each patient. There is a need for immense basic research results related to genes and cells for treatment, which is why I have a lot to request from KRIBB and IBS.

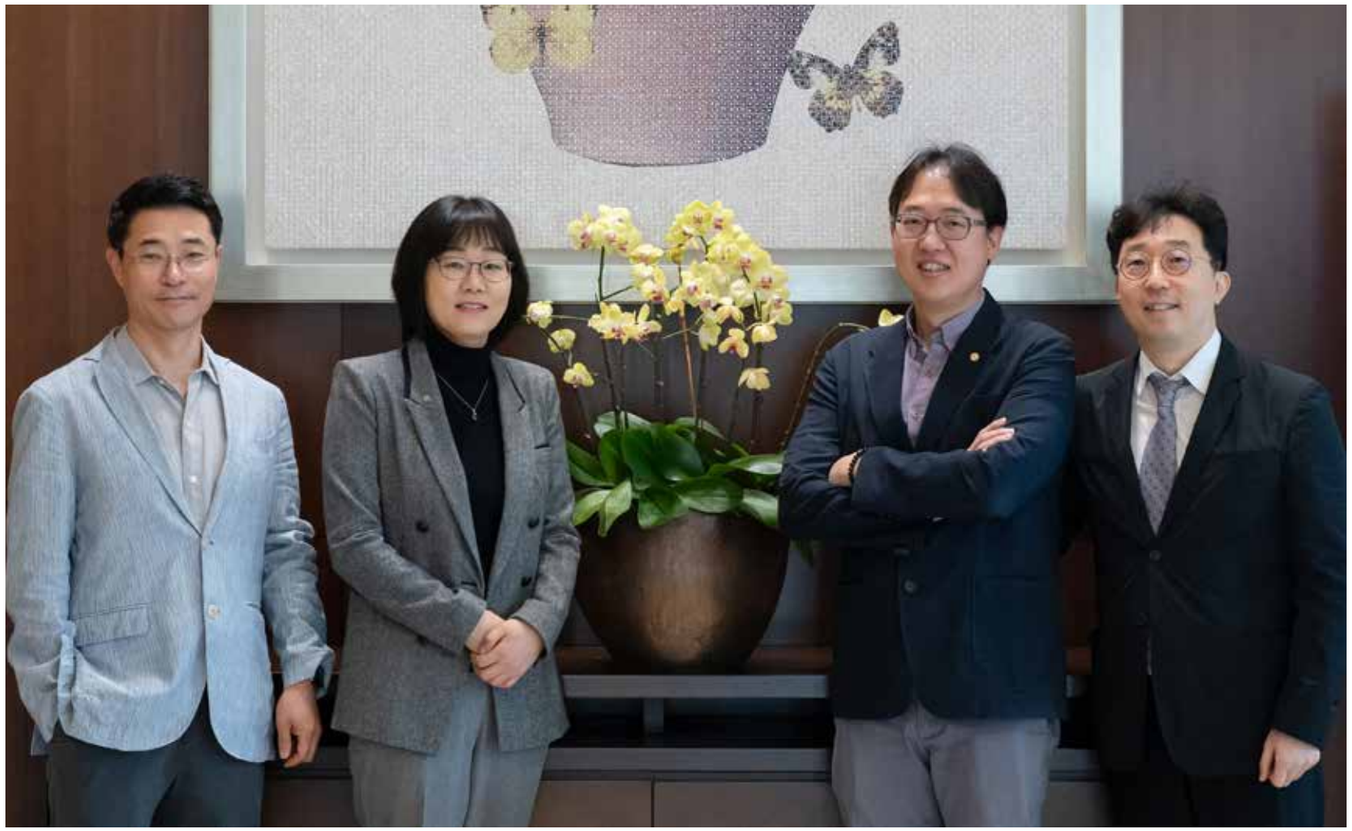
:: Undertakings to strengthen competitiveness in cell and gene therapy

Despite its late start, Korea has made noteworthy achievements in the biotech sector. This is also true for cell and gene therapy, which is changing the paradigm of the biotech sector. Experts we spoke to emphasized the importance of collaboration and division of roles among R&D and clinical organizations for Korea to take a bigger leap forward. What must be done first to get us there?

Jeong-Hun Kim — In drug development and cell and gene therapy R&D, role division and collaboration are crucial, and I think we can find a clue in today's dialogue. IBS is an institution that specializes in basic research, whereas KRIBB has researchers who are skilled in basic research and others who are good at clinical research, so I think it can play a role as an intermediary or a hub. At the same time, people like me, on the final tip of the R&D spectrum, can play a role in administering the therapeutic drugs developed for patients, and even providing the sources for basic research needed for cell and gene therapy R&D. So far, the division of roles and collaboration have proceeded smoothly, but they'll need to be emphasized more in the field of cell and gene therapy.

Kyung-Sook Chung —— I agree. There are more than 7,000 rare diseases, which is a huge number, but the number of patients affected by those diseases is relatively small, which makes common platform technology crucial. With platform technology, it can be applied to diverse diseases, even if they involve different genes. It's important to develop a cure for each disease, but it is also necessary to advance and diversify the platform technology, and I think this should be undertaken by KRIBB. It is essential to secure platform technology so as to build a strong fence to retain our intellectual properties, which are our national assets. It is important to develop and export treatments, but as Professor Kim Jeong-hun mentioned, Korea can serve as a hub for rare disease treatment. In this regard, I think it is also the role of public institutions such as ours to create such fences and barriers.

Jang-Hwan Kim —— As a continuation of what I said earlier, in the case of places that focus on research, such as KRIBB and the IBS, it is difficult to consider development as well. That's why I'm saying that we should clearly separate research and development conceptually, so that those who are involved the research stage can take on more creative and challenging research. If you think about it, the cost of research is relatively small compared to development because there is a lot more going on in the development phase, so I think that researchers should continue to focus on research, but there needs to be more attention to the concept of what happens at the end and how development actually happens. As Professor Kim pointed out, one of our If you think about it, the amount of money that goes into the research phase is relatively small compared to the development phase, and there's a lot more going on in the development phase. So, I think that researchers should continue to focus on research, but at the same time, pay attention to how things proceed at the end and how development actually proceeds. As Professor Kim Jeong-hun pointed out, I think KRIBB should play more of an intermediary role between research and development.



Bon-Kyoung Koo — As for R&D, division of roles, and collaboration, we can find great examples in the aerospace and defense industries. In the case of the development of the Nuri, the Korean launch vehicle, under the supervision of the Korea Aerospace Research Institute, more than 100 companies had their names listed as participating companies, and the development of the Korean fighter jet was also developed in this way and resulted in a world-class outcome. Although it may not be applied in the same way, if this approach can be taken in the biomedical field, especially cell and gene therapy, we'll be able to gain an edge in the global market. If we designate the biotech industry a new growth engine and have research institutes performing pivotal roles in R&D with the participation of multiple companies, don't you think we'll be able to create national wealth in the same way as the aerospace and defense industries have done?

:: Concerns related to cell and gene therapy and countermeasures

With the current system, it is difficult to keep up with the technological advancement of cell and gene therapy, which is rapidly becoming a new growth engine and growing market with immense potential. There are some areas where Korea is displaying excellence, but there are also areas where we lack. What do we need to prepare for and what do we need to improve to drive the growth of our cell and gene therapy industry?

Jeong-Hun Kim —— It is true that clinical development is also important for cell and gene therapy. However, although I'm not a renowned researcher or have a lot of money, I was still able to prepare for a clinical trial. How was that possible? Because of researchers, like Koo Bon-kyoung and. Chung Kyung-sook, who helped me step by step. About 10 of us worked together, and we quickly got almost to the end. Of course, our work has been halted in the development phase, and we haven't even been able to give it a shot because it costs about KRW 2 billion. What I realized through this experience is that researchers can push forward if they work together. At the same time, I also realized the need for a contract development and manufacturing organization (CDMO) beyond just a contract manufacturing organization (CMO) that can provide services from R&D to clinical trials and manufacturing.

Kyung-Sook Chung —— Unfortunately, KRIBB cannot serve as a CDMO because we cannot equip ourselves with a mass production system to make research viruses or research gene and cell therapies that are of sufficient quality to replace animal testing. This sort of work is instead undertaken by domestic biotech companies like Samsung Biologics and Celltrion. Having said that, in terms of mass production, I think Korea has sufficient production technology and just needs to build excellent pipelines and create the content. Another thing to note is that many domestic pharmaceutical companies have also reached a level where they can carry out synthetic biology R&D, so I think the development of gene and cell therapy will be able to proceed a bit faster if consortiums are organized among companies or of research institutes and companies to proceed with the entire process of R&D, clinical research, and manufacturing.

Jang-Hwan Kim —— Here's something to think about. The industrial output of biotech or medical science, including the field of cell and gene therapy, is always a treatment agent. In the case of related businesses or industries, mechanical engineering, and chemistry, they produce outputs without clinical trials, so in those fields, development of technology can lead to commercialization quite fast. In biotech, on the other hand, even if you develop technology, it takes a long time to commercialize, as it needs to go through preclinical and clinical phases. So, your patent strategy as to how you manage your patents is absolutely critical.

This is also an issue that necessitates the separation of research and development.

Bon-Kyoung Koo — Clinical trials are still an important part of cell and gene therapy development, although in a different way than before. In the case of rare diseases, one aspect that needs to be considered is that the conventional process of testing the drug candidate is not possible and the only alternative is to test the stability of the platform technology. It's actually a great risk and undertaking to take one step further. Of course, all clinical trials are a challenge, but when it comes to rare diseases, I believe it is necessary to secure data to a certain extent and ensure stability and conduct clinical trials under the state's supervision. In other words, the platform may be developed in the traditional way, but at the end of the day, the question of what kind of drug should be made and when and how requires a more multi-faceted and thorough examination.

:: Expert suggestions for advancing cell and gene therapy

Korea is not a top-tier country in cell and gene therapy. However, the foundation and conditions are sufficient for Korea to reach the top. What do we need to do now to go beyond being the top-class in related fields and become a biotech powerhouse? We asked the experts for their suggestions.

Jang-Hwan Kim — Objectively speaking, it's hard to say that Korea is a global leader in cell and gene therapy, but it's also hard to say that there is a country currently in the driver's seat and leading the R&D and market in this particular field. In other words, with enough support and R&D from now on, we have the potential to become a global leader. So, I think we need to take a closer look at what we need to overcome technologically, whether it's related to gene therapy or cell therapy. Another important thing is that researchers, the key players in the R&D process, should make efforts to better understand the end point of cell and gene therapy R&D – that is, how therapeutics are developed and how they are made.

Jeong-Hun Kim — Again, I think the role of KRIBB is important. Korea may have shortcomings in other aspects, but from the perspective of the end user, Korea is ahead in terms of applications. That is, Korea is at the forefront when it comes to medical technology, and this is something that multinational companies around the world would agree with. Since we have the best health technology, we can run the most effective clinical trials at the lowest cost. With excellence in each of these elements, as long as there are entities that can play the role of an intermediary, mediator, or headquarters and so on, Korea will be able to lead the global race for supremacy in cell and gene therapy. I would like to see KRIBB, whose work lies somewhere between basic and clinical research, play that role. I believe it has the qualifications and capabilities to do so.

