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125 Gwahak-ro, Yuseong-gu, Daejeon 34141, Korea Tel.: +82-42-860-4114 Fax.: +82-42-861-1759



BIOTECH FOR ECONOMIC GROWTH AND BETTER LIVING STANDARDS

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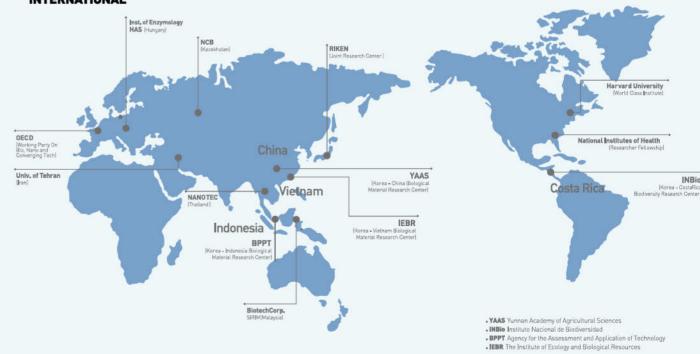
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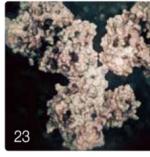
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What Drives Job Creation in the Bio Industry?

Jang-Seong Kim, Vice President of KRIBB

The Fourth Industrial Revolution, characterized by artificial intelligence and robots, is filled with more uncertainty than hope. Jobs are the main reason for this. Machines have long taken over the traditional labor industries, such as manufacturing and the service industries. Around the world today, we are preoccupied with finding solutions to resolve the issue of excess labor in the face of the ever-decreasing number of jobs.

However, crises may also be our opportunities. While there will be jobs taken over by advances in science and technology, the same advances may also create new jobs. The Bio industry is in the center of this change. After having witnessed a major turning point with the development of gene analysis and editing as well as other various technologies, Biotechnology(BT) now holds great potential to generate massive added-value by impacting its closely linked sectors such as Bio medicine, medical facilities, pharmaceuticals, chemistry, energy, food, electronics, and environment. The science and technology powerhouses of the world, including Europe, the U.S., Japan, and China, are already investing heavily in BT to improve quality of life and to lead the industries of the future.

Nonetheless, it is critical for professional groups of experts to validate the benefits and risks of BT as it is a practice that deals with life. Moreover, because the area of BT has many exceptions and variables, we cannot depend on artificial intelligence alone since it only runs based on predefined algorithms.

This is where we need cross-validations and joint research by well-

trained BT experts. Therefore, BT has a major effect in creating quality jobs. For instance, producing research outcomes of value and commercializing such findings cannot be handled by a few decision-makers. This is only possible when we have expert researchers, engineers, and administrators in BT and successful collaboration among them. Here, the Korean government has designated BT as a core industry in the Fourth Industrial Revolution and decided to foster experts by 2025 and create 35,000 new jobs.

There remains challenges that we have to solve in order to usher in a bright future with rosy prospects for BT. First, we need to work to reduce various regulations that can impede the development of the BT sector. One such example is that there are additional safety tests to perform when a new antibody or cell is brought to Korea from abroad for research, even if it has already been validated. This additional step is critical for safety, but having to re-validate substances that were already validated in other markets may slow down the pace of research. Another issue to think or consider about is that there still are many nations which do not legally tolerate active research in gene modification.

Against this backdrop, the Korean government is holding the Special BT Committee meetings to listen to the voices of the industry and is actively involved in improving regulations that can reform the R&D framework. It is encouraging to see that the support for research expenses and performance assessment are becoming more rational. Moreover, unlike the past, the



government has introduced an innovative policy which can terminate projects in progress if it is determined to be difficult to reap the desired results.

Improvements in regulations drive start-ups in BT and new businesses to attract new labor. In order for this virtuous cycle to work well, bioclusters need to be developed, where all the sectors that are relevant to BT can come together. Bioclusters that include bio research facilities, production facilities, and administrative organizations can create synergistic effects in the sector. A BT ecosystem is favorable to nurture the necessary bio talents for the industry. For example, bioclusters can effectively run joint training

programs for developing data analysts or engineers by facilitating the joint collaboration between the industry, academia, and research institutions.

The era of the Fourth Industrial Revolution, the development of BT, and job creation is not just wave to ride on. It is a flow that has to be created through the close collaboration and communication among the government, the scientific community, and private businesses. When there are numerous cases of successful commercialization of BT research, many new jobs will be created as well. Now is the time for the experts to deliberate meticulously and invest pre-emptively to prepare for the new future.



Another Secret Revealed by Microorganisms

KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY, ANTICANCER AGENT RESEARCH CENTER

Humankind originally used plants that were known to have therapeutic effects based on experience. Medicinal plants, so-called herbs, have been in use for a long period of time and built the foundation of traditional medicine. The effective ingredients of such plants identified by traditional medicine were purified and produced as drugs in the modern world and became the foundation for modern-day medicine. Until recently, much of our health depended on these plants. However, since Alexander Fleming's discovery of penicillin, fungi and microorganisms have taken over the role that was traditionally played by plants.

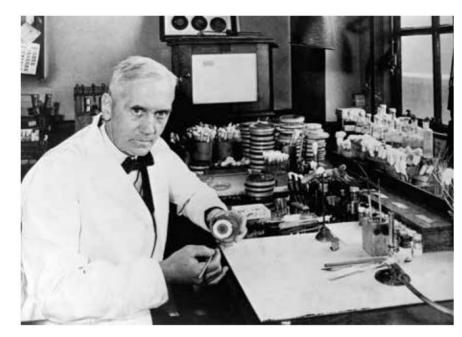
Most modern drugs originate from living organisms. Aspirin, which opened the door to modern pharmaceuticals, was extracted from meadowsweet, which was used as a painkiller together with willow. Morphine, which is widely used as an anesthetic, was produced from poppy extract. Tamiflu, a well-known treatment for influenza, is also purified from the pods of star anise, a type of spice. Other famous examples include the anticancer drug Taxol produced with materials from yew, the painkiller Prialt derived from cone snails, and the antihypertension drug captopril developed from snake venom.

It is easily understood why many pharmacological agents come from living organisms. It is because of our long-term experiences, where the characteristics of the organism or the treatment mechanism of the agents are well-known, that we are able to easily develop new drugs. Traditionally, the milky liquid from poppy buds was used as a strong anesthetic or sedative. And the



The influenza drug Tamiflu was developed from extract of the pods of star anise, a type of spice. Beyond Tamiflu, many drugs are also derived from living organisms.

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The discovery of penicillin from green mold by Alexander Fleming changed the history of medicine. Photo taken from his lab in 1943.

poison of cone snails is a strong neurotoxin that can block pain signals, and the snake venom inhibits the ACE enzymes in the blood vessels. By leveraging our knowledge of the characteristics of agents derived from living organisms, the direction for new drug development and the target agents can easily be determined.

Life is the best teacher

On the other hand, when an agent is well known for its characteristics and medicinal effects, it is likely that the related research and results have already been conducted and discovered. In fact, in the modern world, most extracts and organisms used as traditional medicine have been analyzed and are available in the market as commercial drugs. While new drugs, based on naturally extracted substances, are gaining more popularity, most of these new natural drugs focus more on reducing the side effects of existing drugs and enhancing

medicinal effects rather than providing new treatment effects. It is now a practical challenge to discover completely new effects from the existing plants and animals. Thus, since the mid-20th century, fungi and bacteria began to emerge as the new mines for drug ingredients. The most well-known example is antibiotics. By coincidence, Sir Alexander Fleming discovered the sterilization effects of penicillium, which was a surprising ability not found in plants and animals. After penicillin, Selman Waksman successfully isolated streptomycin from the microorganism streptomyces that lived in soil. Streptomycin proved its value by successfully treating pneumonia and tuberculosis, which were not treatable using the previous extracts from plants and

The discovery of penicillin and streptomycin marked a turning point for scientists from many leading countries to



After the war, Japan actively engaged in research on antibiotics, led by RIKEN. The photograph shows the antibiotics produced in Japan in the 1950s. The manufacturer is KAKEN (科研製業株式会社, formerly 科研化学株式会社), a spin-off business from RIKEN. © KAKEN

search for pharmacological agents from fungi and other microorganisms. These were ideal research targets to look for new bioactive substances. They are genetically diverse due to their short reproduction and generation cycles. Naturally, these organisms produce substances that are not easily found in other organisms. Moreover, with their smaller size and relatively easier conditions for reproduction, they are easily cultured in a laboratory in large volumes and are more suitable for separation and purification into the desired agents. Bacteria living in extreme conditions are likely to synthesize substances that are unpredictable as their metabolisms differ from the typical environment.

RIKEN (Rikagaku Kenkyūjyo) of Japan led the research in actinomycetes and delivered significant results, especially in identifying and purifying new antibiotics. While Korea fell behind in its research infrastructure, Korea Research Institute of Bioscience and Biotechnology (KRIBB) collaborated with RIKEN to develop its research capability, with the result that it now stands on par with the leading groups around the world.

Anticancer Agent Research Center, searching for new substances from life

The Anticancer Agent Research Center of KRIBB is a center dedicated to finding new medicine substances from fungi and bacteria in Korea. The center's goal is to provide new anticancer substances that are totally different from existing drugs from the metabolites of microorganisms that can selectively suppress the divisions and metastasis of cancer cells. Currently, the microbiologist who played the key role in the collaboration with RIKEN, Dr. Jong Seog Ahn, is taking on the leadership role of the Research Center.

Why anticancer substances instead of

antibiotics? As cancer has many causes and complex physiological effects, it is difficult to find a mechanism that can apply to all cancer types. Preventing or treating cancer is also difficult since such a mechanism has not yet been defined. Even today, many researchers are working to reveal the mechanism of cancer through various approaches, including genomics or proteomics. Moreover, the study of microorganisms may provide insights about cancer that are completely distinct from the research on the genes and proteins of cancer cells.

