

Newsletter

# NanoSky

From KING SKYFRONT to the world - NanoMedical Innovation

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## COINS' Innovation Platform that leads to Future Health Care

### Contents

#### 2 Talking about Incubation

**Looking ahead to the Cooperation with the World, Establish a Research·Incubation Support System**

ATSUMI Hiroshi, SHIMAZAKI Makoto, NAGAI Koji

#### 6 Interview with Scientists

**Create COVID-19 Vaccine Using the Combination of Partially Double-Stranded mRNA and Nanomachines**

UCHIDA Satoshi

#### 8 Research Highlight

**Nano-DDS (Epirubicin-loaded nanomedicines) beat immune checkpoint blockade resistance in Malignant Brain tumors (Glioblastoma)**

KINOH Hiroaki

#### 10 Round-Table Talk

**Heart to Heart Talk by iCONM Foreign Scientists**

TOCKARY Theofilus A., QUADER Sabina, ABBASI Saed

#### 12 Listen to COINS' Members My job and Challenge

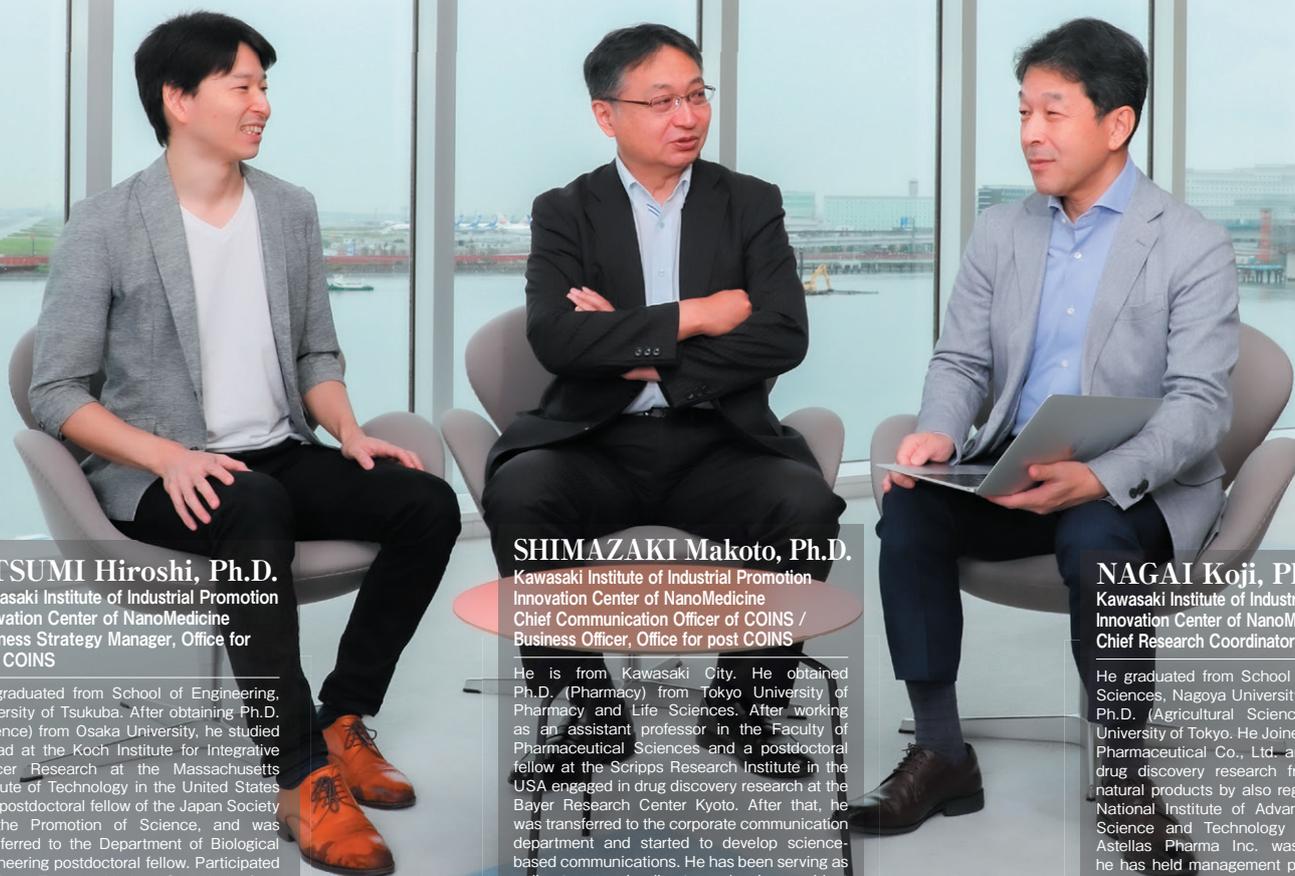
TSUCHIYA Chieko, DIRISALA Anjaneyulu, OHTAKE Tomoyuki, KARIYA Yuko