Kyung-Sook Chung —— There are some things that we have done well and others things not so much. Korea can become an advanced country in the field of cell and gene therapy by further developing our strengths and working to improve upon our shortcomings. For example, in the case of adult stem cells, we have made quite an achievement, but the problem is that we are stuck there. This is because our pipelines for gene cells, immune cells, and genetically modified cells, which require more advanced technology, are somewhat weak. If we miss out on this chance, countries that are ahead of the game will acquire all related patents, and we'll have to pay a lot to use those technologies. So I'd like to see more investment in the development of cell and gene therapy aimed at treating rare and intractable diseases. If we don't jump the technological hurdle now, we're going to cross the finish line much later than our competitors.

Bon-Kyoung Koo —— I agree that the status and role of KRIBB as a government-funded research institute is more important than ever. I believe it is the responsibility of government-funded research institutes to focus their efforts on areas that are directly related to national competitiveness. As I mentioned earlier, we can find precedents in the aerospace and defense industries. The mission of KRIBB is clear in the field of biotech, especially in the field of cell and gene therapy that's becoming increasingly important. If large-scale investments and support are made, and if KRIBB fulfills its status and role as a government-funded research institute, all related issues will be resolved naturally. In this regard, it can be said that the biotech sector will follow a new path that has not been traveled before. I believe Korea will be able to gain global competitiveness in biotech and cell and gene therapy, just as we have done in the aerospace and defense industries.

The exuberant interview was not without any disagreements, but the experts, who ultimately share the same vision and goals, could always find a common ground. They were all candid in their thoughts about the current issues with Korea's cell and gene therapy and biotech R&D and industries. The points they made will ultimately serve as the basis for improvements that will usher in a brighter future for these sectors. During the conversation that lasted more than two hours, all four experts agreed that Korea will be a key player in the global race for technological supremacy in the field of cell and gene therapy.

Possibility of One-Shot Targeted Therapy for **Intractable and Chronic Diseases**

Cell and Gene Therapy Changing People's Lives and the Future of Humanity

Cell therapy and gene therapy are rapidly emerging as the future of biopharmaceuticals, following biologics and protein therapies (first generation) and antibody drugs (second generation). With the growing prevalence of chronic diseases such as cancer, intractable diseases, and diabetes due to changes in lifestyle and environmental factors among other causes, there has been a growing interest in gene therapy and cell therapy. According to the World Health Organization (WHO), around 10 million people died from cancer worldwide in 2020, and this number is expected to continue to rise. Korea is no exception: a total of 82,688 people died from cancer in Korea in 2021, accounting for 26.0% of the country's total deaths of 317,680.

In 2022, cancer remained as the number one cause of death in Korea. According to Statistics Korea's Statistics on the Causes of Death in 2022, the cancer mortality rate was 162.7 (per 100,000), the highest among all causes of death. It is worth noting that, besides cancer, most of the top 10 causes of death were a diseases or chronic condition. Heart disease (65.8 per 100,000), COVID-19 (61.0), pneumonia (52.1), cerebrovascular disease (49.6), suicide (25.2), Alzheimer's disease (22.7), diabetes (21.8), hypertension (15.1), and liver disease (14.7) were in the top 10. As shown, the only non-disease cause of death was suicide. Notably, dementia-related deaths, including Alzheimer's disease, were recorded at 14,136, a staggering 36.6% increase from the previous year.

Literally, gene therapy uses genes and cell therapy uses living cells to treat diseases. Gene therapy has gone from being a theoretical possibility to a practical technology, as evidenced by the application of CRISPR, a form of genetic editing technology called the "genetic scissors." Cell therapy, which had been used mainly to regenerate skin and cartilage using skin cells or chondrocytes, is now being more widely applied thanks to research on stem cells and immune cells targeting cancer and degenerative diseases.

Cell and gene therapy **changing the biotech paradigm**

As such, cell and gene therapy (CGT) is attracting attention as a fundamental therapeutic technology that is expected to enable the treatment of intractable diseases such as cancer, neurodegenerative diseases, and congenital genetic diseases. Until now, it has faced difficulties in R&D and commercialization due to the lack of effectiveness in the body and bioethics issues due to the use of living cells for treatment. However, in recent years, advances in cell culture and gene manipulation technologies have helped resolve many of those issues, and some CGTs have received marketing approval in the United States and Europe, thereby exhibiting their potential as a new future growth engine.

CGT seems particularly promising because of its effectiveness. The biggest advantages of CGT are that the therapeutic substance can be expressed in the body for a long time with just a single administration, and gene transfer and expression can be artificially controlled. It is also possible to correct mutated genes by gene recombination, and it leads to fewer side effects, as it acts only on specific areas. That is, CGT is a customized therapy that can produce long-lasting therapeutic effects without side effects. Of course, the CGT market has extremely high growth potential, but the process from R&D to commercialization is difficult and time-consuming. In fact, as of 2023, only 14 CGT products have been approved by the US FDA. As such, the barriers to entry are high, and so are the prices. However, these downsides have highlighted the fact that the global CGT market is actually a "blue ocean."

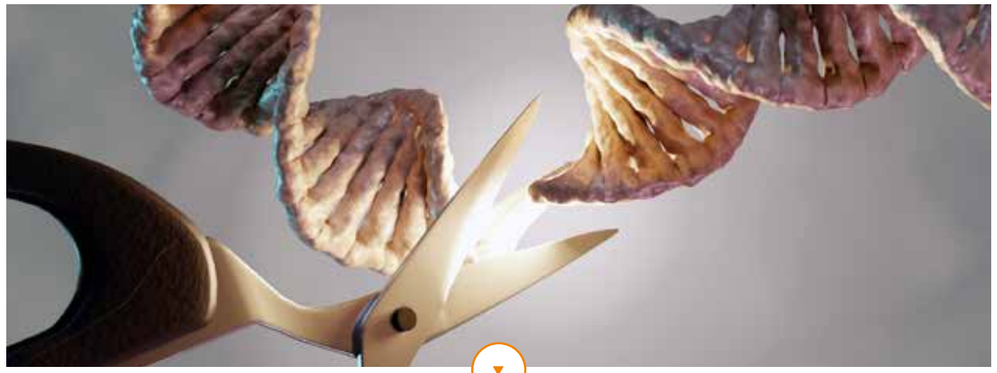
In fact, according to the *Global Cell and Gene Therapy (CGT) Market Forecast* published in June by the National Biotech Policy Research Center, the CGT market is expected to grow from USD 4.67 billion in 2021 to USD 41.77 billion (approx. KRW 57 trillion) in 2027. The Korea Health Industry Development Institute also released a report projecting that the global CGT market size, which was USD 10.67 billion in 2022, will surpass the USD 16,330 million mark in 2023 and reach USD 55,509 million (approximately KRW 77 trillion) in 2026. The Korea Bio-economy Research Center of the Korea Biotechnology Industry Organization noted an uptrend in the global CGT investment, which recorded USD 12.6 billion (approx. KRW 17 trillion) in 2022. As of January this year, more than 2,200 CGT clinical trials are underway, and there are 1,457 CGT development companies worldwide, up 11% year-on-year.

Global biotech companies increasing investment in CGT to **"seize the blue ocean"**

With the growth of the CGT and related markets, global pharmaceutical and biotechnology companies are increasing their investments in CGT R&D to take the lead. According to the report, *Global Cell and Gene Therapy Market Outlook and Open Innovation Trends,* published by the Korea Health Industry Development Institute (KHIDI) in *Health Industry Brief* (No. 352), Novartis, a pharmaceutical company that traditionally focused on synthetic drugs, reduced the target share of synthetic drug sales from 70% to less than half, with plans to increase the share of gene therapy and protein recombinant therapy to 20%. Pfizer, on the other hand, is planning collaborations with two cell and gene therapy companies, and Bayer is in the process of acquiring gene editing technology from a biotech company for USD 1 billion (approx. KRW 1.35 trillion).

Although the CGT market was considered to be in its infancy with few approved drugs until the mid-2010s, the market is growing rapidly with an increased number of approved drugs, triggering intensifying competition among global pharmaceutical and biotech companies. In particular, there are more and more companies are pursuing open innovation to carry out R&D more efficiently by collaborating with external entities, instead of than handling the entire value chain of drug development on its own, according to a report by the KHIDI. In fact, Takeda invested USD 62 billion (approx. KRW 84 trillion) to acquire a rare disease treatment development company and emerged as one of the top-ranking global pharmaceutical companies. Global pharmaceutical giants such as AstraZeneca and Abbvie are also investing tens of billions of dollars annually to introduce CGT technologies and acquire related companies.

Global pharmaceutical and biotech companies are seeing tangible results as a result of increasing their investment in R&D for CGT products. To date, only 14 CGT products have been approved by the US FDA, but the steep price tags and promising efficacy of CGT are driving R&D and commercialization efforts. In fact, in 2017, Novartis' Kymriah, the first immune cell therapy (chimeric antigen receptor (CAR) T-cell therapy), was catapulted into the global limelight when it was approved by the US FDA. Kymriah is the first personalized, genetically modified T-cell therapy for patients with B-cell acute lymphocytic leukemia, and it was approved by the Ministry of Food and Drug Safety of Korea and marketed in Korea at the price of KRW 320 million. CARVYKTI, which was approved by the FDA this year, is a CAR-T cell therapy developed by Johnson & Johnson and Legend Bio, and it costs USD 465,000 (about KRW 630 million). Bluebird Bio's ZYNTEGLO, a treatment for the rare disease called beta-thalassemia, broke the record for the most expensive CGT (USD 2.8 million).



Tackling intractable diseases with genetic scissor **and stem cell technology**

Pharmaceutical and biotech R&D, including CGT, is moving toward a new future with advances in gene technology and analytical techniques. “Genetic scissors” technology, for instance, has advanced by leaps and bounds in a short period of time. The currently developed genetic scissors include zinc-finger nucleases (ZFNs), TALENs, and CRISPR-Cas9, which are referred to as the first, second, and third generation gene editing tools, respectively. Gene editing technology has been in the spotlight since the reveal of CRISPR-Cas9, the third generation, two years ago. This technology can be used to eliminate genetic diseases caused by faulty genes in early stages. It involves introducing special enzymes into cells, where the enzymes act like scissors to find and cut the desired DNA. For example, hemophilia, a condition in which the blood does not clot and therefore bleeding cannot be stopped, could be cured if the causative gene can be fixed using genetic scissors.

Cell therapy is another breakthrough in biotechnology. Cell therapeutics use living cells for treatment. Since the early 20th century, living cells have been used directly in medical treatment, such as blood transfusions and bone marrow transplants. Since then, advances in genetic engineering and cell culture technology have broadened the range of targets and diseases targeted by cell therapy, thereby increasing its applications and medical importance. The types of cells used in cell therapy are mainly divided into stem cells, immune cells, and skin and cartilage cells. Stem cells, in particular, can be further subdivided into embryonic stem cells, induced pluripotent stem cells (iPS), and adult stem cells, while immune cells are subdivided into dendritic cells and T cells.