As witnessed in the discovery of antibiotics, fungi and bacteria produce various metabolites. Among them, there are still many compounds that are unknown to us and some with structures that scientists cannot yet imagine. As the structures of the compounds determine their physiological functions, there might be substances produced by fungi or bacteria that interact with cancer cells in ways we have not yet identified. By finding such substances, we can discover new metabolic pathways of cancer cells and be able to produce anticancer agents based on such findings. The Anticancer Agent Research Center



View of KRIBB. The Anticancer Agent Research Center is a research group managed by KRIBB, which carries out research to find medicine substances from microorganisms.



Three anticancer agents were announced by the Anticancer Agent Research Center in 2017.

These were isolated from the actinomycetes found in soil from Ulleungdo of Gyeongbuk Province, Korea.

focuses on finding the starting materials that can be used as anticancer agents. A starting material refers to a substance that can have an impact on physiological activity by interfering with the metabolic mechanism of a disease. While such a substance cannot be used as medicine itself, it is known as a 'starting material' as it serves as the basis for developing new drugs. However, such substances are hard to find in microorganisms where the detailed characteristic and the metabolic mechanisms are already well-understood.

Therefore, the main task for the Anticancer Agent Research Center is to discover new microorganisms that are not yet known, or culture already-known microorganisms in new conditions and develop new biosynthesis processes. The Anticancer Agent Research Center believes that actinomycetes are the likely starting point, as much research has already been conducted in the development of antibiotic substances. Another area of interest is fungi. As the biosynthesis processes of fungi have yet to be fully studied, there is great potential for offering new metabolites. The result of one such research was fusarisetin, a substance patented by the center in 2011.

Fusarisetin, the essence of research by the Anticancer Agent Research Center

Fusarisetin is a low molecular weight substance with a unique structure. It has a five-ringed structure, which has not been seen in any other metabolites previously known. The Research Center isolated fusarisetin from *Fusarium sp.* in 2010, patented it in 2011, and published related journal papers. The center has high hopes that fusarisetin is involved in the metastasis of the cancer cells and can be utilized as an anticancer agent.

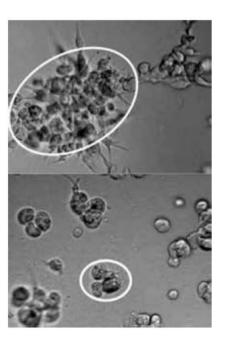
The five rings of fusarisetin are of different structures. As a substance with such a five-ring structure has never been synthesized or discovered before, it was a significant breakthrough in the field of organic chemistry. Leaving its potential as an anticancer agent aside, it became a challenge to organically synthesize fusarisetin as it was of a new structure that was difficult to manufacture.

The first institute that showed interest was the Shanghai Institute of Organic Chemistry (SIOC) under the Chinese Academy of Sciences (CAS). Associate Director Jong Seog Ahn remembered that

he received an interesting mail from SIOC about six months after he published his paper in April 2011.

"A researcher at SIOC contacted me via mail around November 2011 to request whether we can send them a sample of the fusarisetin that we had isolated so that they could perform a cross-check with their synthesized fusarisetin."

It was surprising news to the center. As fusarisetin had a complex molecular structure, its artificial synthesis was very difficult. However, it was successfully manufactured at a lab within only six months from the center's publication. At that time, the Research Center's concern was the low yield rate as we had to extract and purify fusarisetin from the fungi. If it could be artificially produced, the pace of the research was likely to gain more momentum.



Anticancer effects of fusarisetin A, discovered by the Anticancer Agent Research Center in 2011. Cancer cells that grew well on typical broth culture (above) did not grow when fusarisetin A was present. (below) © Jang et al. / American Chemical Society

Molecular structure of fusarisetin A. With its 5-ring complex structure, it provided a good challenge for biochemists.

"Many scientists usually share information on such findings. However, as we had so little to use for our own research, we could not readily send over a sample. Thus, due to low yield, we proposed that they send us the synthesized sample where we could verify it against our sample. However, there were no follow up communications. Then, in early 2012, SIOC published a paper announcing the synthesis of the substance." Researchers from the U.S. also showed interest following China. A research team located at UC San Diego made public their successful synthesis of fusarisetin in the Journal of the American Chemical Society (JACS). Soon after, another Chinese team, beyond SIOC, published their paper in the Angewandte Chemie. Within just one year from discovery, fusarisetin was successfully manufactured in three locations.

In between basic research and industrialization

Fusarisetin is an exemplary outcome of the consolidated research efforts of the research center. The center studied the metabolism of fungi and identified a novel substance that was not known to the world and revealed how it was related to cancer. By looking at high-potential candidate species, new agents were identified and isolated, and a new cancer metastasis mechanism

was verified. Moreover, more research papers were published in the year following the initial publication, which presented another pressing task. That was, the issue over patents and follow-up research.

"We published our paper after we had obtained the patent over the substance fusarisetin. However, even after our publication, colleagues in the field of organic chemistry advised us to present the compound of novel chemical structure together with its production methods. This meant that we had to file for the patent once we make public announcement of the structure and the method to synthesize it. The reason was because the production method of substances is also subject to patents.

While open information sharing among the scientific community is one of the key values of research, a detailed patent application strategy is also necessary in the current day where bioscience evolves each day with ever-growing industrial implications. This is even more important for the basic research areas pursued by the Anticancer Agent Research Center,

where businesses cannot easily participate, because it is difficult to anticipate the future applications of such findings in the industry.

Recently, the center has been preparing itself for the next step. It intends to define the detailed mechanism of how fusarisetin impacts the metastasis of cancer. The center is studying the mechanism of how fusarisetin inhibits the physiological activity of cancer cells and preparing to publish the findings in 2018. The center is pushing forward with the research as a competing group, UC San Diego, has already understood the link between fusarisetn and cancer and has produced derivatives that can be used as pharmacological agents. The research center is also driving for future research to obtain new substances by leveraging genetic editing technology by editing the genes of species whose physiological activities are well understood. Once this research is on track, it will not only allow us to obtain new substances from living organisms but also produce novel substances by using easily controlled microorganisms. 33



The Anticancer Agent Research Center continues to improve its research capacity through active collaboration with global research institutions, including RIKEN. Photo of the Joint Symposium held together with RIKEN in 2017.

Q. The research center seems to have taken an unique approach in identifying new anticancer agents. Is there a particular reason why you became interested in anticancer agents as a microbiologist?

A. In 1977, the Budapest Treaty was signed. Before that, patents were given when substances produced by microorganisms were submitted. However, the Treaty added the requirement that the microogranism should also be provided in order to gain patent approval. Korea joined the treaty in 1987 and it was made effective in Korea in 1988. Following the Treaty, any application for international patents required the isolation and culturing of the host microorganism. I joined the former institute of KRIBB in 1985 as a lead researcher. It was my role back then as a young scientist to identify useful bioactive materials from microorganisms to ensure that we could prepare against the Budapest Treaty. While in this role, I learned the research protocol of RIKEN in Japan. At that time, the spotlight was more on intercellular signaling and its relation to cancer, and the 'Antibiotic Agent Research Lab' of RIKEN was interested in regulating the signaling system of cancer cells by using physiologically active substances from microorganisms. I also started to gain interest in cancer cells and continued my research in the field even after I returned to Korea.

Q. What was your collaboration with RIKEN?

A. I have my personal network with RIKEN researchers. When I was working at RIKEN, I got to know Dr. Osada Hiroyuki who is two years older than I am. He was the youngest researcher in the Antibiotic Agent Research Lab, studying the signaling pathways of cancer cells. That encounter helped me build

Interview with

Dr. Jong Seog Ahn

Associate Director of the Anticancer Agent Research Center

the official collaboration research partnership between KRIBB and the Antibiotic Agent Research Lab of RIKEN after more than 10 years. We formed a joint RIKEN-KRIBB research unit in RIKEN to carry out our joint research. From the collaboration with RIKEN, we learned their know-how and were able to raise the research capability of Korea. It is an experience where I deeply felt the importance of international cooperation.

while also moderating our pace not to prematurely announce our results, which may damage our patents and rights. At the same time, it is important to maintain our network with international research groups, as was experienced with RIKEN. Based on such efforts, I hope that we can find new anticancer mechanisms and any starting materials that can be used for treatments or used as clues for development anticancer drugs and be able to reach the clinical testing stage.

Q. What are your priorities as you lead a group of professional researchers?



deliver performance



Research for Others and Not for Self

INPYO CHOI, ASSOCIATE DIRECTOR OF IMMUNOTHERAPY CONVERGENCE RESEARCH GROUP

Cancer is regarded one of the most lethal diseases facing humanity. It is also the number one cause of death in Korea. Cancer is a disease of ancient historical origin with records dating as far back as the time of Hippocrates and has held the title of the worst incurable disease throughout human history. As such, the study of cancer is a great challenge for many researchers. Yet, cancer research is also a holy mission for the researchers seeking to find the cure for the many patients that suffer even today. In this journey, Associate Director Inpyo Choi of the Immunotherapy Convergence Research Group at Korea Research Institute of Bioscience and Biotechnology is more of a calm observer of life than a researcher wielding the weapon of sharp rationality. On a still chilly day in the spring of 2018, Associate Director Choi shared his research philosophy and his thoughts on his life as a researcher.

From cytokine to cell, and from cell to cancer

Associate Director Choi is an immunologist. His initial area of research was on cytokines, particularly interleukin-6. Interleukin-6 is a protein that is involved in the activation of immunocyte B-cells and inflammation. Later, he became interested in interleukin-18, which showed anticancer effects. As his interest shifted, Associate Director Choi began to focus more on the cell itself than on the immunocytes that these proteins activated. His research in cancer finally began as he started to study NK cells (Natural Killer Cell).

You are studying cancer as an immunologist. Why were you interested in cancer?