#### 14 Activity Report

- Topics
- Turn adversity into chance! Establish a new online communication method
- Editor's note

# Looking ahead to the Cooperation with the World, Establish a Research·Incubation Support System

The Center of Open Innovation Network for Smart Health (COINS) is about to reach the final stage of its finalization. We asked Dr. ATSUMI Hiroshi, Business Strategy Manager, Office for post COINS, Dr. SHIMAZAKI Makoto, Chief Communication Officer of COINS / Business Officer, Office for post COINS and Dr. NAGAI Koji, Chief Research Coordinator of COINS, about the strategy for strengthening support and the future vision.



**ATSUMI Hiroshi, Ph.D.**  
Kawasaki Institute of Industrial Promotion  
Innovation Center of NanoMedicine  
Business Strategy Manager, Office for  
post COINS

He graduated from School of Engineering, University of Tsukuba. After obtaining Ph.D. (Science) from Osaka University, he studied abroad at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology in the United States as a postdoctoral fellow of the Japan Society for the Promotion of Science, and was transferred to the Department of Biological Engineering postdoctoral fellow. Participated in Fast Track Initiative Co., Ltd. from September 2018, and concurrently started working at iCONM from December of the same year.

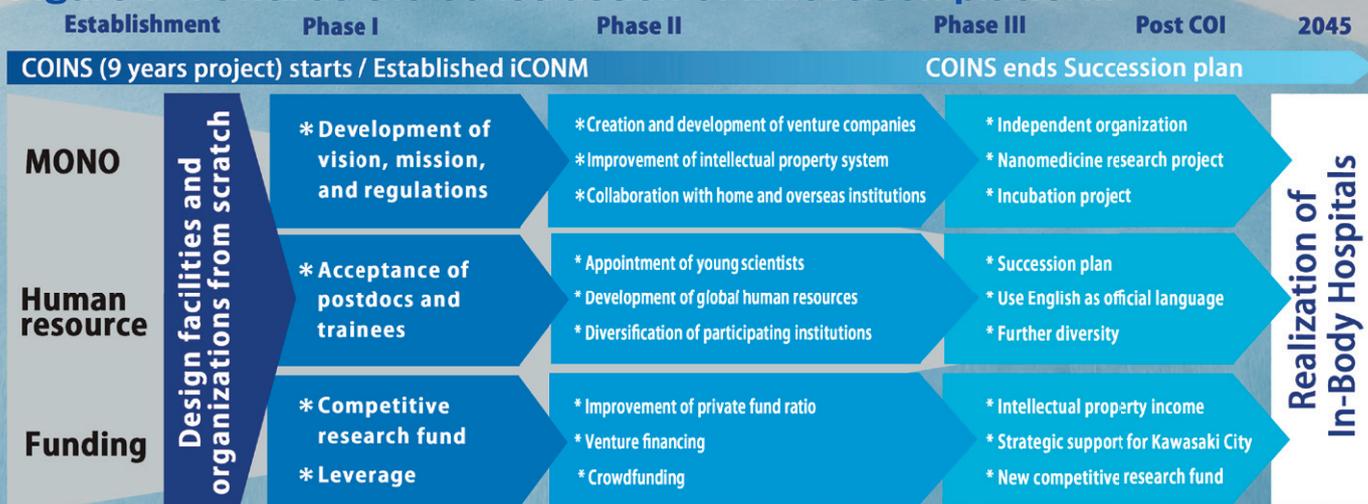
**SHIMAZAKI Makoto, Ph.D.**  
Kawasaki Institute of Industrial Promotion  
Innovation Center of NanoMedicine  
Chief Communication Officer of COINS /  
Business Officer, Office for post COINS

He is from Kawasaki City. He obtained Ph.D. (Pharmacy) from Tokyo University of Pharmacy and Life Sciences. After working as an assistant professor in the Faculty of Pharmaceutical Sciences and a postdoctoral fellow at the Scripps Research Institute in the USA engaged in drug discovery research at the Bayer Research Center Kyoto. After that, he was transferred to the corporate communication department and started to develop science-based communications. He has been serving as a director, a senior director and a vice president of communications, mainly in foreign-affiliated pharmaceutical companies and currently working for iCONM since May, 2019.

**NAGAI Koji, Ph.D.**  
Kawasaki Institute of Industrial Promotion  
Innovation Center of NanoMedicine  
Chief Research Coordinator of COINS

He graduated from School of Agricultural Sciences, Nagoya University and obtained Ph.D. (Agricultural Sciences) from The University of Tokyo. He joined Yamanouchi Pharmaceutical Co., Ltd. and engaged in drug discovery research from fermented natural products by also registering at the National Institute of Advanced Industrial Science and Technology (AIST). Since Astellas Pharma Inc. was inaugurated, he has held management positions at the research laboratories. Then, he served as a director of the research laboratory at Taiho Pharmaceutical Co., Ltd. and has been working at iCONM since May 2019.