Cells have a fixed lifespan and die after a certain period of time after fulfilling their role, although there are differences across different types of cells. Stem cells, for instance, are responsible for continuously producing new cells, and they share something in common with genetic scissors in that they can both be applied to combat incurable diseases and explore the origins of life. However, while gene editing is a technology used to alter a trait, stem cells are used to create cells with the same trait. Stem cell research is challenging because stem cells need to be extracted and cultured, but culturing stem cells and controlling the process is difficult because the lab has a different environment from that of the body. To solve these problems, researchers have recently been using induced pluripotent stem cells, which are derived by turning back the hands of time for cells that have already differentiated into somatic cells so that they can gain the properties of stem cells.

KRIBB producing excellent R&D results and engaging in **large-scale technology transfers**

In line with these technological advancements and environmental changes, KRIBB, Korea’s leading government-funded research institute in the biotech sector, has been producing excellent research results. In 2021, Dr. Kim Yong-sam and GenKOre, a company founded by KRIBB, jointly developed CRISPR-Cas12f1, miniature CRISPR genetic scissors that are smaller than CRISPR-Cas9, that can be used to treat various genetic diseases. They also successfully developed a correction technology with which corrections could be made without cutting DNA, thereby increasing the applicability of the technology to treat genetic diseases that cannot be accessed with conventional genetic scissors.

KRIBB is also paving the way for the treatment of intractable cancer without side effects by developing cell therapy technology. A team led by Dr. Choi In-pyo from the KRIBB Immunotherapy Research Center succeeded in isolating and differentiating highly active natural killer (NK) cells from hematopoietic stem cells and multiplying them in large amounts. Hematopoietic stem cells are stem cells that produce all kinds of cells, from blood cells to immune cells, throughout their lives, while NK cells are a type of lymphocyte cells that selectively kill cells that are harmful to the body.

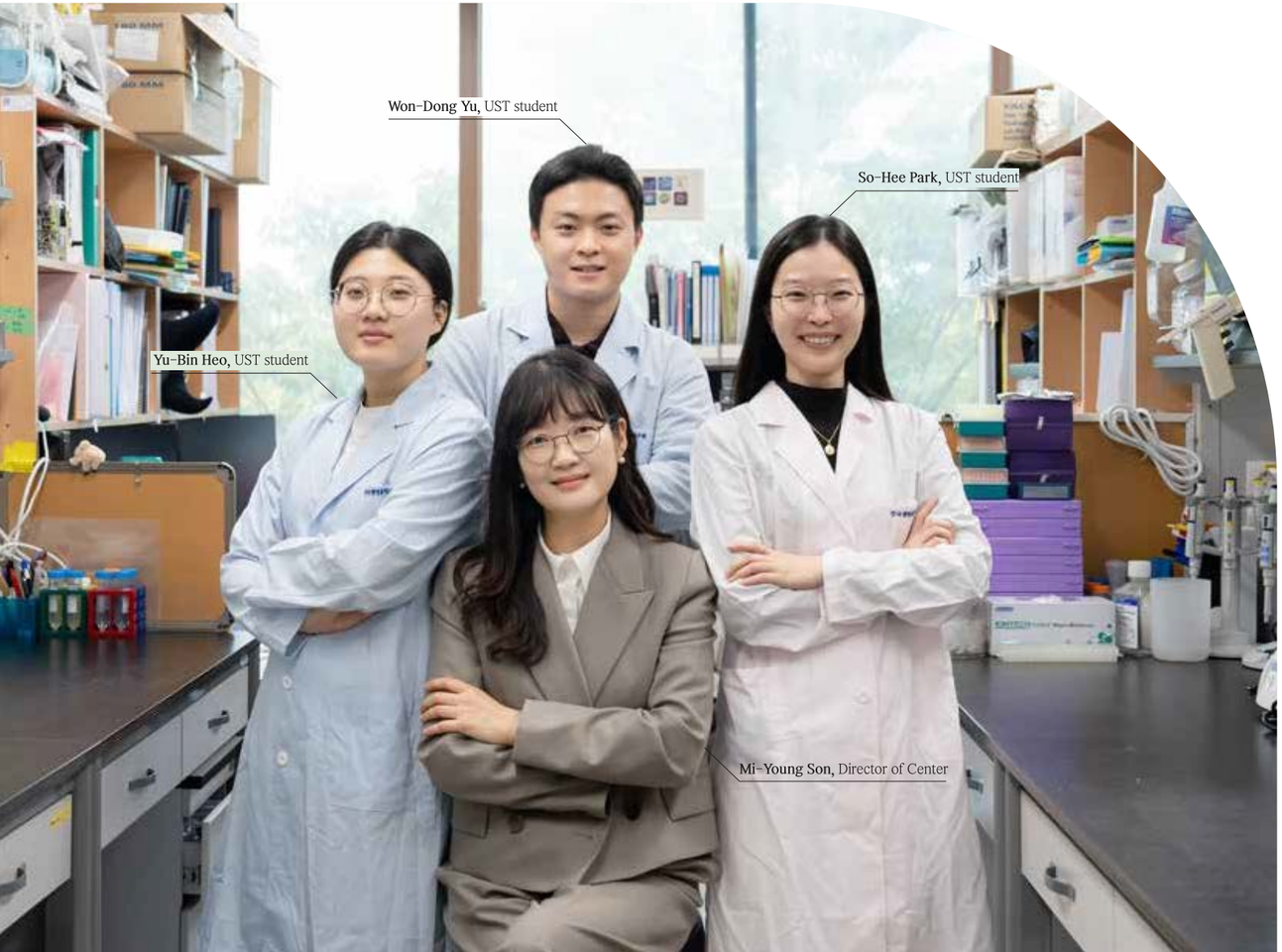
KRIBB is currently developing a CAR-NK anti-cancer therapy with the introduction of a chimeric antigen receptor (CAR) gene design with enhanced anti-cancer efficacy. CARs are receptor proteins that consist of an outer part with antibodies that are involved in cell proliferation and an inner part that is responsible for immune system activation. A research team led by Dr. Kim Tae-don at the KRIBB Immunotherapy Research Center developed CAR-NK cells that compensate for the shortcomings of CAR-T cells and maximize anti-cancer effects based on previous technologies. In 2019, the team also successfully developed a proliferative human organ (liver) simulation model using human pluripotent stem cells that can differentiate into almost any type of body cells in the human body.

In the past, people believed that the generation and differentiation of cells, from fertilization and generation to birth, were not within the realm of human technology, but rather the laws of nature. However, it has been proven that the generation and differentiation of cells is possible with science and technology, as witnessed by gene editing and stem cell therapy. As a result, global pharmaceutical and biotechnology companies and countries around the world are viewing cell and gene therapy as a new growth engine of the future. Korea, which has relatively little experience and has not made much financial investment in the development of CGT, is now focusing its R&D investment and providing policy support to develop related technologies. In line with this, KRIBB is also concentrating on relevant research to lead K-biotech and boost Korea’s CGT capabilities to a global level.

Ambitious Undertakings to **Extend People's Health Span**

Stem Cell Convergenece Research Center

The Stem Cell Convergence Research Center is a major research center staffed with around 50 people. The main areas of research are stem cells and organoids made using stem cells. They also carry out research on advanced biopharmaceuticals such as gene therapy and cell therapy. The center has been named Stem Cell Convergence Research Center because it undertakes a broad range of studies related to stem cells. Dr. Son Mi-young, who oversees the center, joined KRIBB as a full-time researcher at the Development & Differentiation Research Center in 2005 and continued her research in the field of stem cells at the Regenerative Medicine Research Center and the Stem Cell Research Center. It is based on the philosophy of "convergence" that Son runs the research center, stressing the importance of bringing and fusing together resources, expertise, and so on. In addition to striving for convergence among researchers within the Stem Cell Convergence Research Center, she also actively collaborates with KRIBB researchers from other fields whenever they seek her expertise.



"In late 2022, U.S. President Joe Biden announced that the United States will no longer require animal testing results for drug development. As such, it has become crucial to develop alternative models and test methods that can replace animal testing. Under these circumstances, researchers around the world are finding it most useful to use organoids, which can mimic human organs and thus enable human body-based research from the preclinical stage," explained Son. These days, animal testing is being discouraged not only due to ethical concerns, but also from a scientific perspective. In order to overcome the limitations caused by the species differences between human and animal models, it is necessary to verify the results of animal experiments using human cell models or human organ models. This is why organoids, the physiological model system that most closely resembles human organs, are utilized as experimental models. Organoids also have high differentiation capabilities and contain stem cells with regenerative capabilities, making them a promising technology that may be applied to regenerative therapy. That is, by directly implanting an organoid into the lesion, it can serve as a regenerative therapeutic agent.

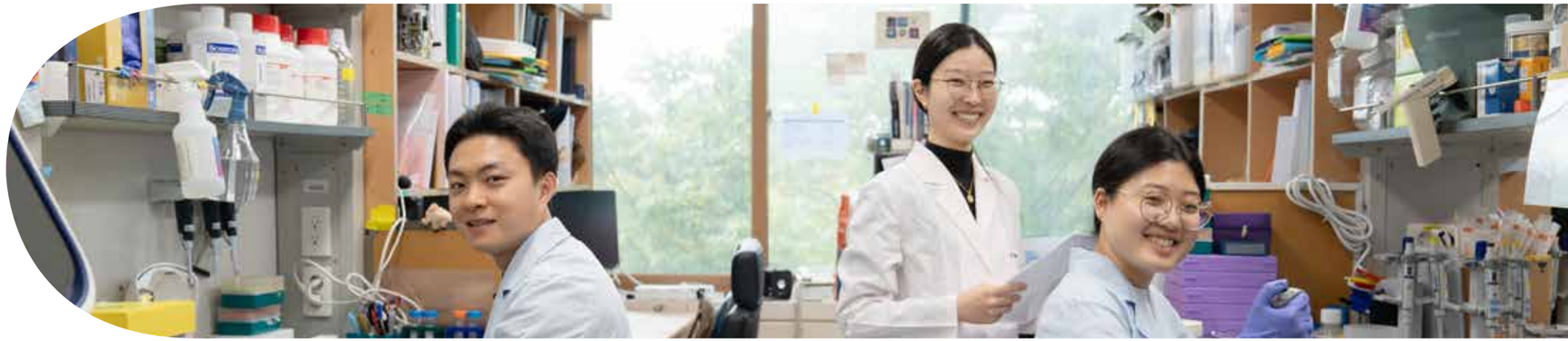
Organoids thrust into the global limelight

An organoid is a three-dimensional cell aggregate consisting of various cell types of human organ or tissue, with a tissue structure similar to a living organism and characteristic functions of the target organ. They are also known as "mini-organs" or "organ mimics."
There are mainly two ways to create organoids. It is by using either adult stem cells or pluripotent stem cells, but in the case of using embryonic stem cells, a type of pluripotent stem cell, there are ethical concerns relating to destroying the embryos. In consideration of this issue, in 2006, Professor Yamanaka's team at Kyoto University developed a reprogramming technology to introduce specific genes into differentiated somatic cells collected from patients, thereby creating induced pluripotent stem cells that have the same properties as embryonic stem cells but do not raise any ethical issues. The KRIBB Stem Cell Convergence Research Center has the world's best technology in the field of organoids created using induced pluripotent stem cells. With the growing importance of organoids, the center is gaining more prominence on the world stage.