I started my early research in the study of cytokines. As cytokines play the role of "messengers" among immunocytes, they

are key to understanding the immune responses and the consequent treatment mechanism. This was what got me interested. However, as I continued, I realized that the immune cell itself was more important than the messengers. So, I shifted my focus to NK cells, which directly attack the cancer cells. From my basic study on how NK cells are produced, I became interested in how the NK cells attack cancer, and started my research on its treatment. In other words, I started my research in the field of basic science and have naturally moved towards clinical research. In fact, cancer is a very interesting topic to immunologists as cancer cells in the lesions, unlike other diseases, evade the immune system.

Carrying out clinical research at KRIBB, a basic science research institute, does not sound easy. Is there any collaboration with external institutions?

There was a point in time where we really

NK cells, there was no technology to mass produce NK cells and we had no idea how the technology that we developed might be applied in practice. Then, after learning about our research on NK cells, Seoul Asan Medical Center(AMC) proposed to apply the newest anti-cancer therapy to their patients. With that, we conducted co-research with the Department of Hematology of Asan Medical Center in 2007 and 2008. Afterwards, we were able to perform more systematic research after signing the MOU, starting our official collaboration, and launching the AMC-KRIBB Clinical Research Center at Seoul Asan Medical Center. KRIBB provided the research results, anti-cancer treatments, and the expert researchers while Asan Hospital provided the facilities and infrastructure necessary for producing NK cells.

began our clinical research. Just 10 years

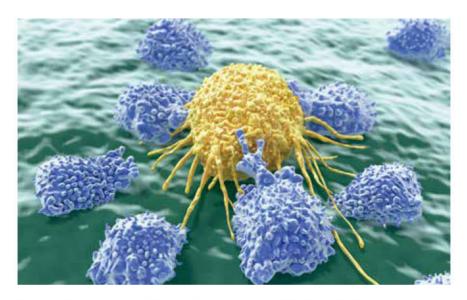
ago, during the days when I was studying

Was it the first joint research project with an external institution?

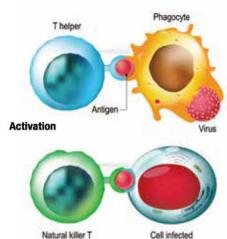
Yes, it was. We have quite a number of joint projects with hospitals now, but there were almost no such cases back then. There were several challenges to resolve. We had to send researchers back and forth and take care of the relevant administrative processes. In particular, it was not easy to resolve many sensitive issues, such as obtaining the approval for clinical trials from the Ministry of Food and Drug Safety and defining the quality management protocol. We were fortunate to have overcome these obstacles with the active support from KRIBB as well as from the Ministry.

Which stage is your research at now?

We have completed the pre-clinical stage and obtained the approval from the Ministry of Food and Drug Safety and



Electronic microscope image of NK cells attacking cancer. Associate Director Choi began to gain interest in cancer treatment as he studied NK cells. © Juan Gaertner/shutterstock.com



Difference between T cells and NK cells.

T cells attack pathogens by indirect approaches through the activation of the immune response. In contrast, NK cells directly attack and kill the cells of our tissues that are infected.

Lysis

are now carrying out Phase 1 and 2 of the clinical trials. Everyone is at around the same stage globally. There are no cases of commercialization to date. Like most medical technology, it will take some time until we can fully apply such advances to real practice.

Ever-growing complexity of the research environment, but a natural change

As shown from the conflict over CRISPR, the issue of intellectual property and patents in the field of Biotechnology (BT) is a key issue for researchers and this cannot be easily overlooked. With the bright outlook of the BT industry and with its huge potential in terms of added value, its commercial use has now become ever more important. However, issues of intellectual property entail diverse factors from industry valuation to legal issues that pose great challenges for researchers. Having moved his career from basic science to clinical technology, how would Associate Director Choi view such changes in the research world?

As cancer research directly links to clinical medical technology, it seems that there would be sensitive issues around the rights to treatment technologies. Are these big challenges for you?

As a matter of fact, we are focusing more care on patents and technologies as we started the Convergence Research Group. We have an IP team consisting of patent attorneys and a technology socialization team consisting of technology evaluation

experts within the research group. Of course, this is a major burden compared to simply working on basic research, but I think it is more of a reflection of how big the field of biotechnology has become in our society. This is a change that researchers have to adapt to despite the difficulty. We do get support from many stakeholders.

How does the Research Group respond to intellectual property related issues?

Nowadays, we seek advice from patent attorneys or patent offices from the initial proposal stage of the research. We check whether there are any previous studies, any potential issues with research rights and potential violations of any patents and for any conflicts that might occur in the future before starting the research.

Regarding clinical treatments, how will the scope of research change at the Research Group?

We are not stopping at just culturing NK cells, but are developing treatments that converge immunology and genetics and leverage gene editing technology. In particular, we believe that Big Data analysis should be applied for treatments. Previously, the study of biology focused on the central dogma and ways to simplify and revert back to the metabolic mechanism. Now, after having identified multiple variables and observed many exceptions, the study of theoretical biology has become more complex. This has resulted in a dramatic increase in the number of variables that need to be considered when applying the theories to practice with our patients. In order to process such a diverse set of variables, the human brain alone is not enough. We need the largescale analysis that is supported by artificial intelligence.



Immunotherapy Convergence Research Group started full-scale clinical research through the collaboration with Seoul Asan Medical Center. A researcher reviewing the clinical data analysis results. © Seung-Joon Nahm

At the core of the research environment lies the 'good' researchers

The Convergence Research Group of KRIBB was founded as the result of KRIBB-wide deliberations on how to respond to the changing research environment. The formation and structure of the Convergence Research Group is a reflection of the significance of BT in our everyday society. How do Associate Director Choi and the Immunotherapy Convergence Research Group prepare themselves for change?

I understand that the Convergence Research Group was launched as KRIBB's solution to respond to the changing environment. What are the most important ideas as you manage the Convergence Research Group?

The Convergence Research Group conducts its research in a single location.

Previous research institutions established through the support of the government or KRIBB mostly had their researchers continue with their research at their original locations. For example, past jointresearch projects between KRIBB and partner universities or businesses were conducted remotely with researchers at their original locations. However, the Convergence Research Group has all the key individuals, KRIBB researchers as well as researchers from the sub-division for anti-cancer treatment from Korea Research Institute of Chemical Technology (KRICT), in the same location. Now, we also have the researchers from Korea Basic Science Institute (KBSI), who are already equipped with the pre-clinical testing technology. These are the people who have been seconded to our Convergence Research Center for joint research. As mentioned earlier, in the clinical testing stage, we have our researchers stationed at Seoul Asan Medical Center to work together with the hospital to produce cells and monitor the patients.

Are there any difficulties in communication as the members come from diverse backgrounds?

Of course there are. When there are researchers from different backgrounds, there are differences in the terminology they use and even in the way they understand the same phenomena. Communicating was not easy at first and it took us quite some time to adjust and adapt. We overcame such differences through many meetings and joint sessions. I think the role of director is very important in this process, because the director has to find the optimal approach by facilitating the conversations between many researchers. As we need diverse perspectives, especially in today's complex research environment, there should be efforts to find harmony among the opinions rather than having the director hand down instructions.

What is the key criteria for selecting the researchers?

I think the most important criteria is the



The research environment has changed drastically as BioTech has been highlighted as the industry of the future. Now, there is more interest in not just the research but in how to manage the rights over related outcomes. Associate Director Choi comments that the researchers need to adapt to such changes. © Seung-Joon Nahm

mindset as a researcher. I look at three things when defining a good researcher. First, have good ideas. Good ideas include scientific ideas as well as a positive mindset. As there will be many difficulties and challenges in the course of research, we direly need a positive attitude to step up from our failures and to make a leap forward.

Second, have good habits. This also does not only refer to lab techniques, but to the life habits that may have a direct or indirect impact on the overall research life. Good researchers should be able to control their own lives and have a positive impact on their work. Having regular meetings to share opinions, continuously reading a certain amount of papers, or refraining from hobby activities that may interfere with work can all be good habits.

Third, have good relationships. The research of today cannot be carried out alone. Each individual should be committed to his or her own part and yet be able to share his or her research results, and the researcher should continue to work closely with other local and global institutions so as to have access to new information. In particular, as the researchers need to have firm perspectives, they may also tend to be stubborn, and it is important to continuously interact with other researchers so as not to become inflexible. The Convergence Research Group has been sending our researchers to other institutions including the University of Washington and Baylor University for 1 to 2 years for training to continue our global collaboration.

If so, are there any research principles or habits that you abide by?

I try to have my daily tasks set up as systematically as possible and to follow them. I have set up my meeting hours or external meetings at a certain frequency or have a certain number of papers to read within a week. Once you systematically plan your day, this will become a habit and you will be able to keep consistent and continue with the research without many ups and downs.

'Values' bigger than scientific performance or economic success are important

Associate Director Choi is a very devoted religious man. At a glance, it may not seem to fit, having a deeply religious person in the field of biology, which has major conflicts with religion over issues such as evolution and paleontology. However, religion has a very special meaning for Associate Director Choi as he can find answers in religion for questions to which he cannot find answers from science. How do his studies of science and religion complement each other in the research

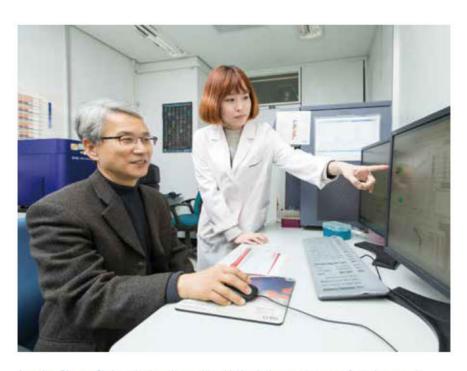
As a devoted religious person and biologist, I wonder how you maintain the balance between the two identities.

life of Associate Director Choi?

For me, science and region are not antagonistic fields. Rather, I believe the questions that are not in the scope of science and those that cannot be answered by science, such as the meaning of life or other metaphysical values, can be answered by religion. They mutually complement one another, and even more so in the study of bioscience.

Specifically, what part of biology do you think is linked to religion?