**Figure 1 Towards the construction of innovation platform**



## iCONM's intellectual property, public relations, promotion of startup support, etc. helped acceleration of internal and external activities.

### ■ Please introduce yourself first.

**ATSUMI:** I had worked in Boston for six years as a postdoctoral fellow in biological engineering, so that could brush up my academic career. In Boston life, people from all over the world influenced my thoughts and changed my career little by little. These changes, of course, help my scientific research, and make me think “research” does not have to be science and how I could approach the future society I envisioned. Eventually, those changes fascinate me. Compared to Boston where startups ecosystem already works very well, Japan was still immature. I returned to Japan with hoping that Japanese academia and companies would be revitalized through the support of startups. Now I have been a member of iCONM for two years.

**SHIMAZAKI:** After working at university, I was involved in drug discovery research for many years as a senior scientist at a pharmaceutical company, but one day I assumed a position at the department of communications which I had no experience, what was more, it was as the director position and this situation confused me quite bit. Unlike other industries, public relations of pharmaceutical companies are inevitably “defensive” because of regulations such as the Pharmaceutical Affairs Law. I later knew that this assignment was to change the culture and promote science-based communications. Since then, I have been engaged in the communication jobs for pharmaceutical business for 16 years and joined iCONM one and half years ago.

**NAGAI:** I had been engaged in drug discovery research since I joined the company, but when I became a manager in my mid-40s, I found myself that a job of bringing together a research team and contributing to the company is surprisingly suitable. About 10 years later, when I felt the probability of success of pharmaceuticals was low and it was in a period of change, I learned about COINS / iCONM. I thought it would be fascinating to support the efforts of academia and startups to start businesses so then I changed my job.

### ■ What was your impression when you joined COINS/iCONM first.

**SHIMAZAKI:** Returning to Academia, the feeling of spreading science to the world as a non-profit organization was new experience. What companies send out is perceived as profitable, so public relations have also been concerned about that point. My motivation is to be able to convey what I have fostered to young people in my experience of transforming communications of pharmaceutical companies into science-based ones.

**NAGAI:** I was surprised that COINS / iCONM was very different from the image of academia I had before.

COINS has set a challenging goal of realizing “In-Body Hospitals” in 2045, and is working on research through industry-academia-government collaboration by breaking down the goal by



backcasting from its ideal form. When I saw it working in good shape, I thought it was new.

**ATSUMI:** I like to think about the future. “In-Body Hospitals” aiming for 2045 is exactly the health care of our future that should be realized, and I am excited to shape my future by myself.

### ■ What is the current status of COINS / iCONM?

**NAGAI:** COINS started its operation in 2013, and iCONM was established in April 2015 with the support of Kawasaki City (Fig. 1). In Phase I of COINS, we focused on developing a platform such as creating organizations and regulations, enhancing facilities, and hiring staff, and in Phase II, we proceeded with research and social implementation. Now, in Phase III of the final stage, we joined and strengthen the strategy of the research support system including intellectual property and public relations as well as promoting R & D themes.

At iCONM, satellite laboratories from various research institutes have been consolidated, and collaboration has accelerated, hasn't it? iCONM is smaller compare with universities, so it is easier to operate. I think this strength is also working in the COVID-19 pandemic. Because we were the first to take measures against the new coronavirus infection, scientists who could not conduct their research at the university were doing the research at this satellite lab. Here, the R&D of the project can be continued with almost no delay.

**SHIMAZAKI:** Intellectual property (IP) counseling sessions for scientists are regularly held mainly by those who have been engaged in the licensing function at pharmaceutical companies (see Vol.7). IP experts may also be invited from outside. It is necessary to map out an IP strategy before publishing new research results, and it is important to coordinate the contents and timing of papers, conference presentations, and press releases (Fig. 2). There are various types of media. The

**Figure 2 Platform function**





contents of newspapers, magazines, and Web media for the general public tend to become thinner in order to pursue understandability. On the other hand, the contents of media for professionals and industries are richer and more scientifically accurate. As COINS / iCONM is a public institution, information on lay media and local newspapers is important especially for the citizens of Kawasaki to understand our activities, and if we want to connect to the licensing department of companies, it is mainly a specialized media. It is important to publicize in a way that suits our purpose, such as in professional journals and industry newspapers. Of course, the licensing opportunities expand if we publicize in both, so the communication strategy in the way that suits the appealing parties is valuable. Lately, we also published press releases in English on overseas science communication sites. When we posted the results of biological test on the chemoimmunotherapy for glioblastoma (see p.8) by Dr. Kino the other day, we earned over 8,000 views.