KRIBB's organoid technology

Leading the advances in organoid technology at home and abroad

In 2018, the team led by Son Mi-young developed and presented intestinal organoid maturation technology. In order to replace substitute lab animals, it is necessary to be able to simulate not only the shape but also the characteristic function of each organ, and this is referred to as "maturation." Director Son and her team devised an *in vitro* maturation technique to recreate the human intestinal environment in the laboratory and developed a mature intestinal organoid model with all the physiological characteristics and functionality of the intestines of a human adult. This was the world's first achievement in overcoming the immaturity issue of three-dimensional intestinal organoids differentiated from stem cells. The technology was transferred to a company specializing in organoids in 2022. "Intestinal organoids can be used in a variety of ways. First, they are vital as a model to evaluate the absorption of drugs. More than 90% of new drugs developed by pharmaceutical companies are orally administered. They need to be absorbed through the gut to be effective, and thsi can be assessed with intestinal organoids. Intestinal organoids can also be used as a model for inflammatory bowel disease. Inflammatory bowel disease has high incidence, but there are no drugs that directly target this condition, so there is a need for a good disease model for treatment. If we can create an inflammatory bowel disease model with intestinal organoids and treat it with drugs, it can be complementary to animal experiments," said Son Mi-young. Gut organoids are also important as a model for studying the microbiome, as the intestine is the organ where microbiome, or a collection of microorganisms, is most prevalent in the body. Highly functional intestinal organoids can also be used in regenerative therapy. The Stem Cell Convergence Research



Center is unparalleled in the field of liver organoid research. The organoid-based toxicity assessment platform project of the Ministry of Food and Drug Safety of Korea is being conducted at the Stem Cell Convergence Research Center, and guidelines for toxicity assessment test methods using liver organoids are currently being prepared for submission to the OECD. In addition, the center is also carrying out research on kidney organoids, lung organoids, brain organoids, and cancer organoids. One of the achievements made by the center in the field of organoids was the establishment of a system of artificial test subjects to evaluate drug effects without testing on animals. The system, which is equipped with a wide range of organoid models under development at the center, is even more meaningful because it is the fruit of the combined efforts of numerous researchers within the center, explains Son Mi-young.

The Stem Cell Convergence Research Center reaching out to the public

Son Mi-young says, “No matter how busy I am, I give lectures to high school students about four or five times a year. From about two years ago, I have been mentoring science high school studentsthrough a project called ‘R&E.’ I believe that students who are interested in biotech must know about organoid technology, which may possibly replace animal testing in the future. I meet with students thinking that they will someday follow my footsteps in this field of research.” Researchers at the Stem Cell Convergence Research Center often appear as lecturers at various educational programs such as Open Lab and Little Biotechnologists, as well as lectures for the general public at science centers and various other institutions. This is to directly inform the public of the importance of research undertaken by KRIBB as a government-funded research institute. “The public knows that most drugs have been tested on animals. It’s now time for a paradigm shift, however, and we want to let people know that we are leading the way in this regard. We want people to know that we are working harder, faster, and more progressively in organoid research than any other organization funded by their tax money.”

Paving the way for Korea’s advanced biotechnology based on convergence

In addition to organoids, another area of research at the Stem Cell Convergence Research Center is the development of gene therapy and cell therapy. It is worth noting that the center is capable of expanding its scope of research to all kinds of areas associated with the keyword, stem cell, and this served as the background of the transition from “Stem Cell Research Center” to “Stem Cell Convergence Research Center.” The word, “convergence,” in the name also means “research collaboration.” The center carries out collaborative research so that researchers from other centers of KRIBB can take advantage of various model systems that are rooted in stem cell technology. Convergence within the center is also considered paramount. This is the value that Son Mi-young, the head of the center, believes in. “The members of our center are genuinely happy when someone within the center produces great results. You must be able to applaud the success of your colleagues in order for you to gain opportunities yourself. Research is not something you can do alone. You have to do it together with others. And you have to trust each other. No one at our center turns their back on the work against each other, and as the director of hte center, I am very grateful for that." Meanwhile, Sohn emphasizes the importance of the roles of full-time researchers, students, postdocs, and contract researchers in making the center work. She says that the center has a great group of researchers, regardless of their job titles and functions, and is looking forward to further growth in the future. Dr. Son also emphasized the fact that full-time researchers, students, postdoc fellows, and contract researchers all play pivotal roles at the center. She expects that with such an excellent group of researchers, regardless of their job titles and duties, the center will grow and advance further in the future. “In the first few years after our establishment, we saw a lot of achievements coming from senior researchers, but more recently, the younger generation of researchers has really stepped up to the plate. I feel that the center is becoming very strong, and we have the capacity to work together to achieve great things with a long-term perspective,” said Son. Son says that after the organoids are commercialized, the center’s focus will be on artificial organs. Since organoids are still only a few millimeters in size, the center is working on a project to scale them up to the size of actual human organs. “The members of our center are working hard to give patients suffering from intractable diseases the opportunity to receive new therapies. Research in all fields within the center, including the development of alternative testing methods using organoids, increased efficiency of the drug development process based on disease modeling, cell therapy, gene therapy, organoid-based regenerative therapy, and development of new stem cells, are all aimed at extending people’s health span. We will continue to strive to extend health spans, not just life spans.”

2022 Korea Science and Technology Fair

2023 Daedeok Innopolis Research Achievement Exhibition

2023 Daejeon Science Camp (for middle school students)

Stem Cell Convergence Research Center researchers & research details

Proactively Dealing with National Challenges

Division of Research on National Challenges

The Division of Research on National Challenges, an important department of KRIBB that deals with national agenda, was established in January 2019. To fulfill its responsibilities as part of a government-funded research institute, the division strives to solve national and social issues, prepare for potential disasters in the future, defend Korea's technological hegemony, and more. Following a reorganization, the Division of Research on National Challenges now consists of six centers: Infectious Disease Research Center, Environmental Diseases Research Center, Biodefense Research Center, Stem Cell Convergence Research Center, Bionanotechnology Research Center, and Plant Systems Engineering Research Center. These centers work closely together to identify topics that may become part of the national agenda and strive to secure relevant technologies. Chung Kyung-sook, who joined the Division of Research on National Challenges after serving as the head of the Biomedical Translational Research Center and the Division of Systems Biology and Bioengineering, leads the division with gentle charisma. She ensures that each center has enough autonomy while working together to accomplish the great mission of the division. We sat down with Chung Kyung-sook to learn more about the present and future of the Division of Research on National Challenges.

Six centers come together to tackle national challenges

When the Division of Research on National Challenges was incepted in 2019, it consisted of five organizations: the Infectious Disease Research Center, Environmental Diseases Research Center, Stem Cell Convergence Research Center, Biodefense Research Center, and Aging Research Center. Later, the Aging Research Center was expanded as the Aging Convergence Research Center, and with the establishment of Synthetic Biology and Bioengineering Research Institute within KRIBB, the Bionanotechnology Research Center and Plant Systems Engineering Research Center became affiliated with the Division of Research on National Challenges. Each center carries out independent research, but they do share something in common, and it's the fact that they address national agendas. First, the Infectious Disease Research Center seeks to secure technology for treatment, prevention, and diagnosis of new and variant infectious diseases that can lead to national crises. It has, for instance, developed and transferred cutting-edge vaccines, super antibiotics, and diagnostic technologies. The Environmental Diseases Research Center analyzes the harmfulness of environmental hazards such as particulate matter and microplastics to the human body and conducts disease impact analysis on hazardous factors for each organ. Through these efforts, the center has been acquiring the technologies for discovering key candidate substances and developing therapeutics. The Stem Cell Convergence Research Center is dedicated to developing key technologies related to advanced biopharmaceuticals, such as stem cell convergence technology for developing alternatives to animal testing by using stem cells and organoids and developing artificial organs as well as gene and cell therapy, in addition to building a platform that can be used for industry-academia-research partnerships. The Bionanotechnology Research Center, on the other hand, has developed and commercialized frontier technologies for diagnosis and treatment of intractable diseases and infectious diseases using advanced bionanotechnology and materials. They are striving to secure fundamental technologies for advanced healthcare platforms to prevent diseases and provide personalized healthcare services. The Plant Systems Engineering Research Center is working on the world's most efficient plant improvement technology. Its main area of research is the development of green bio-resource acceleration technology aimed at boosting photosynthesis efficiency, through which it aims to contribute to combating climate change and food shortages. The Biodefense Research Center is developing technologies to be prepared against biological and chemical warfare and terrorism, along with the Agency for Defense Development. It endeavors to apply KRIBB's technologies to the areas of national defense and develop them further for both civilian and military use.

Plant_Large-scale commercialization of working group plans

Producing greater results through close cooperation

The six centers undertaken convergence research in various ways. The Infectious Disease Research Center and the Bionanotechnology Research Center, in particular, often need to work closely together. For example, the Infectious Disease Research Center develops content and the Bionanotechnology Research Center develops diagnostic technology, thereby conducting interdisciplinary research aligned with the national agenda. Meanwhile, if the Biodefense Research Center, for example, develops a defense mechanism against biological weapons, it may be tested using various organoids developed by the Stem Cell Convergence Research Center. Since national agendas are determined and get changed in unpredictable ways, the six centers under the Division of Research on National Challenges routinely analyze domestic conditions and trends to identify topics, and this is why it is paramount to conduct joint research with domestic and overseas entities, engage in international cooperation, and maintain ties with hospitals.

Within KRIBB, topics are also identified by operating working groups. For example, the Plant Systems Engineering Research Center's research on enhancing the efficiency of photosynthesis originated from an idea proposed by a working group. "Researchers who are interested in the same research topic get together to discuss it freely, regardless of which center or position they belong to. Once a topic is created through a discussion, we initiate working group activities with the help of the Research Planning Office. Then, we hold a symposium to exchange opinions on what direction the research should go and plan the project. As such, in-house working groups play a vital role in identifying research topics." Multi-faceted efforts are being made toward international cooperation. The centers maintain close ties with the members of the global network in their respective fields. For example, the Infectious Disease Research Center is establishing itself as an international infectious disease hub for the Global Research Collaboration for Infectious Disease Preparedness (GLoPID-R), a network of major infectious disease research support organizations worldwide. In the case of the Stem Cell Convergence Research Center, it communicates with the National Aeronautics and Space Administration (NASA) and the Korea Aerospace Research Institute (KARI) to conduct space biotech research in the field of artificial organs. In the field of advanced biopharmaceuticals, the center has signed an MOU with Cambridge University in the United Kingdom and joined the Miller Consortium to conduct world-class research.