As a biologist, life stands at the center



Associate Director Choi emphasizes that positive thinking is the most important factor in research. It means that one can only be a good researcher when overcoming failures and focusing once more on the research. © Seung-Joon Nahm

of my research. The field of my study, immunology in particular, shows us how we fight against the internal and external illnesses to protect our lives, and how articulately life continues on through our daily lives. Naturally, as a biologist, I marvel at and at the same time am awed by life and its phenomena. Meanwhile, life also stands at the center of religion. As we know, since all religions respect others and talk of the importance of life, religion could be seen as an attitude of reverence we have toward our lives and all living things in this world. So, while science and religion may explain life through different approaches, they ultimately can be seen as connected.

What impact did religion have on your research life?

Frankly, I agonized over the divide and harmony of science and religion in my early research days. However, once I came to realize that religion is a 'fundamental reason and explanation for life,' my beliefs have become the guiding light of my research life. I was able to commit myself to the study of cancer for a long time because it was not research for my self interest as a scientific researcher, but because I had the belief that I had to give back to the world by pursuing research for others. Of course, I may have developed these beliefs for many reasons in the natural course of my research, but for me, my religious belief has provided the guiding light to my life as a researcher. Religion can be of great support, especially in clinical research. We need about 2 to 3 weeks to culture cells when we are treating patients with

NK cells, and many patients do not make it through this time. When this happens at the cancer wing, where death is always nearby, it is not just remorse I feel, but I start to question the basic nature of life itself.

I believe you might have felt frustrated when giving treatment to the patients.

The truth is, many scientists, including myself, don't really know much about cancer or immunology. What we do know is quite limited. While we say it jokingly, it is true that cancer cells or viruses know more about immunology than we do, because these pathogens or lesions slyly evade the immune system. Nature is superior to people. Researchers like myself should know more about the immune system than nature. Unfortunately, we are still falling behind and continue to encounter unfortunate moments. Nonetheless, we feel a great sense of accomplishment when we see almost hopeless patients reach full recovery with the treatment we have developed. The survival rate of the patients who have received our clinical treatment for leukemia has improved by 3-4 times. These are some of the outcomes that the Research Group is really proud of.

In what fields do you plan to keep challenging yourself?

I hope to apply our current research to fields currently without treatments, including liver and pancreatic cancer. I would like to focus more on areas that require help from myself and my fellow researchers rather than on quick commercial wins. I believe that it is my duty and reward as a researcher to help even a single patient recover with our research and gain his or her life back. ***



Biological Resources Archive for the Bioeconomy Era:

Korean Collection for Type Cultures

The OECD anticipates that by 2030, a bioeconomy era will have arrived, where biotechnology (BT) and information technology (IT) will merge with other technologies and play a central role in resolving serious global problems regarding health, food, energy, and environment. This prospect has led advanced countries to prepare appropriate national measures to procure biological resources, the base materials in the bioindustry, and to discover and protect biomaterials. In particular, biological resources are viewed as increasingly more valuable based on: (1)

the Convention on Biological Diversity (CBD), an agreement concluded for the protection of biospecies on Earth, and (2) the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, adopted at the 10th Meeting of the Conference of the Parties to the CBD. The Nagoya Protocol states that any use of genetic resources from an organism (animals, plants, and microorganisms) shall be subject to the prior informed consent of the country providing such resources, and

that any benefits arising from the use of the corresponding genetic resources (monetary and non-monetary benefits) shall be shared upon mutually agreed terms. This is a protocol on 'Access to Genetic Resources and the Fair and Equitable Sharing of Benefits.'

To take proactive measures for such global situations and prepare for the 21st century post genome era, a Korean Collection for Type Cultures (KCTC) is underway at the Korea Research Institute of Bioscience and Biotechnology. Based on the tasks performed at the former Korean Collection for Type Cultures, the KCTC will be the 'global biological resource bank supporting the leading nations in bioscience.' The center will research and develop biological resources, establish collaborative networks through the exchange of resources and information among domestic and overseas biological resource banks, establish databases of biological resources, and provide foreign assistance.

As the nation's largest biological resource databank, the KCTC systematically and consistently collects and preserves information on biotechnology, standard microorganisms, patented microorganisms, animal or plant cell lines, microalgae, fertilized eggs, and genomic research resources. The KCTC also produces direct

information on the chemotaxonomy, molecular phylogeny, and bioinformatics of microorganisms to be used in the taxonomic research and investigation of new biological resources. Furthermore, the KCTC performs research and development for the discovery and longterm preservation of useful resources. With an aim to lead the advancement of biological resource management in Korea, the KCTC is taking efforts to establish a computerized system for comprehensive and efficient management of biological resource data, and to procure new and highvalue biological resource data regarding microbial therapeutics, human symbiotic bacteria, probiotics, and plant symbiotic bacteria, required in the treatment of diseases, healthcare, and manufacturing eco-friendly agricultural products.

The international cooperation for the conservation and sustainable use of microbial resources is another responsibility of the KCTC. The representative resource centers in 12 Asian countries (Cambodia, China, Indonesia, Japan, Korea, Lao, Malaysia, Mongolia, Myanmar, Philippines, Thailand, and Vietnam), which are together promoting the cooperation in the fields of biological resources through the Asian Consortium for the Conservation and Sustainable Use of Microbial Resources (ACM). Among the four Task Forces (TFs) operated by the ACM, the Management of Material Transfer (MMT) is under the goal of facilitating international exchange of resources between biological resource centers such as KTCT based on the CBD and the Nagoya Protocol; the KCTC is currently discussing the methods of resource exchange by participating in the MMT-TF. The KCTC also supports the ACM Human Resource Development programs.

Furthermore, the KCTC stores any

data regarding the research outcomes which include theses, patents, reports, and technology summary. Based on the Article 25, Paragraphs 13 and 14 of the Regulations on the Management, etc. of National Research Development Projects, the research outcomes containing the information on microbial, animal, plant, or genetic resources may be deposited at the KCTC. The collected data are then informatized and managed by the system available to the researchers of the Industry-University-Institute Collaboration.

Biological resources are limited to specific regions and valued for their rarity, which place them at the heart of high-value producing bioindustries. Thus, the development of biological resources and efficient use of the developed data may be the determinants of victory in the battle for resources. In fact, with the Nagoya Protocol taking effect, the research fields of cosmetics and pharmaceuticals that rely heavily on overseas biological resources, are likely to have to face increased costs. To solve this problem, it is essential that valuable components be extracted from

diverse biological resources for future research and application, and to discover naturally growing animals and plants that can replace the overseas biological resources. In addition, a system should be established for the efficient management of biological resource data required by the research and production from the Industry-University-Institute Collaboration. By forming a collaborative network with the relevant domestic and overseas institutions, the KCTC will sufficiently carry out its function as a biological resource infrastructure through which original biological resources in Korea can be utilized.

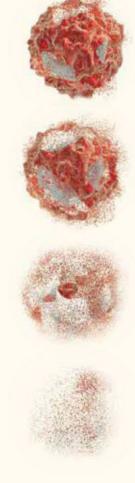


Through regular workshops, the KCTC provides trainings on biological resource management to the researchers in Korea. Shown in the photo is the 34th Biological Resource Cultivation and Conservation Technology Workshop.

Elucidating the **Genetic Mechanism**of Apoptosis Involved in

Cancer Drug Resistance

To maintain the normal state of health. the cells in our body constantly exchange signals and induce the death of aged or damaged cells to prevent them from becoming abnormal. However, cancer cells, which carry certain genetic mutations, resist apoptosis and proliferate indefinitely. A team led by Dr. Mi Sun Won at the Personalized Genomic Medicine Research Center (PGMRC) has elucidated the mechanism behind the suppression of extrinsic apoptosis mediated by DNA damage-induced apoptotic suppressor (DDIAS), whose expression increases in lung cancer and liver cancer. This suggests DDIAS, which suppresses cancer cell apoptosis, as a new therapeutic target in lung and liver cancers, thereby demonstrating the possibility of developing newer drugs against cancer drug resistance. Dr. Won's team previously reported the function of DDIAS in suppressing apoptosis, after discovering the FLJ25416 gene with increased expression in colon cancer for the first time and named it DDIAS. The team showed that decreasing the level of DDIAS proteins did not affect normal cells, but led cancer cells to the apoptotic pathway.



In the present study, a mechanism by which DDIAS regulates extrinsic apoptosis has been newly elucidated. Extrinsic apoptosis occurs when Fas-associated protein with death domain (FADD), a shared adaptor protein among receptors, forms a death-inducing signaling complex (DISC) of procaspase-8, upon the binding between the extracellular ligands (TNFα, TRAIL, FasL, etc.) and the apoptosis-inducing

receptors (TNFR, DR4/5, Fas, etc.). In the apoptotic pathway, the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) binds to the DR4 and DR5 receptors to induce apoptosis. Numerous cancer cells are known to have resistance against TRAIL as a result of defective TRAIL receptor regulation and a lack of the DISC component.

Through this study, Dr. Won's team has discovered that coadministration of a DDIAS suppressor (DDIAS siRNA) could effectively induce the apoptosis of cancer cells that were shown to be resistant to TRAIL. This study was the first to shed light on the function of DDIAS with regards to TRAIL. The elucidated mechanism involved the binding of FADD to the DDIAS protein; this inhibited the binding of procaspase-8 and prevented the formation of the DISC. It was also found that DDIAS was functioning as a dualcontrol that prevents apoptosis in cancer cells by facilitating the degradation of procaspase-8, a key protein in apoptosis.

The present study has elucidated the detailed mechanism of apoptosis suppression by the DDIAS protein and demonstrated a possibility of an effective anticancer treatment where TRAIL resistance can be overcome, by the coadministration of TRAIL and DDIA suppressor. By verifying the potential of DDIAS as a candidate therapeutic target gene in anticancer treatment, this study suggests the potential diverse applications of DDIAS in the development of therapeutic agents for cancers in different parts of the body, such as the lungs and liver.

Jeong Min Lee et al., "Multivalent Structure-Specific RNA Binder with Extremely Stable Target Binding but Reduced Interaction to Nonspecific RNAs", *Angewandte Chemie*, 2017, DOI: 10.1002/ange.201709153 Development of a Multivalent Protein Optical Sensor for

Ultrasensitive DNA Detection

Protein probes exhibiting specific binding to a biomarker may prove useful in early disease diagnosis. As a regulator of gene expression in biological organisms, microRNA (miRNA) plays a central role in the metabolic processes in the organism's body. It is a widely used biomarker in the diagnosis of specific diseases such as cancer and heart disorders. The present study involves the synthesis and evaluation of multiple protein isoforms that can selectively bind to targeted or non-targeted miRNAs and shows how multivalent interactions can be applied to sensors for biomarker detection.

The Hazards Monitoring Bionano Research Center (Dr. Taejoon Kang) and a team of professors at KAIST (Dept. of Chemistry; Prof. Yong-Won Jung and Prof. Bong-Su Kim) developed a novel multivalent PAZ protein, which specifically binds to double-stranded RNAs, and used a gold nanowire optical sensor for successful ultrasensitive DNA detection.

The team combined a number of PAZ proteins with various structures of 2mer, 4mer, and 24mer peptides to synthesize the multivalent PAZ protein, and confirmed that the multivalent protein (24mer-PAZ) exhibited a far stronger binding to double-

stranded DNAs than to PAZ monomers. This indicates the enhanced binding of the protein to the target biological molecule, with consequent ultrasensitive detection of the biomarker genes.

However, one problem regarding DNA detection emerged, as the protein was found to have acquired not only an enhanced binding to the target biological molecule, but also an increased nonspecific binding to single-stranded genes. Such a nonspecific binding reduces the signal-tonoise ratio, thereby lowering the sensitivity of the biosensor.

This led the research team to develop a protein (24mer-PAZ+2, 24mer-PAZ-3) that binds only to the target gene with high specificity but not to non-target genes, by adjusting the surface charge of the protein through protein engineering. The results showed that reforming the protein surface charge significantly reduced instances of non-specific binding. Notably, the 24mer multivalent form of PAZ+2

protein (24mer-PAZ+2) was opted as the multivalent protein optimized for detection of double-stranded RNA, as it exhibited the highest signal-to-noise ratio in the surface plasmon resonance analysis. The team confirmed that applying the 24mer-PAZ+2 protein to the gold nanowire surface-enhanced Raman scattering sensor could detect the miRNA at an extremely low Attomolar concentration (6.02×105 DNAs in 1 L of the solvent), and that the technique allowed the simultaneous detection of three miRNAs from the liver cells and heart cells.

It is anticipated that the future research by the team will lead to the development of a biosensor, as well as protein probes specifically binding to a wide array of biomarkers. The present study is likely to make a substantial contribution to the development of highly sensitive and specific techniques for disease diagnosis based on the use of protein probes. ***

Joo-Young Im et al., "DDIAS suppresses TRAIL-mediated apoptosis by inhibiting DISC formation and destabilizing caspase-8 in cancer cells", *Oncogene*, 2017, DOI: 10.1038/s41388-017-0025-y

An 'United Team' Across Time and Field

ASSOCIATE DIRECTOR SEUNG GOO LEE AND SENIOR RESEARCHER DAE-HEE LEE AT THE SYNTHETIC BIOLOGY AND BIOENGINEERING RESEARCH CENTER OF KRIBB

Bioengineered Confidence: Synthetic Biology

1

The Synthetic Biology and Bioengineering Research Center seem to cover a wide array of fields. How many teams do you have at the center?

Dae-Hee Lee Actually, a research center is a minimal unit in the organization of KRIBB. So, one would expect that each center must be moving as a single unit, but that's not what happens in many cases. If you're in the same team, you ought to be

sharing ideas and resources, but the scope of bioscience is so large that the information to be shared often gets differentiated according to the major or research specialty, even within a center. On the contrary, our center is different—in our case, the whole center is almost a single united team.

Seung Goo Lee In other words, we have an excellent division of labor. As science and technology advances, the relevant fields get subdivided, which tends to isolate each specific research activity. Our team is specialized for group work based on a well-thought-out division of labor that everyone agrees upon.

Is the unique culture of your center related to your research field, Synthetic Biology?

Dae-Hee Lee Perhaps, Synthetic Biology is a field you cannot study on your own. It is a field that integrates knowledge from such

In any field, the senior-junior relationship can often turn awkward between two men with an age gap spanning a decade, especially in a Confucian cultural area that emphasizes courtesy toward elders. Nonetheless, such stereotypes seem no longer valid. In a modern research environment, differences in age and experience do not obstruct the researchers in a collaborative team. The key is how they can help and what kind of potential they see in each other. A team united with a single goal despite of various academic backgrounds and career paths—the story of the Synthetic Biology and Bioengineering Research Center—unfolds through a conversation between the senior, Associate Director Seung Goo Lee, and the junior, Senior Researcher Dae-Hee Lee.

diverse fields as analyzing the characteristics of an organism, discovering useful traits, searching for ways to use those traits, and developing a system for mass production. Collaboration among specialists is a prerequisite.

Seung Goo Lee For example, with Dr. Dae-Hee Lee, his study focuses on Metabolic Engineering using CRISPR as a motif. It is what helps microorganisms to produce useful substances by changing their phenotypes. On the other hand, Dr. Ha Seong Kim at our center focuses on design which is the first step in Synthetic Biology research. The part he plays is extracting useful genetic traits and finding an appropriate microorganism for the design. Dr. Soo-jin Yeom optimizes the function of actual enzymes, and Dr. Hyewon Lee tests the cellular function in a microenvironment using microhydrodynamics. These are all different fields, but they are learning from one another under the single theme of Synthetic Biology.

It feels the organization of your human resources resembles a process in a fab.

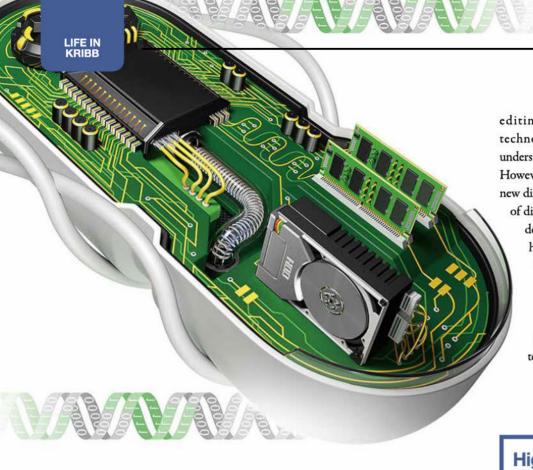
Dae-Hee Lee It wouldn't be entirely wrong. Synthetic Biology creates new technology through the synergistic interaction among different fields. That's why it has attracted much attention as we're looking ahead at the Fourth Industrial Revolution.

Seung Goo Lee In fact, there are many different views, but the common ground is the search for a way to apply molecular biology to engineering. "Bioengineered confidence" so to speak, is based on the discoveries made in biology and molecular biology.

Does it mean that Synthetic Biology is closer to the area of engineering than basic science?



ASSOCIATE DIRECTOR SEUNG GOO LEE



Synthetic Biology can be described as the "programming" of life. It is closer to process work than a single research field as it engineers biology to carry out the desired function.

© Liang Zong and Yan Liang / Nature

Seung Goo Lee Not closer, but engineeringoriented, I would say. For example, in nature, rain may fall and let the water flow, then a waterway is paved on the ground. To find and use such waterways is different from designing a canal for trapping the water to supply it to an area far from the river—the outcome may be the same, but the two are different.

Dae-Hee Lee So the focus is on the optimum arrangement of knowledge for better application rather than a new discovery. At times it is difficult to let others see its importance. There are those that view Synthetic Biology as ambiguous.

Seung Goo Lee To illustrate, we have CRISPR as the technology for gene

editing. Once you understand the technology, then it becomes easy to understand its application to other fields. However, Synthetic Biology is not about new discoveries, but about the integration of diverse techniques developed for the

diverse techniques developed for the design and mass synthesis of DNA, high-speed profiling, automated data analysis, and so on. We may say that the field emerged so naturally when we realized, 'now we have the resources to try this level of research,' based on the existing technological foundations.

High Hopes for Research that Meets the Needs

2

Synthetic Biology is a relatively new field. When were you first interested in the field?

Dae-Hee Lee The word Synthetic Biology didn't exist when I got my Ph.D. in 2007. At that time, Systems Biology was on the rise. I studied Metabolic Engineering for my Ph.D., and I was introduced to Systems Biology during my post-doc years at UC San Diego. My advisor was an expert in the field, so I focused my interest on it for three and half years of my research with him. The first time I was introduced to Synthetic Biology

was when I came back to Korea in 2012 and started working at KRIBB. The two fields, Systems Biology and Synthetic Biology, had numerous interfaces, and when Associate Director Seung Goo Lee began full-scale research in Synthetic Biology, I joined in.

Seung Goo Lee From my point of view, Synthetic Biology appeared highly practical, like research on reactors or fermentation processes. Utility is the key to engineering. So I'd been keeping my interest in Synthetic Biology until I submitted the first research plan to the Ministry of Science and Technology in 2007. Based on this plan, I could embark on serious research in Synthetic Biology in 2010.

Q.
It seems both of you considered utility more important than the value as knowledge.

Seung Goo Lee I always focus my decisions on utility. When I was a freshman at university—that was before KRIBB was founded—Dr. Moon-Hee Han, who was the first President of KRIBB, came to a seminar and explained the utility of genetic engineering using pomatoes as an example. I remember how he explained utility before the technology.

I recall pomatoes were a truly powerful message. But wasn't it a failure regarding utility?

Seung Goo Lee I think it was all about the technological process. At that time, neither tomatoes nor potatoes were worth much as a crop so the technology could not be completed. However, I think pomatoes had a profound influence on subsequent

research by showing what possible outcomes could be gained through uniting molecular biology and breeding techniques and focusing people's interests in the field. Just a single photo of pomatoes explains a lot.