Infectious Disease - Asia-Pacific Infectious Disease Shield (APIS), a regional hub project led by Korea; APIS Kick-off Conference

Striving to promote people's health and safety

"Even if the centers within the Division of Research on National Challenges had been affiliated with different divisions instead, there wouldn't have been any problems in pursuing joint research. However, I believe it is more efficient to have one organization dedicated to the national agenda deal with pandemic situations that may arise again. I think even the public would find it more preferable and more reassuring to have a division dedicated to the national agenda, which is the Division of Research on National Challenges, within KRIBB," said Chung. Chung encourages members of the division to conduct research desired by the state and the people, rather than research that suit their personal agendas and goals. This is due to the nature of the division's commitment to the national agenda. However, since each center is an organization with its own expertise, she wants to guarantee them their autonomy without interfering as much as possible. Chung said, "I try to organize interdisciplinary research projects that span multiple centers so that many researchers can work together. Individualism seems to be a trend these days, so I'm trying to think of ways for researchers to work together, while keeping the desire for individualism in mind. Also, as the head of the division, I think I should serve as an umbrella for the staff, and it's important to raise their morale because they face considerable challenges, having to deal with the government." During the COVID-19 pandemic, members of the Division of Research on National Challenges worked in collaboration with other departments to respond to a series of challenges. They created relevant information materials, tested diagnostic kits and treatments, and worked tirelessly to keep citizens safe. They also actively get involved in public relations activities as a way to reassure the public. They participate in the activities organized by the KRIBB Public Relations Office to inform the public about their work and answer their questions. They also communicate with the public in various other ways such as providing education at middle and high schools for free and writing books. They also work together with hospitals to explain the development of new treatments to patients with rare diseases.

Bionanotechnology center's COVID-19 diagnostic kit

Aspiring to develop first-in-class drugs

"We've mainly been playing a fast follower role In the field of disease treatment and diagnosis, but our R&D level has improved considerably by now. In this day and age, one original technology can feed the entire nation. The Division of Research on National Challenges hopes to develop and possess a number of internationally competitive technologies in the next four to five years. We want to develop first-in-class drugs that can improve people's lives globally," said Chung. If the Division of Research on National Challenges' R&D projects progress as Chung hopes, KRIBB will gain greater reputation and prominence as an institution serving public interests. It will be possible to deal with subsequent pandemics with greater ease and promote the quality of life by opening the way for treatment of rare diseases. "Taking diseases that cause blindness as an example, which is my area of research, blindness can be very depressing and debilitating. If we can cure diseases that cause disabilities, we can contribute to solving the issue of shrinking working-age population and boost satisfaction with life in general. If we don't have the core technology to do this, we will have to rely on imports and be dependent on countries that have the technology. It is the duty and vision of our division to develop original technologies and first-in-class medications, and this is also my personal ambition," said Chung. KRIBB is currently poised to establish the Advanced Biomedical Research Center. When it opens in 2024, it will be transferred a part of the Division of Research on National Challenges, and the two will serve as the main pillars, conducting research to tackle national challenges. "If you look at the history of drug development, first there were herbal remedies, then there were small molecules, and then there were third-generation therapeutics like antibodies, proteins, and peptides. The fourth generation of therapies that we are moving towards is advanced biopharmaceuticals, which require a new research organization and infrastructure because the development methodology is entirely different from those of preceding drugs," explained Chung. Even after the establishment of the Advanced Biomedical Research Center, the Division of Research on National Challenges will continue to fulfill its mission to deal with national challenges. The head of the division hopes that the government will provide long-term and stable support for the continuation of related research. Chung commented, "The members of the Division of Research on National Challenges are conducting research for our country and people, rather than in their own area of interest. I hope that the government will provide long-term and stable support for the important research of our division to continue by establishing a hundred-year plan."

Activities with the Rare Disease Research Council of Government-funded Research Institutes

My Never-Ending **Curiosity**

Dr. Hyang-Sook Yoo

Dr. Hyang-Sook Yoo began her career in Korea at the Genetic Engineering Center of the Korea Institute of Science and Technology (KIST), the precursor to KRIBB. She remained with the organization when it was relocated to Daedeok Innopolis in Daejeon in 1990 and when it was reorganized as Biotechnology Institute in 1995 and as KRIBB in 2001. She served as head of the Biochemistry Laboratory, Cell Cycle Signaling Laboratory, Human Genome Research Center, Molecular Cell Biology Research Division, Frontier Human Genome Functional Research Project, and the Fred Hutchinson Collaborative Research Center. These days, her day begins in the KRIBB alumni room. Even after her retirement, Dr. Yoo still visits every day to read scientific journals. Her latest interest has been the National Integrated Bio Big Data Project, which will be officially launched in 2024. Dr. Yoo says that her "hope" is to see Korean bio big data get built, which she has been looking forward to for a long time.

Starting genetic engineering **at the molecular level**

Q1 What made you decide to follow the path of a scientist?

When I was in elementary school, I was in the choir of a Christian broadcasting station. I was good at singing, and when I was in middle school, I started thinking about becoming a vocalist when I grew up. Then, I came across a lecture. It was 1962, and the per capita income in Korea was less than $100 at the time. The lecturer's statement that the science fields must be developed to achieve economic revival really struck me. I wanted to do something for our country, so I decided to become a scientist. In high school, I chose to specialize in science, and in my senior year, I began aspiring to be a doctor, but my father told me that a woman shouldn't be a doctor, so I went to pharmacy school. Then I wanted to be a researcher, so I went to graduate school, despite my father's objections, and developed an anti-cancer drug. After giving cancerous mice a drug I compounded, I saw that the cancer cells stopped growing, but I couldn't figure out how the drug killed only cancer cells and not normal cells. That's where my life began. I had to answer the questions I had. That was the early 1970s, and genetic engineering at the molecular level was just starting to take off in the United States. I wanted to study in the United States, so while I was in graduate school, I began preparing to study abroad. I received a Fulbright scholarship to study in the U.S., and I received my master's and doctoral degrees in molecular biology and genetic engineering, so I was there when genetic engineering at the molecular level first started.

Q2 How and when did you initially join KRIBB?

While I was working as a postdoctoral fellow and contemplating whether to continue my research in the U.S., my father advised me to serve our country after my studies. I agreed with him. I had a strong desire to contribute to our nation, so I returned to Korea in 1987. The predecessor of KRIBB, the Genetic Engineering Center at KIST, was established in 1985. I joined in 1987 and I lived and worked in Seoul, and then in 1990, the Genetic Engineering Center was separated from KIST and relocated to the current Daedeok Innopolis in Daejeon.

Q3 What was the atmosphere like at KRIBB in the 1990s?

It was great. There were about 30 doctoral-level researchers, and the total number of researchers, including non-doctoral researchers, was fewer than 100. We were all very close, creating synergy together and undertaking joint research. Recalling this region in the 1990s, there were several other labs nearby, but it was mostly mountains and farmlands. We had to take a bus to get to Chungnam National University, and there weren't even traffic lights at the intersection. The researchers organized a union and got an apartment in Yongjeon-dong. We had to wear rain boots to go to work on rainy days because the roads were mostly unpaved.

"After giving cancerous mice a drug I compounded,
I saw that the cancer cells stopped growing,
but I couldn't figure out how the drug killed
only cancer cells and not normal cells.

That's where my life began.
I had to answer the questions I had."

From genome to **personalized medicine**

Q4 Tell us a little bit about your research at KRIBB.

When I first joined the Genetic Engineering Center, I thought hard about what to research. The area of my postdoc research after I got my Ph.D. was gene expression, and I wanted to continue researching that area, but it was difficult because it was my advisor's specialty. I felt the need to research a new area independently, so I went to an international conference, where I realized that there was a type of yeast that was slightly different from the bread-making yeast I was studying and hadn't been studied at all. I judged that I'd have a competitive edge if I started studying it right away.

The research I conducted independently after joining KRIBB was on *Schizosaccharomyces pombe,* or fission yeast. My research involved mutating the fission yeast to find genes that change the cell cycle, with support from the G7 project, a national technology development project, from 1990 to 2000, and through 10 years of research, I helped lay the groundwork for genetic engineering and molecular biology research.

In 1990, the Human Genome Project began in the United States. It was a move to reveal the arrangements of the DNA making up genes now that they had genetic analysis technology. The project was carried out simultaneously with researchers from various countries, who shared their data in real time, and after collecting, analyzing, and matching the data, the project was completed in 2003. Although Korea did not participate in the project at that time, KRIBB began to expand the scope of related research by etablishing the Genome Research Center, the Genome Research Society, and so on. In 1999, the government of Korea launched the Frontier Research and Development Project, and the Human Genome Functional Research Project Group was established. I was selected as the head of the group, and I helped conduct the study for about 10 years.

"The research I conducted independently after joining KRIBB was on Schizosaccharomyces pombe, or fission yeast. My research involved mutating the fission yeast to find genes that change the cell cycle."

Q5 What is the genome and why is it important?

The genome is the entire set of the genes that govern the process of birth, growth, aging, and death. All living things need the information contained in the genome to survive. The reason the genome is important is that the nucleotide sequences of our genes determine our being. The nucleotide sequence of a gene can have a couple of different bases, and when that's the case, the protein it creates may be different. For example, if a gene fails to make the right amount of protein at the right time and doesn't allow a cell to grow properly, it can become a cancerous cell. As such, the genome is important because it directly affects our health. By knowing your DNA sequence, you can find out where you have mutations and prevent the onset of diseases by using the "genetic scissors" technology or by drug therapy. This is why personalized medicine is so important, as it allows us to be proactive in managing our health.

Q6 In 2020, you published "Vaccine Outlook(2): A Call for Diversification of Vaccination Strategies" in *Bio in Global: Global Trends Report No. 57* published by the National Biotech Policy Research Center. Could you please provide a brief explanation?

After my retirement, the National Biotech Policy Research Center asked me to write a paper on the latest research trends. So, I started reading journals to see what the latest issues were, and I came across an article in the November 2019 issue of *Nature* about the need to diversify vaccination strategies. This was before the COVID-19 pandemic, and it was a time when there was a resurgence of measles in Europe. I found out that a lot of Europeans hadn't been vaccinated against measles because many were anti-vaxxers. For vaccine development, clinical studies were typically conducted with young adults and middle-aged people, so the vaccines often weren't suitable for young kids or seniors. The article pointed out that vaccines had been developed with a one-size-fits-all approach and that needed to change. That is, just as with customized medicine, vaccines should be developed specially for kids, for seniors, and so on. Looking back, I think it was similar to what we saw during the pandemic, where we were in a hurry to get the vaccines approved, so clinical trials were carried out with mostly young adults and middle-aged people first, and only after some time did we have a vaccine strategy for older people and children. It has become clear that in the future, we will need to develop vaccines and drugs for different age groups, rather than taking a one-size-fits-all approach.

Going back to personalized medicine, if we have people's genetic information, it will be possible to tailor treatments to each individual. It is said that from 2024, the government will start a national project to build integrated bio big data on one million people. I feel hopeful that the project that I had been advocating since the 2000s but had not been accepted has finally begun.

Q7 In 2009, KRIBB and Pfizer announced that they would jointly promote the development of biologics. What kind of research was conducted at that time and what was the significance?