Dae-Hee Lee To add to that, Synthetic Biology lets you pursue the truth based purely on the facts. In the U.S., it is not uncommon to find people who have private labs in a warehouse for biological experiments, the term used is "DIY Biology." Most of the experiments they perform relate to Synthetic Biology, and one reason why the field has attracted so many of the general public is the concrete outcome. Like pomatoes.

Q. The recent achievement at the center; how close would you say it is to the kind of concrete progress as Pomatoes?

Seung Goo Lee We use microorganisms. We develop the microbes that can send signals when they encounter a beneficial substance and those that can detect hazardous substances and remove them. So, our ultimate goal is to create microorganisms that can sense the target (sensor), make decisions (logic circuit), and coordinate (gene control). The technology required for each of these steps has been developed to a certain level at the Center. Our goal from now on is to enable the "encoding" for the organism to acquire the desired function, by combining the techniques that have been developed so far. This will resemble the process of loading a program on an electronic device.

It sounds just like a process in software engineering.



"Pomato" was a keyword that left a powerful impression in the 1980s. Although it is said to be a failure as a crop plant, the pomato is still popular in horticulture. The photo depicts the pomato commercialized by a British gardening company. © Thompson & Morgan



Dr. Dae-Hee Lee was selected as a Young Korean Academy of Science and Technology (Y-KAST) recipient by the Korean Academy of Science and Technology. This award was based on his highly appraised potential research capability and creativity. Since February 2017, the Y-KAST has managed political activities and overseas collaborations as the "Young Academy," mainly run by young scientists below 45 years of age.

Dae-Hee Lee Just as in other fields of engineering, the strategy in Synthetic Biology is to realize through repeating the same process. All engineering fields advance by repeating the design, build, test, and learn.

0

What would you say is the level of research at KRIBB compared to overseas research status?

Dae-Hee Lee Abroad, several industries have already been established, to the extent that there are seminars dedicated to Synthetic Biology industries.

Seung Goo Lee A diversity of Foundries is being established, mostly led by the U.S. and the U.K. Much advancement has been made in Korea too, concerning individual projects, although we need to

have the frame for continuous promotion of the platform technology. If we attach weight only to the short-term outcomes, all those studies that require fostering would stop and become defensive. Those with integrated research with huge potential would perish after a mere demonstration.

Q.

They do tend to push towards a rapid outcome. It may be owing to insecurity.

Seung Goo Lee I agree. I spent a few years being a window of communication with the researchers of Synthetic Biology in the U.K., and what I keenly realized was that the British do not give up on their hopes for success easily. It seemed, once they've made a decision based on serious reflection, they'd push through to the end even though the outcome is still invisible and unclear. That's probably how they could pioneer in so many fields.

A Leader's Role is to Observe and Communicate

3.

Q.

The researchers at the center have diverse backgrounds, and I understand communication is not

always easy when your research areas deviate. Despite this, your team can move organically as one team. What's your secret?

Dae-Hee Lee For a team to move together in one direction, I think communication is the key. Fortunately, our center is good at that. We often share research ideas as well as personal thoughts and worries. One may say that letting private lives enter the realm of work could cause some disconcerting situations or problems of privacy, but it certainly is very helpful for us to create synergy because we share so much of ourselves.

Seung Goo Lee As the Associate Director, I make keen observations of my fellow researchers. In doing so, I am trying to see how they analyze and interpret given information or results because I can merge their ideas only when I know the process behind each idea. For communication, I try to attain at least a general understanding of their special areas and to comprehend their individual ways of thinking. I believe that, when I do my best playing the role of the mediator, the center as one team can lead outstanding integrated research.

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Then you must be making great efforts as the Associate Director.

Dae-Hee Lee I like to work with people with similar backgrounds. It makes communication easy. Considering this, our Director never seems afraid to delve into new areas of study.

Seung Goo Lee Actually, if you look at it closely, individual researchers are not overly different from one another. There are certain points that they share, and knowing

this, I could unite them. It is true that, at our center, all those people with different perspectives gather together to pursue a common goal, but I also intentionally try to induce those within the same field to have different perspectives.

For them to have different perspectives?

Seung Goo Lee If everyone is looking in a single direction, then you get a single outcome from the efforts of many. However, if everyone is looking at something from different directions, then the outcomes will be diverse. It is the same at the center. A true synergy is born when every researcher is looking at different sides and directions according to their own specific background and field while, under a relaxed presumption, they are working to achieve a shared goal. That's why I am trying to acquire the understanding of diverse fields to the best of my efforts before I communicate

information to our researchers.

Dae-Hee Lee The Associate Director's policy has been a great help to me. Although Synthetic Biology innately requires knowledge from diverse fields, I learned much while working with the other researchers at the center.

What future goals do you have in mind?

Seung Goo Lee I want our center to be the global top-notch research group in the field of Synthetic Biology. It will certainly require a substantial amount of time. We may be small now, but one day I'd like to see the center become as world-renowned as the Broad Institute in the U.S. When each of us does our best in our own field and creates synergy, and when each one of our researchers becomes a world-class expert, I believe that dream will come true. IR



Associate Director Lee stressed that "Observation" was one of the essential roles of a center director since it is the responsibility of the director to be the medium through which the ideas of different researchers interchange. © Seung-Joon Nahm



From ideas to product commercialization

PLASMAPP.

A SUCCESSFUL EXAMPLE OF KRIBB STARTUP FOSTERING PROGRAM

"We were able to take bold actions in our research thanks to the support offered by the Korea Research Institute of Bioscience and Biotechnology (KRIBB). We will continue to pioneer new markets with technologically certified products through close cooperation with the KRIBB," said Yubong Lim, CEO of Plasmapp co., Itd. Plasmapp is an innovative manufacturing company specializing in medical plasma sterilizers that was founded in March 2015. Mr. Lim emphasized that the production of a single product requires great support and interest, just like how it takes the entire community to raise a single child.

Lim was a physics student. He worked for a big company after completing his Master's degree, but quit his job after three years to continue his education. He entered a doctoral program in the plasma lab at KAIST. He investigated sterilization technology using plasma, and saw the potential for commercialization. "Sterilizers using plasma technologies were already available in the market. However, my original plasma technology reduced sterilization time by 5 minutes from 1 hour. Sterilization operations are easier with our range of sterilizers, such as small sterilizing pouches as well as large sterilizing machines."

Mentors, the key to success for startups

However, creating a business was a daunting task to realize simply based on a promising potential. Lim had to juggle everything on his own from research, production, accounting, and marketing in the early days of the business as it took a quite a while to establish a team. "It was very challenging to handle everything and make decisions all alone for my startup. Once, the project I had worked on for 6 months ended up in vain as I had not thoroughly researched regulations related to the application of plasma technology to medical devices." His unfamiliarity with biological experiment protocols was another obstacle in microbial research. He needed a mentor to ask for advice, and a partner to grow with.

KRIBB became his mentor. Lim was finally able to learn about biological analysis methods and related information needed to test the sterilization performance largely owing to researchers at KRIBB. "I received much advice from doctors at KRIBB. It was nothing like formal consultation, but more like simple tips. What non-experts need most, though, is this kind of simple key information. It helps me decide where

to start when I feel like I am hitting a dead end. For people like me who are launching businesses in unfamiliar areas, getting pieces of advice from a public research institute is like finding an oasis in a desert."

The first product finally created with the help of many

Lim took his failures and lack of experience as an opportunity. He made painstaking efforts for his ideas and original technology, and participated in multiple startup support programs including the private investment-based Tech-Incubator Program for Startup (TIPS), Techin-Biz project, KRIBB Venture Capital (VC) Investment with the Bio Investment Mentor Group, and Bio Core Facility Project, which are carried out by KRIBB. Lim explained that this series of programs was organized with great efficiency to allow startups to obtain quality support for their businesses from expert research institutes. "The support



A small exhibition at the lobby of Plasmapp headquarters demonstrating the history of Plasmapp going through a number of adjustments for the final commercialization of the products we know today.

© Seung-Joon Nahm

of KRIBB to promising bio companies including the TIPS guaranteed maximum freedom to express the unique personality of every venture while supervising the entire process from idea to product commercialization," added Lim.

The toughest part of the business was marketing and various administrative procedures. Plasmapp was having trouble in channeling new markets, as it had yet to establish a marketing strategy based on a thorough analysis of the medical sterilizer market. In addition, the company had to establish a system for production such as Korea Good Manufacturing Practice (KGMP) for medication production and quality management required for new drug development. Further, Lim had to obtain intellectual rights for his technologies. Most importantly, he had to secure startup capital to build and expand the business. KRIBB provided support for business operation and project management in four stages through the Techin-Biz Project.

It first assisted him with establishing a marketing and entry strategy based on market research for dentistry and sterilizer markets; second, it helped him obtain production system certificates including KGMP and KFDA; third, it assisted with the survey of plasma sterilizer patent trends to acquire intellectual rights; and finally, it supported advertising the technology of Plasmapp through international exhibitions. "You can witness the status of Korean biotech industry at international exhibitions. As Korean manufacturing is globally acclaimed, there is an enormous interest in Korean medical devices in the international market," said Lim.

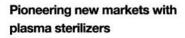
TIPS and KRIBB bio investment mentor group's VC helped securing investors. Lim explained "we received an investment worth 4 billion KRW in 2015. The amount of investments we obtained until 2017 totals 11 billion KRW." He added, "there are currently only two sterilizers in the world that obtained the plasma



sterilizer certification from the American Food and Drug Administration (FDA). We are now sparing no effort to become the third one to obtain the certificate with the all-out support of KRIBB." He also mentioned his plan to enter the European and American markets after 2018 upon acquiring the FDA certificate.

Plasmapp moved into the KRIBB SME

Plasmapp moved into the KRIBB SME Support Center and has received overall management support through the life-cycle startup fostering program since August 2015. Through the Bio Core Facility Project, the company receives research funds for the production of medical sterilizing pouches using its original plasma technology.



Plasmapp now counts 45 employees working at well-organized divisions of technology development, research, product

manufacturing, and management support with the all-out support of KRIBB. It has finally produced its test products for commercialization through countless trials and errors. Its industrial plasma equipment has been sold to big domestic companies. The manufacturing of personal sterilizers was started in March. "I personally consider 2018 as the year when everything will come to fruition. I am confident that we will survive the critical evaluation of the market. We are trained through multiple failures and countless test product production. The technology of Plasmapp is unquestionable." The blueprint of Lim's business does not settle with medical sterilizers. He plans to expand his business areas to plasma sterilizers for children and dermatological sterilizers. Both areas are related to bioscience and engineering, thus Plasmapp will continue its technological cooperation and safety testing with KRIBB. "In fact, we did not have much to request to KRIBB so

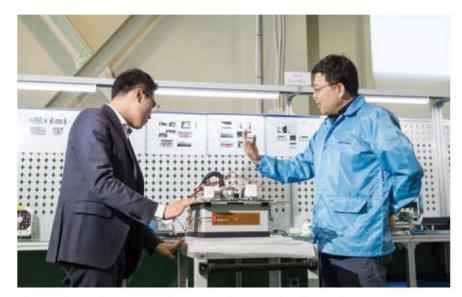




Upper. A plasma sterilizer of a foreign company. Its sterilization performance is excellent, however, its price and large volume are drawbacks. © Seung-Joon Nahm

Lower. Sterlink in operation, the product launched by Plasmapp. The company plans to expand its business areas to more diverse product lines. © Seung-Joon Nahm

far. Our requests would be consulting for simple tips or funding at best. However, our upcoming projects will require greater support from the planning stage. We expect that we can cooperate in diverse ways from expert consultation to joint research in the future," said Lim. **



Plasmapp does not have many problems today, as it has a number of experts for every area in our company, although the most daunting mission in its early days was to obtain expert advice. Fortunately, Plasmapp received great support from KRIBB researchers. © Seung-Joon Nahm

A Paradigm for the Future of Bioindustry

THE FRAMEWORK PLAN FOR BIOTECHNOLOGY PROMOTION

The Framework Plan for Biotechnology Promotion is the top-level legal plan in Biotechnology R&D that is established by equal participation of the eight related divisions, including the Ministry of Science and ICT, based on the Biotechnology Support Act. The Framework Plan is written every 10 years by integrating and coordinating the detailed plans from each division, and it is revised and amended step by step every five years. With the termination of the Second Framework Plan (2007–2016), the government established and announced the Third Framework Plan for Biotechnology Promotion (Bio-Vision 2025), utilizing accumulated research data and industrial capacities to prepare for national-level strategic promotion of bioindustry in Korea, in the face of a new economic paradigm to be associated with the arrival of the bioeconomy era and fourth industrial revolution.

The field of bioindustry, which focuses on health, food, and energy, is a stable and employment-intensive industry that ensures consistent demand and produces high-quality jobs with a large employment inducement coefficient (Bioindustry (15.8) > Manufacturing industry (9.4)). Moreover, as a response to the consistent demand for bioscience to solve such social problems as population aging, infectious diseases, and unhealthy food, the bioeconomy era has been suggested as a new paradigm, in which human welfare and economic growth including job creation can be concurrently achieved.

The Three Subfields of Bioindustry and the Rapidly Changing Global Market

Bioindustry is broadly divided into the subfields of red (health), green (food), and white (environment and energy). Red represents the pharmaceutical and medical fields to which new drug development, genomics, brain science, and digital healthcare techniques belong. Green, the

bioscience of agriculture and food, governs seed, intelligent farming, new materials in agriculture and fisheries, and animalor plant-based drug therapies. White, the fields of biomaterials and energy, includes bioenergy, biochemistry, maritime fisheries, and environmental biology.

Major nations around the world have each devised a national plan for bioeconomy promotion to achieve market leadership and technology pre-emption. The U.S. has established the National Bioeconomy Blueprint (2012), promoting a large-scale initiative that includes the activation of R&D investments by government and private companies, thereby attaining a high share of the global market (40.2%, 2016). Advanced nations have adopted policies for creating national, technologicallydifferentiated brands based on core platform technology they possess in specific fields in which they are the strongest. In Switzerland, the proportion of overall exportation dedicated to the pharmaceutical industry is around 30%, while in the Netherlands, agriculture and



seed businesses represent 40% of global seed distribution.

Currently, the present status of

technological development in each bioindustry in Korea shows that high standards of technological power have been achieved in areas such as large-scale exportation of new drug technology (a total of 28 technology transfers over four years between 2013 and 2016); collection of clinical big data in genomics (National Agricultural Genome Program (2014-2021), Korea Biobank Project (2008-present)); and acquisition of seed localization and breeding techniques (300 patents for new varieties). Nevertheless, considering the heavy reliance on importation in the areas of new materials for agriculture and fisheries (48% of core materials in food, clothing, and drugs based on agricultural resources are being imported) and biochemical materials (quantities corresponding to an annual 350 billion won are being imported), and a lack of operational and managerial techniques that create problems of reliable profitability in the bioenergy industry, there is a strong need to improve biotechnological

This status is reflected in the national competitiveness of Korea in bioindustry, which was reported to be approximately 62.2% compared with the U.S. (100%) (Japan 78.7%, China 48.8%) and a market share that was 26.8 trillion won, which is around 1.7% of the global market share (1,598.8 trillion won).

The First and Second Framework Plans for Biotechnology Promotion have allowed for the accumulation in the past of national research competence with the following outcomes: a 2.2-fold increase in government investment in bioindustry R&D; an 8.8 % reduction in the technology gap between Korea and

advanced countries; and the development of 110,000 human resources with Masters or Ph.D. degrees. However, bioindustry in Korea is still small in scale in comparison to advanced countries in terms of global industrial competitiveness. Such issues should be resolved in the near future, and policies should be implemented to prepare for the arrival of the bioeconomy era.

Reinforcing International Competitiveness in Bioindustry: Starting with Infrastructure for Innovation

To increase the global bioindustry market share, the Third Framework Plan for Biotechnology Promotion puts forward three promotion strategies: "Bio-R&D Innovation"; "Bioeconomy Creation"; and "National Ecosystem Foundation." One feature of bioindustry is that it is the winners in technological development that attract the market. This is demonstrated by the global market being dominated by 20 pharmaceutical companies (56%, 2014) and 10 seed businesses (74%, 2009). Thus, the plan promotes projects destined to be the first global Bio-R&D to be distinguished from traditional R&D that is both innovative and appropriate for the bioeconomy. It also promotes systematic unitary support strategies from R&D through commercialization, leading eventually to market success for innovative technologies. Finally, as a strategy to realize a full-scale bioeconomy, the government is to play the role of "mediator" and "supporter," providing assistance to private research activities.

As part of the plan to promote this Bio-R&D innovation-based industry, future-oriented innovative studies will be supported, while a full-cycle R&D chain will be procured through cooperation with private corporations, along with the

establishment of global open innovation and the encouragement of integrated research in bioindustry. To consolidate the bioeconomy ecosystem, convergence of human resources will be promoted, new industrial platforms will be created, and job opportunities through science start-ups and commercialization will be created. Plans for network formation and specialization of diverse business clusters will be devised for the virtuous circle of technology \Rightarrow business \Rightarrow growth \Rightarrow reinvestment, in order to lay the groundwork for realizing the bioeconomy using hospitals as innovation poles.

Furthermore, with the goal of establishing a citizen-led, national ecosystem foundation for the realization of the bioeconomy, efforts will be made to procure a national innovation pivot by i) reinforcing the role of the control tower (special committee for bioindustry) in policy enforcement by government departments and executing the R&D budget more efficiently; and ii) revising the relevant laws to create an innovative research environment and strengthening business competence. Revolutionary bioindustry regulations will induce market advancement of new technology in a timely manner for market pre-emption, and plans are underway for the establishment of infrastructure for technology, resources, and information, which will establish an innovative platform for bioindustry.

Bio-R&D promotion policies based on the Framework Plan for Biotechnology Promotion are likely to produce the following positive effects: development of innovative technology and creation of future bioindustry through the cooperation of a diversity of academia and industry; development of a virtuous cycle of investment climate for bioindustry; and creation of new jobs and enhanced employment.



A Public Diplomat in Bioscience

THE NEW ENGLAND BIOSCIENCE SOCIETY

The contribution of Koreans in the field of science working overseas has increased both in terms of quality and quantity. Currently, Korean scientists across the globe are leading diverse projects as pivotal players in the network connecting Korea to the world. The New England Bioscience Society (NEBS) is a representative society that encourages vigorous exchange among Korean scientists. It is based in the U.S., a leading nation that harbors the world's top-notch science and technology.

Established in 1984, the New England Bioscience Society (NEBS) consists of Korean scientists and clinicians specialized in bioscience and biomedical science who are currently living in the New England region, including Massachusetts, New Hampshire, Rhode Island, Vermont, Maine, and Connecticut. The 35-year long history and tradition of NEBS began

when a small private club was established for reading and discussing academic journals. Today, it has become the most widely known Korean bioscience society in the U.S. where around 450 scientists and clinicians from bioscience and biomedical science converge.

The members of NEBS are from diverse universities including Harvard, MIT, Yale, Tufts, Brandeis, Brown, Boston, and University of Pennsylvania, and around thirty bioscience research centers and bioventure enterprises.

NEBS was established with the purpose of academic exchange through a network formed by Korean bioscientists in the New England region. Since its establishment, the society has produced over 2,000 scientists, playing a pivotal role in the field of life sciences in Korea and the U.S. It is making an active contribution to the collaboration of bioscientists based concurrently in Korea and the U.S. by promoting continuous interchange among alumni via its website

(www.nebskorea.com).