When the Frontier R&D Project began, there was no genome research base in Kore, and a system to discover and analyze genes in large quantities by the Human Genome Functional Research Project Group while carrying out the project. The plan was to study the functions of genes after establishing that type of foundation. Each human being has more than 40,000 genes, and not all of them could be analyzed, so we started looking for genes associated with stomach and liver cancer. This was a study that hadn't been done in the West, where the incidence of lung and colon cancer is relatively higher. At that time, researchers from Pfizer were traveling around Asia because they recognized the potential of the Asian pharmaceutical market. Pfizer, which had been developing drugs for Westerners, didn't have any drugs for stomach and liver cancer. When the company realized that our project group was working on stomach and liver cancer genes, they proposed that we conduct a joint study. They wanted us to find the targets, and they would use their compounds to develop the drug. Pfizer funded the research for two years, and we were able to study gene functions in detail. After the two years, Pfizer disbanded the anti-cancer drug team. We weren't able to develop any biologics with Pfizer, but it was an opportunity for us to refine the targets we had gather and perfect our research on gene functions.

Curiosity drives **my research**

Q8 A study you participated in, "The Origin and Genomic Diversity of Asians," was published in *Science* in 2009. What was the experience like?

Researchers from Korea, China, and Japan got together to compare the genetic sequences of Asians. We took the representative DNA samples of different ethnic groups to find out when and where mutations occurred. By compiling data that compare only areas of high variation and tracing the mutations, we realized that Southeast Asians migrated mainly from the south to the north. When our paper was published in *Science,* it garnered a great deal of attention, and it was rewarding to accomplish this as a collaborative study. It was especially meaningful that Korea was able to lead a study that involved multiple countries.

Q9 You became an honorary researcher after retiring from KRIBB. What role did you take on?

After retiring from KRIBB, I remained an honorary researcher until I was 70. With my life-long experience as a researcher, I listened to the concerns of researchers and gave them advice. I also gave advice on problems and directions in experiments. Recently, I have been active in the Bioscience & Biotechnology Cooperative. Together with the other members, I advise venture businesses, educate visitors to the lab, and teach students.

Q10 Do you have any advice for the other members of KRIBB regarding research life?

I'd like say that you just have to work hard, but when you work hard, you'll encounter trouble here and there. Looking back to when I was a lab director, there were times when researchers with different lifestyles would argue, and I think we all need to try to understand each other and make concessions.
Also, there are many times when things don't work out in research, and my advice is to give up if you've repeated the same thing three times and it doesn't work. That is, don't be afraid to try a different approach.
My last piece of advice would be to stay curious. I started my research from the curiosity about the mechanism of the anti-cancer drug I compounded, and it has led me all the way here today. I still get excited when I read journals in the alumni room, and it makes me want to begin all kinds of research. As long as you don't lose your curiosity, it will help you to do your own research. So, be curious and enjoy your research.

"I still get excited when I read journals in the alumni room,
and it makes me want to begin all kinds of research.

As long as you don't lose your curiosity,
it will help you to do your own research.

So, be curious and enjoy your research."

A rewarding experience to build **a foundation for genomic research in Korea**

Q11 You were selected as the Woman Scientist of the Year 2014 in the Promotion category. For what contributions were you given this honor?

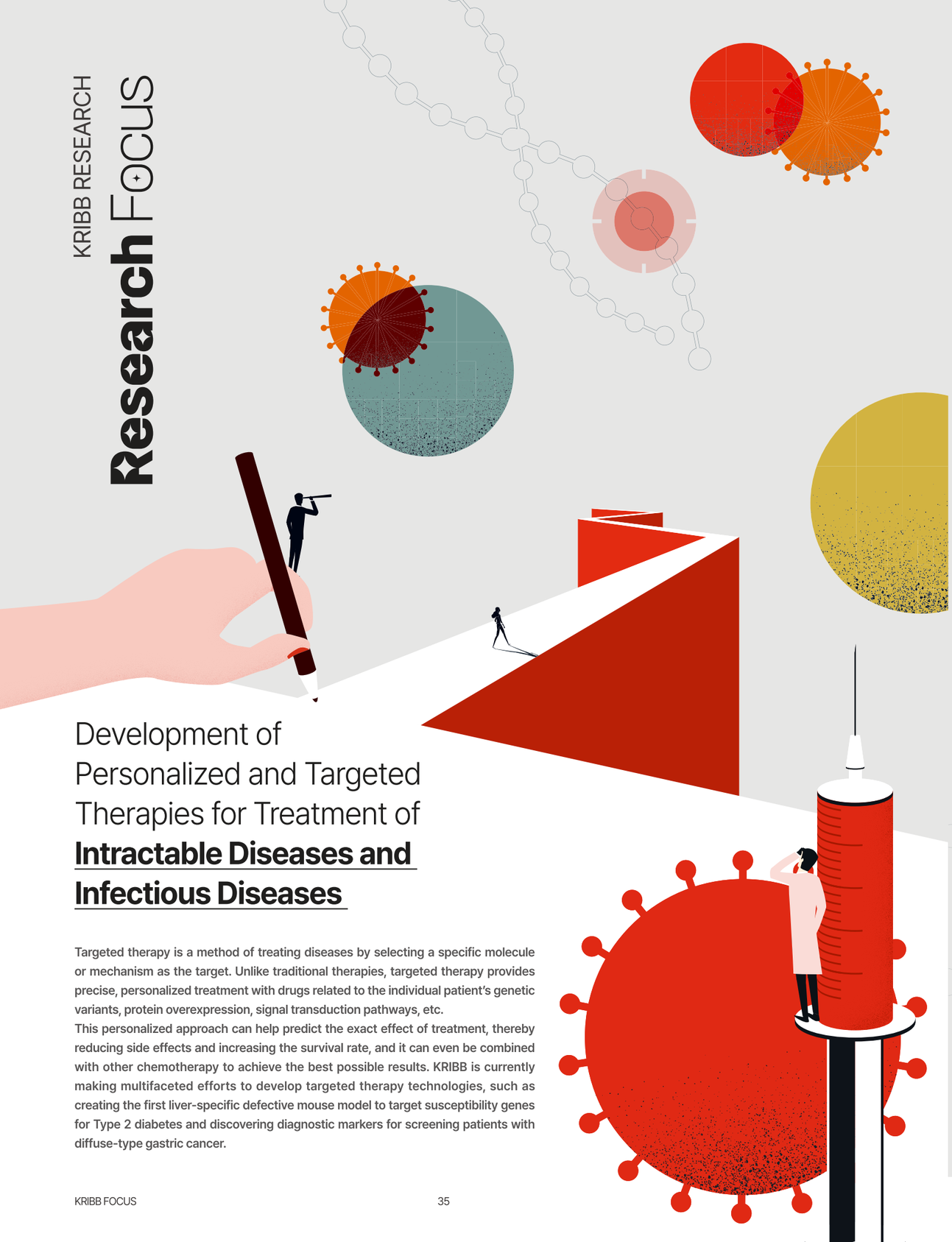
In the 1990s, when Daedeok Innopolis was established, there weren't a lot of women researchers, and those of us who were here were often treated unfairly. In order to promote the rights of female researchers, Dr. Oh Se-hwa of the Korea Research Institute of Chemical Technology (KRICT) formed the Association of Korean Woman Scientists and Engineers (KWSE). While carrying out various activities such as setting up a daycare center in the research complex, we turned our attention to overseas. After the formation of the KWSE, a number of policies were introduced to support women scientists and engineers in Korea, but the situation in other parts of Asia was still backward. We felt the need to form a network, so we formed the Asia & Pacific Nation Network (APNN), and I became the head. We held a meeting once a year to identify problems and propose policies for women in science and technology. I believe I was named the Woman Scientist of the Year 2014 in the Promotion category in recognition of those exchange efforts.

Q12 How would you evaluate your research and activities so far? It must have been very rewarding.

My research life stemmed from my curiosity. I have no regrets because I did what I wanted to do, but one thing I find regrettable is that I was unable to create an anti-cancer drug. On the other hand, I feel an incredible sense of fulfillment for having laid the foundation for genomic research in Korea through the Frontier R&D Project. It makes me proud to see researchers, who just started out during the early days of the project, publish excellent papers now.

Q13 Please tell us about your future plans as a researcher.

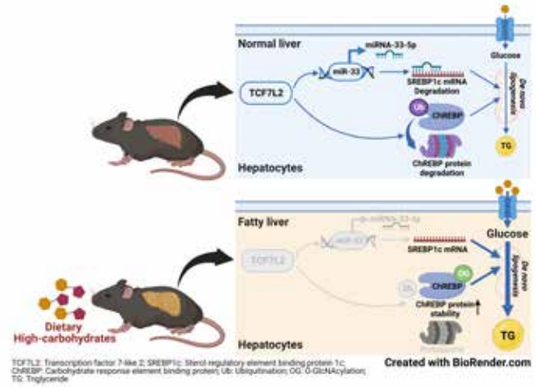
For personalized medicine, basic knowledge is essential. University students, especially pharmacy students, need to know about pharmacogenomics, but there is not much education about it. I am planning to write a book on pharmacogenomics as a 10-year project. I also hope to serve as an advisor for the national integrated bio big data project. If I get the chance, I'd like to help the project proceed smoothly by sharing my experience. It is my hope to see Korean bio big data built properly during my remaining days as a researcher.



Development of Personalized and Targeted Therapies for Treatment of **Intractable Diseases and Infectious Diseases**

Targeted therapy is a method of treating diseases by selecting a specific molecule or mechanism as the target. Unlike traditional therapies, targeted therapy provides precise, personalized treatment with drugs related to the individual patient's genetic variants, protein overexpression, signal transduction pathways, etc.
This personalized approach can help predict the exact effect of treatment, thereby reducing side effects and increasing the survival rate, and it can even be combined with other chemotherapy to achieve the best possible results. KRIBB is currently making multifaceted efforts to develop targeted therapy technologies, such as creating the first liver-specific defective mouse model to target susceptibility genes for Type 2 diabetes and discovering diagnostic markers for screening patients with diffuse-type gastric cancer.

01 Could the diabetes genes provide a breakthrough in the development of a treatment non-alcoholic fatty liver disease?



The liver, the largest organ in the body, performs a variety of comprehensive functions such as digestion, hormone metabolism, detoxification, and sterilization, and this is why the statement, "90% of all diseases are due to the liver," has caught people's attention.

Nonalcoholic fatty liver disease (NAFLD) is a condition in which there is a buildup of fat in the liver that accounts for 5% of the liver's weight or more. It is a broad concept that includes everything from steatosis, which is simply an accumulation of lipids in cells, to nonalcoholic steatohepatitis, which is accompanied by inflammation and liver cell damage.

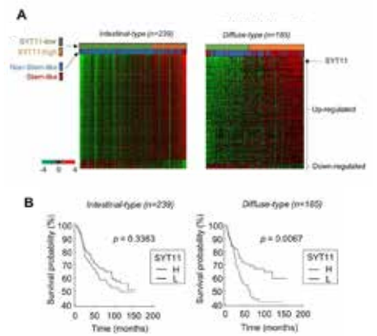
This is considered a "blue ocean," with no regulatory-approved therapies to date, despite its increasing prevalence and various complications, as the age of onset is dropping globally.

The research team led by Dr. Oh Kyoung-jin at the KRIBB Metabolic Regulation Research Center noted that NAFLD patients with Type 2 diabetes have a poor metabolic profile and are at high risk of rapidly progressing to advanced nonalcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma (HCC) and conducted a study targeting TCF7L2, a diabetes-related gene that is reduced in the liver tissue of patients with NAFLD and NASH. With the hypothesis that the reduced expression level of TCF7L2 induces fat accumulation in the liver, a mouse model that specifically lacks TCF7L2 in hepatocytes was created for an *in vivo* functional study.

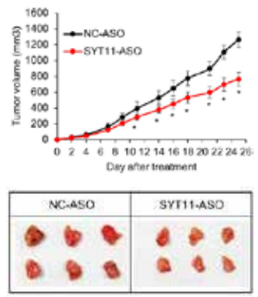
Dr. Oh was the first to identify that the diabetic gene, TCF7L2, may contribute to the control of NAFLD by regulating fat biosynthesis through the autonomous mechanisms of hepatocytes. Also, by providing a clear mechanism and a target for potent therapy, he provided clues to revealing the association and coexistence of NAFLD and Type 2 diabetes at the same time.

* Reference : Lee, Da Som, et al. "Tcf7l2 in hepatocytes regulates de novo lipogenesis in diet-induced non-alcoholic fatty liver disease in mice." *Diabetologia 66.5* (2023): 931-954.

02 Diffuse-type stomach cancer, a threat to people in their 20s and 30s



A) Transcriptome analysis results of gastric cancer patient tissues / B) Survival rate analysis of gastric cancer patients



Tumor suppression in mice transplanted gastric cancer stem-like cells (GCSCs) after the administration of SYT11-ASO

Stomach cancer is common in Korea, with its prevalence increasingly sharply among people aged 40 and older and peaking past the age of 70. However, unlike general stomach cancer, the diffuse-type gastric cancer occurs mostly in young people. It is characterized by small cancer cells penetrating through the stomach lining and grow extensively, and it is difficult to treat because it is an underdiagnosed and highly aggressive cancer that metastasizes quickly.

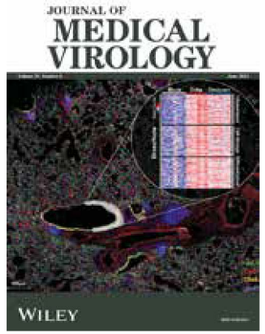
Concerns about the diffuse-type gastric cancer can now be alleviated with the development of an inhibitor and diagnostic marker for the treatment of diffuse-type gastric cancer by Dr. Won Mi-seon, a lead researcher of the KRIBB Personalized Genomic Medicine Research Center.

The research team led by Dr. Won discovered the synaptotagmin 11 (SYT11) gene, which is highly associated with the development and malignancy of gastric cancer, and developed a SYT11 inhibitor (SYT11-ASO) for targeted therapy for patients with stomach cancer. They also discovered a diagnostic marker to screen for diffuse-type gastric cancer for treatment and improved the efficiency of SYT11-ASO treatment. This study confirmed the applicability of SYT11 inhibitors not only to diffuse gastric cancer, but also to brain tumors, ovarian cancer, and drug-resistant carcinomas with the characteristics of cancer stem cells, or tumor-initiating cells.

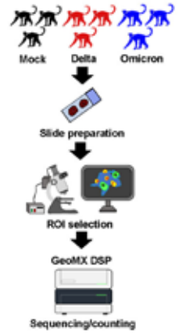
SYT11-related technologies are expected to help diagnose, predict the prognosis, and develop treatment strategies for patients with refractory gastric cancer, which has been hampered by the lack of targeted therapy agents. It is also expected to present new possibilities for the treatment of intractable cancers with characteristics of cancer stem cells that have no therapeutic alternatives clinically and to develop a new anti-cancer drug market.

* Reference : Kim, Bo-Kyung, et al. "Synaptotagmin 11 scaffolds MKK7–JNK signaling process to promote stem-like molecular subtype gastric cancer oncogenesis." *Journal of Experimental & Clinical Cancer Research* 41.1 (2022): 1-17.

03 Immune response in the lung to coronavirus mutations



Identification of local immune response to COVID-19 variants



Experimental design of GeoMx digital spatial profiling.

SARS-CoV-2, the virus that causes COVID-19, has had variants emerge a number of times since its first appearance in 2019, and they include alpha, beta, delta, and omicron variants. When a variant emerges, there is a great deal of interest in its transmission pathways and lesions, but few studies have focused on the immune response to infection with the variant.

A research team led by Dr. Hong Jung-joo, a researcher at the KRIBB National Primate Research Center (also a researcher at the Korea Preclinical Evaluation Center) identified local immune responses in the lung microstructure to delta and omicron variants in a primate model of coronavirus infection using the latest spatial transcriptome analysis methods for the first time.

Using a primate infection model, the researchers observed how the delta and omicron variants caused changes in the small structures inside the lungs. They found that lungs infected with both variants showed an increase in genes related to inflammation and cellular responses.

“By using a primate model that is phylogenetically closest to humans, we have identified the local immune response in the lung to COVID-19 variants at the molecular level, suggesting that variant-specific immune-related gene expression may influence the course of the disease,” said Dr. Hong.

This was the first study to analyze the local immune response in the lung to COVID-19 variants at the molecular level, and it showed the possibility that immune-related gene activation may influence the course of the disease depending on the variant. The findings of this study may potentially be used as a basis for future research on the immune system mechanisms related to new and variant infectious diseases such as coronaviruses, thereby contributing to the diagnosis of infectious diseases and development of treatment strategies.

* Reference : Oh, Taehwan, et al. "Comparative spatial transcriptomic profiling of severe acute respiratory syndrome coronavirus 2 Delta and Omicron variants infections in the lungs of cynomolgus macaques." *Journal of Medical Virology* 95.6 (2023): e28847.

KRIBB ENTREPRENEUR

Contributing to Carbon Neutrality with **Microalgae-based Supplement for Eye Health**

Hee-Sik Kim, Technical Director at Ask Labs and Head of Cell Factory Research Center

In June 2021, Ask Labs was incepted as a research company of KRIBB, with the capital invested by the parent company, Ask Company, and the technologies related to the new microalgae with high lutein productivity and new microalgae with high zeaxanthin and lutein productivity developed by the KRIBB Cell Factory Research Center. Through this, Ask Labs is working on developing and commercializing a supplement for eye health that can replace marigold-derived lutein and zeaxanthin, which is completely imported. Microalgae is a biomaterial with excellent carbon dioxide absorption and removal performance, and developing products utilizing microalgae can be a way of contributing to the carbon neutrality movement. We interviewed Kim Hee-sik, the technical director at Ask Labs and the head of the Cell Factory Research Center, to learn more about the project.

KRIBB-funded technology giving way to the establishment of Ask Labs

It was about five years ago that Kim Hee-sik formed ties with Ask Company through the technology investment project. At that time, the company wanted to be transferred a patented technology that concerned a material for hair loss alleviation from the center. The technology transfer was completed smoothly, and the company launched a shampoo product as a result. Afterwards, Ask Company once again needed the technology of the Cell Factory Research Center, and this time, the company established a research company in close collaboration with the center. The Cell Factory Research Center was in charge of the technology area, while the KRIBB Industry Collaboration Center and the Technology Transfer Center helped with non-technical tasks.

"I had high expectations for the establishment of the research company because of Ask Company was a large company and it was strongly committed to research and development (R&D). It also felt great that the technology I developed would be commercialized. There are many steps that need to be taken to commercialize a technology, and by establishing the research company, we took the first step," said Kim.

Microalgae are single-celled organisms that need to be observed under a microscope and can be used produce a variety of different materials depending on the species. Through years of research, the Cell Factory Research Center succeeded in artificially cultivating microalgae capable of producing lutein and zeaxanthin in large quantities and transferred the technology to Ask Labs. As a result, the research company is now able to produce lutein and zeaxanthin from artificially cultivated microalgae.

Existing eye health supplements mainly use lutein derived from marigolds. Lutein is extracted from marigold petals, which cannot be cultivated in Korea, so all lutein supplements for eye health are currently imported. Marigolds are grown in India and Africa, where it is very warm, and are harvested only a few times a year. As opposed to this, the use of microalgae to produce lutein and zeaxanthin presents many advantages.

Ask Company has set up the production process and commercialization process and is in the process of obtaining certification from the Ministry of Food and Drug Safety (MFDS).

"Microalgae are organisms that fall somewhere between plants and microbes. They can grow in size through photosynthesis and can also be cultivated artificially. They have a considerable advantage over plants in producing substances. The fact that microalgae can be cultivated artificially means that it is possible to establish a production process that can be carried out anywhere, anytime. This is a competitive technology that will not only provide an alternative to [imported supplements for eye health] but also has the potential to make products that can be exported in the future," explained Kim.

Ask Company has set up the production process and commercialization process and is in the process of obtaining certification from the Ministry of Food and Drug Safety (MFDS). The company expects to launch the product in around 2025 after completing the clinical trial, analysis, and certification processes.

Contributing to a carbon-neutral bioindustry ecosystem

At the time of its establishment, Ask Labs had one goal: to contribute to building a carbon-neutral bioindustry ecosystem. Carbon neutrality means absorbing as much carbon dioxide as the amount emitted, thereby making the actual emissions "zero." Since the Paris Agreement in 2016, 121 countries have joined the Climate Ambition Alliance: Net Zero 2050, making carbon neutrality a global issue. Starting with the European Union in 2019, major countries around the world declared their committed to achieving net zero emissions, including Korea in 2020. In 2021, the Korean government enacted and promulgated the Framework Act on Carbon Neutrality and Green Growth to achieve carbon neutrality by 2050 and finalized the draft of the Enforcement Decree in 2022. In pace with this global trend, Ask Labs is striving to contribute to carbon neutrality.

Kim explained, "Microalgae have an excellent ability to absorb and remove carbon dioxide that no other microorganisms have, so using microalgae to produce bio-healthcare materials will contribute to the creation of a carbon-neutral bioindustry

ecosystem. There are few companies practicing carbon neutrality in the bio-healthcare field, and I believe that Ask Labs will be able to play a leading role in this industry. We can also take a step closer to consumers by upholding various values such as carbon neutrality, veganism, and naturalism."

Meanwhile, behind the company's carbon neutral practices is the Cell Factory Research Center. Its main mission is also to contribute to the attainment of net zero emissions. It is conducting research to reduce carbon dioxide with biological technology using microalgae, while creating useful materials. Currently, the center is developing plastic materials using microalgae that feed on carbon dioxide, investigating into the use of microalgae to remove microplastics from the ocean, and conducting research to genetically modify microalgae strains.

"The scope of the work we do at the center is quite broad. We're carrying out various studies dealing with microalgae and microbes, and some of those technologies have been transferred to Ask Labs. We're going to continue to perform R&D in collaboration with various entities."

Setting a good example as a global bio-healthcare company

Currently, Ask Company is endeavoring to build overseas sales networks in the United States, China, Japan, and Vietnam. The products developed by Ask Labs will be sold through the distribution company, Riman Korea. Kim Hee-sik expects that supplements for eye health developed using microalgae will gain attention at home and abroad once they are released.

"There are hardly any companies in the world that utilize microalgae to produce materials. The commercialize of microalgae technologies is still in its early stages, and I think Ask Labs will be able to gain global competitiveness in that regard," said Kim.