Another special feature of NEBS is that it is at the heart of the bioscience and biomedical science network connecting the region of New England in the eastern U.S. The New England region is considered as a mecca of bioscience research in the U.S., as it contains renowned universities, research centers, and enterprises in the life sciences fields. Boston in particular contains globally recognized research centers, including the Harvard Medical School, Children's Hospital Boston, Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Mclean Hospital, Massachusetts General Hospital, Dana-Faber Cancer Institute, Whitehead Institute for Biomedical Research, Joslin Diabetes Center, Wyss Institute, and Broad Institute. While actively interchanging with such diverse institutions, NEBS collects the latest trends in biotechnology and lays the foundation for communication and collaboration among outstanding researchers.

The members of NEBS share presentations on their recent findings at Harvard Medical School in the evening of the last Thursday of each month. This regular seminar has continued steadily and recently celebrated its 262nd meeting in March 2018. In addition to the regular seminars, NEBS holds an annual symposium in May - June each year. The NEBS annual symposium is the largest gathering organized for Korean bioscientists in the U.S., and around 200 bioscientists and related specialists participate every year. NEBS has also organized various workshops and career expos, providing useful information to its members.

At present, NEBS is organizing a "Mentoring Program" for more robust human networking to supplement its regular seminars and annual symposiums.



The annual symposium, one of the key events organized by NEBS. It will be attended by Korean biologists based in New England. © NEBS

The active interchange among scientists based in the New England region is expected to initiate fruitful collaborations in the fields of bioscience and biomedical science. NEBS is also preparing to hold workshops for sharing various information regarding how to write research application forms or how to apply for fellowships. Such open exchange of information among members will provide a springboard for growth for Korean bioscientists.

Faced with an era of endless competition in a borderless world, the rate of scientific advancement is ever increasing. A particular spotlight has been placed on the fast-growing field of life sciences as the future blue chip in science. To keep the pace with such rapid advancement, an upto-date understanding of new research trends and quality academic exchange are essential. In this light, the activities of NEBS based on human networking are closely interconnected with national bioscience research in Korea, and thus, NEBS will undoubtedly serve as a public

diplomat in the field of life sciences.

President Ho-Geun Kwon stated the mission of NEBS is "To support Korean bioscientists in New England, the hub of global bioscience research, so that they may fulfill themselves in their fields, and to create opportunities for their close collaborations that will lead to scientific advancement in Korea." It is highly anticipated that the remarkable activities of NEBS will have a positive influence on national and global bioscience research. IR



An introduction to the annual symposium scheduled on May 1, 2018. © NEBS



KRIBB publishes top 10 promising technologies through 'Core, Red, Green, White Bio'

The Biotech Policy Research Center (Associate Director, Heoung-Yeol Kim) of the Korea Research Institute of Bioscience and Biotechnology (KRIBB) analyzed the most recent innovative research outcomes in the field of biotechnology. It carried out an assessment titled 'Promising Bio Technologies 2018' and published the results on the Biotech INformation Portal (BioIN) (http://www.bioin.or.kr).

Promising future technologies are categorized into four areas, including basic foundation and platform (Core Bio), healthcare (Red Bio), agricultural, livestock, and food (Green Bio), and industrial process, environmental, and ocean science (White Bio).

Core Bio comprises single neuron analysis technology, gene restoration, and synthetic seed technology; Red Bio, in vivo genome editing, organoids-based biomimetics, and next-generation cancer vaccines; Green Bio, simultaneous food hazard-detecting sensors and QT engineering by genome editing; and White Bio, artificial enzyme chain and carbon utilizing photosynthetic

cell factory.

Heoung-Yeol Kim, the Associate Director of the Biotech Policy Research Center, stated, "We selected promising technologies based on recent innovative research outcomes. This set of technologies holds the potential for our vision for future biotechnology. This will create a ripple effect across various technology areas and industries. This selection is a valuable suggestion of promising R&D subjects." He then added, "We will continue to develop bio-custom research techniques for promising biotechnologies. We will dedicate every effort to discover more promising biotechnologies with enhanced prediction accuracy."

In line with this, KRIBB will also continue to develop promising biotechnologies. The bioindustry is one of the key drivers for next-generation growth and promising future industries. Therefore, KRIBB aims to draw national strategies and policy agenda that will help strengthen the national competitiveness in this sector to consolidate Korea's position as a global leader.



The Division of Bioinfrastructure of KRIBB holds a signboard ceremony to celebrate its national appointment as one of the four bioscience institutions

The Division of Bioinfrastructure of

KRIBB (hereafter referred to as the Infra Division; Director of Division, Sang-Rae Lee), which is in charge of establishing and managing the public infrastructure of bioresearch resources, held a signboard ceremony at the headquarters of KRIBB, situated in the city of Daejeon, on February 12, to celebrate the designation in January 2018 as a national 'Biological Resource Center' by the Ministry of Science and ICT (hereafter referred to as MSIT; Minister, Young Min You).

The Infra Division of KRIBB collected information of all biological resources obtained from seven resource banks, officially designated by MSIT for the past three years to establish the advanced bioResource Information System. The division was officially designated as a 'Biological Resource Research Center of MSIT', prior to its operation, to strengthen the utility of biological resources for bioengineering research. As of January 2018, ARIS counted a total of 37,555 species and 1,857,747 registered biological resources, including animals, plants, microorganisms, and human-derived materials.

This signboard ceremony was particularly important because the division designated a total of four official titles, including the existing three (Biological Resource Bank for Biological Research, Biological Resource Agency, Center for Biological Research Outcome Management and Distribution, and Biological Resource Research Center of MSIT)

The Infra Division of KRIBB consists of a total of eight centers – Biological Resource Center, Laboratory Animal Resource Center, Bio-Evaluation Center, Korea National Primate Research Center, Primate Resource Center, Futuristic Animal Resource & Research Center, International Biological Material Research

Center, and ABS Research Support Center – striving to further reinforce the national competitiveness in biological research through biological research and development of infrastructures and resources.

Dr. Sang-Rae Lee, Branch Director of the KRIBB Ochang Branch Institute and Director of the Korea National Primate Research Center of the Infra Division, expressed his gratitude saying, "I truly appreciate the unconditional efforts and passion that every member of our division has dedicated to the establishment of this information center." He added, "This signing ceremony gives us another reason to exert every effort to successfully fulfill our role as a national agency."



33rd anniversary of the foundation of KRIBB "our institute will become a global leader of bioresearch"

KRIBB held the 33rd anniversary of its foundation at 10:00 am on Thursday, February 1, 2018 in the presence of the president, members of the alumni board, fellow researchers, and all employees of KRIBB.

President Kyu-Tae Chang expressed his appreciation and gratitude for the

dedication of every employee during a special award ceremony. During the celebration of this anniversary, which was divided into three sections, opening remark, national merit award ceremony, and celebration performance, the president shared his vision for the future of the

During the award ceremony, employees who made great contributions towards the development of KRIBB in the past year were awarded various award types, including the National Research Council of Science & Technology Presidential Award, Best Research Paper Award, Best Technology Development Award, Best Performance Award, and Best Team Award. The Presidential Award was awarded to both Dr. Kyung-Sook Chung, who developed the original technology for the diagnosis and treatment of rare and incurable diseases and established a new drug pipeline for metastatic gastrointestinal and lung cancers, and administrator Joeeun Kwak, who contributed to the organization of the administrative system of the KRIBB Jeonbuk Branch Institute in the early days of its establishment and formation of both the organizational training programs and a harmonious organizational culture.

The Best Research Paper Award was given to Dr. Oh Seok Kwon, senior researcher of the Hazards Monitoring Bionano Research Center, who succeeded in developing a new electric biosensor based on a conductive nanotube integrating protein (dopamine receptor).

The Best Technology Development Award was awarded to Dr. Ki Sun Kwon of the Aging Research Center, who established a drug development system for the development of substances for sarcopenia management and developed and transferred the technology for age-related sarcopenia prevention and treatment drug.

During the opening remark, president Kyu-Tae Chang stated, "Our goal is to realize the dream of good health and long life for all citizens in a safe and a rich environment. We, as one team, will continue to dedicate all our efforts to become the world's leading research institute and as a major player in the coming era of bioeconomy."



One of the 26 emerging young scientists of Korea, Dr. Dae-Hee Lee, appointed as a member of Y-KAST

Dr. Dae-Hee Lee of the Synthetic Biology and Bioengineering Research Center of KRIBB was appointed as a new member to the Young Korean Academy of Science and Technology (Y-KAST) by the Korean Academy of Science and Technology (KAST), a prestigious institution in the field of science.

Y-KAST, launched in February 2017, is the only Korean academy headed by talented young scientists aged below 45 years. Currently, the academy has 99 members and hosts a range of policy activities and international exchange programs.

The first membership screening was conducted through a public announcement and through a transparent and an unbiased evaluation process. Candidates were evaluated based on potential and creativity as well as research experience. Domestic research outcomes after completing a doctorate program were evaluated with the greatest merit. Young scientists with high potentials for the advancement of science and technology were finally selected as members.

Dr. Dae-Hee Lee of KRIBB previously developed a new type of genomic editing technology 'CRISPR/Cpf1', which can replace genomic scissors. He redesigned this invention into a genomic scissor interference technology. He has become the first scientist in the world to have demonstrated the mechanism of transcription inhibition, and the academy highly valued this achievement. Other scientists who were chosen include emerging stars in various fields of science; Professor Yongkeun Park of KAIST, who caught the attention of the international physics community with his creative investigations of 'one-wave optical phase conjugation mirror' and 'scattering superlens' and Professor Myeongjin Bae of POSTECH, an emerging young female mathematician who solved complex problems in mathematical fluid dynamics. Y-KAST started research exchange with young scientists from Japan, Sweden, US, and Israel. It launched a variety of activities, starting with the 'Young Scientists Talk 2017' held last year in November as an international policy forum for young scientists. The president of KAST, Dr. Myung-Chul Lee, stated "Our KAST spares no effort in helping talented young Korean scientists to establish international networks and grow into global leaders through Y-KAST" He then stressed, "Y-KAST will reinforce its role as a forum for young scientists to voice their opinion on science policy and research

environment." 33