"The scope of the work we do at the center is quite broad.
We're carrying out various studies dealing with microalgae and microbes,
and some of those technologies have been transferred to Ask Labs.
We're going to continue to perform R&D in collaboration with various entities."

Meanwhile, Ask Labs is developing diverse product materials based on microalgae in addition to eye health supplements. With supplement ingredients and functional cosmetics ingredients as its main production areas, the company is conducting R&D in the fields of anti-wrinkle, anti-aging, anti-hair loss, anti-obesity, and muscle strengthening materials.

"I hope that Ask Labs will grow as a company specializing in biomaterials and gain global prominence. That way, it will set a precedent as a successful R&D company and influence the establishment of other R&D companies in the future."

Kim Hee-sik is hoping for an initial public offering (IPO) of Ask Labs. He believes that if the company discloses its management details and sells shares to external investors, it will be able to achieve further growth. He also believes that the company's growth will encourage other research centers at KRIBB to take an interest in commercializing technology. He hopes that more researchers will be interested in commercializing technology because he has experienced how rewarding it is to bring to the market the technologies he has researched and developed.

"Even if you develop a technology for commercialization, it is not easy to publish it in a paper, so many researchers are more interested in developing original technology and writing a good paper. There are also many researchers who don't even know what a research company is. Developing original technologies is essential, but I believe it's also important to commercialize technology and turn them into businesses. This is because most people can only experience science and technology through industrial products."

Kim Hee-sik also conducted research mostly on original technology in the past and faced some difficulties when he switched to technologies for commercialization. At first, it seemed difficult to communicate with non-scientists in creating products together, but as he gained experience, he was able to find ways to better communicate with them.

"Communicating with the people at the company has significantly changed my views. Now, even if I'm developing original technology, I do it with commercialization in mind. I hope that the technologies I develop in the future will find themselves into more people's lives through commercialization."

At present, Kim is responsible for developing new materials and establishing production processes at Ask Labs. Early on in its inception, Kim headed the technology department, but now he is the general manager of a new research center within Ask Labs. He is also continuing his research at the Cell Factory Research Center, while seeking to promote mutual benefits for both the research center and Ask Labs through continued exchanges.

We look forward to seeing Ask Labs emerge as global bio-healthcare company with KRIBB's R&D technology as the driving force behind its stellar growth.

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KRIBB News

Now at KRIBB

01 Identification of the Mechanism by Which Particulate Matter Aggravates Inflammatory Bowel Disease

02 KRIBB Selected as Excellent R&D Achievement in Advanced Bio in the National Strategic Technology Category

03 KRIBB Leads the Future of Biopharmaceuticals by Collaborating with the UK

Identification of the Mechanism by Which Particulate Matter Aggravates Inflammatory Bowel Disease

The Korea Research Institute of Bioscience and Biotechnology (KRIBB; President Kim Jang-seong) announced that a research team led by Dr. Son Mi-young of the KRIBB Stem Cell Research Center has successfully identified the mechanism behind the functional decline of the small intestine in patients with inflammatory bowel disease caused by particulate matter (PM 10) using intestinal organoids.

- It is expected that the newly revealed information on the changes in the intestine caused by exposure to particulate matter and the mechanism of action may be used to develop therapeutic drugs for the functional decline of the gut.

Atmospheric particulate matter, or "fine dust," is a Class 1 carcinogen and is known to cause various diseases such as respiratory diseases, cardiovascular diseases, metabolic disorders, and reproductive anomalies. It is mainly inhaled through the respiratory tract, but it can also enter the body through food and drinking water.

- Studies have reported that while particulate matter ingested through food gets diluted by saliva and digestive juices, some of it gets absorbed into the mucous membranes of the digestive system and spreads to the entire body via the bloodstream, thereby causing gastrointestinal disorders such as inflammatory bowel disease and an imbalance of the gut microbiota.

Particulate matter, which people get easily exposed to in their daily lives, is known to be more harmful to those with underlying medical conditions, but studies on particulate matter and related diseases are concentrated on asthma, atopic syndrome, and the like, and there are almost no studies on its harmful effects on patients with inflammatory bowel disease, whose prevalence is increasing sharply.

- Most of the studies on the harmful effects of particulate matter on the intestine have utilized cancer cell lines, which have limitations in that they are not normal cells and they are not that similar to human body cells in terms of cell diversity and functionality.

Accordingly, the research team used two-dimensional intestinal epithelial cells derived from human pluripotent stem cells and three-dimensional organoid technology to study the effects of particulate matter on inflammatory bowel disease.

- Through this, they confirmed that in the inflammatory bowel disease model exposed to particulate, the calcium signaling system, which plays an important role in the cell, was disturbed, and the breakdown and absorption of protein occurred at a lower rate, which contributed to the worsening of the disease.

"The results of this study newly revealed the mechanism of intestinal function decline caused by particulate matter in patients with inflammation-induced intestinal diseases," said Dr. Son Mi-young, the principal investigator, who then added,

- "It is expected to be used as a new target for treating intestinal function decline caused by harmful environmental factors in patients with underlying medical conditions in the future."

The findings of this study were published in the online edition of *Frontiers in Immunology (IF 8.787),* an authoritative journal in the field of immunology, on June 26. *(Title: Particulate matter 10 exposure affects intestinal functionality in both inflamed 2D intestinal epithelial cell and 3D intestinal organoid models / Corresponding authors: Mi-young Son and Dae-soo Kim / First author: Ye-seul Son and Na-eun Son, student researcher at UST KRIBB campus)*

- This research was supported by the Ministry of Science and ICT's Korea Bio Grand Challenge Project, the government-wide Regenerative Medical Technology Development Project, the Ministry of Food and Drug Safety's Advanced Toxicity Assessment Technology Infrastructure Construction project, the KIST's Air Environment Response Research Project, and the KRIBB program.

KRIBB Selected as Excellent R&D Achievement in Advanced Bio in the National Strategic Technology Category

(MSIT) Selection of Top 100 National R&D Achievements of the Year 2023 (3 cases)

- The Ministry of Science and ICT has finalized the Top 100 National R&D Achievements of the Year 2023 ("Top 100 R&D Achievements") from among 854 candidates either selected or nominated by government ministries, administrations, and agencies based on an evaluation by the Selection and Evaluation Committee composed of 100 experts from industry, academia, and research, as well as a verification session that was open to the general public.
- The Top 100 R&D Achievements selected from among national R&D projects by the government is a scheme designed to enhance the public's understanding of and interest in the role of science and technology in driving national development and to instill a sense of pride among scientists and engineers.
- In the Bio and Ocean Sciences field, the Development and Export of Ultra-Small Gene Scissors Technology by Dr. Kim Yong-sam from the Korea Research Institute of Bioscience and Biotechnology (KRIBB) Genome Editing Research Center was selected as the top achievement. This project involved developing high-performance ultra-small gene scissors technology for gene correction therapy applicable to various types of tissue. A licensing agreement was concluded with an overseas pharmaceutical company for joint development of disease treatments using the technology, and the technology is expected to contribute to the development of treatments for rare genetic disorders for which there are currently no alternative treatments.
- Also, in the Bio and Ocean Sciences field, the Development and Commercialization of Intestinal Organoid Technology Using Stem Cell Differentiation Technology led by Dr. Son Mi-young and the First Discovery of Cells Similar to Blastema, Key to Regeneration in Lizards, in Mammals led by Dr. Kim Jang-hwan were selected as excellent achievements.

(NST) Selection of Excellent Research Achievements of Government-funded Research Institutes in 2023 (2 cases)

- The National Research Council of Science and Technology (NST) discovers and awards outstanding research and development (R&D) achievements to encourage researchers at government-funded research institutions in the field of science and technology to continue undertaking research with a sense of pride. The title of "Excellent Research Achievement" is given to technologies that have led to the creation of great scientific, technological, economic, social, and infrastructural value selected based on the judgment criteria of the selection committee from among the major research projects carried out by government-funded research institutes in the past year.
- In 2023, a total of 15 projects were selected, including 10 projects that were given the Minister of Science and ICT Award and 5 projects that were given the NST Chairperson Award. Among them, KRIBB had two projects recognized for their excellence for the year 2023.
- The award was given to Dr. Son Mi-young (Artificial Blastema Cell Technology) who developed the technology to produce and utilize three-dimensional human intestinal organoids for the first time in the world and transferred the technology to related domestic companies.
- It was also awarded to Dr. Kim Jang-hwan (Development and Commercialization of the Technology for Producing and Utilizing Human Intestinal Organoids) who confirmed that it is possible to artificially induce the production of blastema cells, which are the key to regeneration in animals, in mammals, thereby answering one of the oldest questions in biology, "Why do humans not have the same regenerative ability as lizards?"

- Source: Selection of the Top 100 National R&D Achievements of the Year 2023 (Ministry of Science and ICT, Nov. 9, 2023)

KRIBB Leads the Future of Biopharmaceuticals by Collaborating with the UK

The Korea Research Institute of Bioscience and Biotechnology (KRIBB; President Kim Jang-sung) is endeavoring to strengthen international research collaborations in the field of biopharmaceuticals, including cell and gene therapy and bio big data, which have been designated as national strategic technologies.

On November 20 (Monday), KRIBB announced that it had signed an MOU with the Milner Therapeutics Institute (MTI) of the University of Cambridge in the United Kingdom for research cooperation in the field of biopharmaceuticals and held a joint academic conference to identify areas of strengths of each party as well as common interests.

- Since its establishment in 2015, MTI has become one of the top biopharmaceutical research institutes in Europe in a short period of time and gained unrivaled capacity in developing new drugs based on artificial intelligence technology.

The collaboration, which coincides with President Yoon Suk-yeol's state visit to the UK, includes R&D collaboration with the University of Cambridge, which boasts long tradition and has made innovation across all areas of biotechnology from evolutionary biology to biopharmaceutical development that combines artificial intelligence and bio big data. It also entails KRIBB joining the Milner Affiliate Program*, a global biopharmaceutical consortium where the MTI plays a pivotal role.

* A global consortium in the field of biopharmaceuticals where the MTI plays a pivotal role

The Milner Affiliate Program, which has helped drive the MTI's growth, includes 59 companies, 15 research institutions, and six venture capital firms from around the world, and it brings together and maximizes the capabilities of industry, academia, research institutes, and hospitals in drug development such as joint research, clinical trials, and commercialization.

With the signing of this MOU and registration in the Milner Affiliate Program, KRIBB has taken one step closer to achieving cutting-edge biotech innovation. The institute revealed its plans to undertake joint research with the MTI on promising technologies of the future such as cell and gene therapy, artificial organs, and bio big data first before gradually expanding cooperation in other fields.

"By working together with the Milner Therapeutics Institute, which plays a pivotal role in the strategic alliances established with global pharmaceutical companies, bioventures, and major hospitals, we will expand open innovation in the field of cutting-edge biotech and help strengthen Korea's R&D capabilities in the biopharmaceutical field," said Kim Jang-sung, President of KRIBB.

KRIBB creating a better future
together with the people of Korea
based on research for life
and technology for tomorrow

To promote health and safety among citizens
and drive Korea's innovative growth,

KRIBB is embarking on a new journey
toward a more prosperous tomorrow.

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