**■ Scientists coming from overseas is increasing, and here is becoming more and more multinational. The range of occupations, including you, is expanding, isn't it?**

**SHIMAZAKI:** Greater diversity of members, such as specialty, country of origin and company / academia, the members' opinion reacts with one another to produce new things. I think this is what we should orient it to do so. In order to get good scientists from overseas involved in and bring out their potential, Japanese scientists are encouraged to communicate with foreign scientists. We are thinking every day about how to ignite chemical reactions between the scientists.

**NAGAI:** In last year, we have changed the language from Japanese to English on the General meeting that all the COINS' participating institutions gather and demonstrate their research, and the retreat training camp for human resource development. Foreign scientists have come to speak more actively and come up with ideas, haven't they? I also think that this lays the groundwork for drawing a future in which Japanese scientists will play active roles overseas.

**ATSUMI:** Several people from iCONM office also participated in the last online workshop. The theme was a "Proposal for start-ups in the post-COVID era", which makes me feel that

COINS has taken the next step because the participants from iCONM office actively get involved with the scientists.

**King SkyFront as an ecosystem of R&D · social implementation**

**■ COINS will end next fiscal year. What are you doing for the post-COINS?**

**NAGAI:** We have a good cycle of acquiring new funds based on the outcome so far, and we are now thinking about strategies for how to connect them from next year onwards.

**ATSUMI:** COINS project terminates in 2022, but we are aiming for the realization of "In-Body Hospitals" by 2045. To accomplish our research, a system that can continuously generate innovation in iCONM needs to be established, which would require research funds and other supports. We are also considering efforts to gradually add private funds in addition to the support from Kawasaki City and public research funding. Unlike universities, freshmen do not enter to iCONM, thus, it is necessary to actively incorporate resources such as human resources and funds from outside.

One of the approaches is to have startups collaborate with iCONM and co-create for the completion of the "In-Body Hospitals" and I would like to make innovation happen by interacting scientists with people from companies here. When the startups we work with grow up, I would like to be able to provide them support to play an active role overseas. The ecosystem in Boston, where universities, research institutes, pharmaceutical companies, clinical trial hospitals, and investors are accumulated, has been established in 40-50 years.

I think that there is still a room for improvement in King SkyFront and Kawasaki City. The other day, I saw the perilla that I brought back from my parents' field died on my balcony. In the original field, it grew well with the aid of morning dew and insects, but pests increased in a different environment and it suddenly stopped growing. I keenly felt that without an "ecosystem", it wouldn't grow up like it should. Besides, we need to reconsider assembling key players for "with / post corona", and are also considering the way startups and investors could see our institute by online lab. tour.

**NAGAI:** If the equipment and operation method are properly





built, research should be done online. Our center is close to the Haneda International Airport, also it will connect with Kawasaki side by a bridge next year. I really want to take advantage of this great strength and online networking.

**ATSUMI:** It is time for the big change in iCONM. When you come in about two years, I think it will be changed a lot by then.

**SHIMAZAKI:** It must be changed. About 70 institutions such as Biotech and Healthtech have accumulated in King SkyFront, but social science approach is missing to run the ecosystem, and it would be nice to have some universities to come as well, wouldn't it? I hear that some people want to have a library. It would be nice if there was an IP management office where you could consult with the entire King SkyFront.

**NAGAI:** I think it would be nice to have horizontal cooperation and communication between institutions so that you can talk with acquaintances of other institutions when you take a walk.

**SHIMAZAKI:** Nice if there are café, beer house, Izakaya, Yakitoriya and so on.

**NAGAI:** It might be good to serve alcohol once a week at iCONM.

**ATSUMI:** Entrepreneurs, investors, scientists, artists, and all sort of people interacted at a venture cafe in Boston. On every Thursday, there are events such as pitches and they provide free beers up to three, thus it was crowded with many people. It's good just to go to listen to the talk, use it as a networking place, or just to go for a beer after work.

For example, we could organize an event that one scientist gives 2-3 slides presentation for 5-10 mins on late afternoon on Thursday at iCONM so that we could interact with the people we don't contact daily work. Online would be nice as well.

### ■ Tell us about your expectation and future vision for iCONM.

**ATSUMI:** iCONM has great research facilities which are com-

parable to universities, and the excellent environment where researchers can interact, such as magnet areas. We are working with experts in intellectual property and communication support. From now on, we will develop routes that can access the ecosystem in Japan or overseas beyond King SkyFront.

**NAGAI:** An environment has been cultivated in which academia startups play a central role for engaging in innovative research, and I have the expectation that innovation will come from such a place. I hope the time will come when major pharmaceutical companies, including those from overseas, will line up at iCONM to buy drug seeds in not so long future.

**SHIMAZAKI:** India will become the third largest country in GDP in the world in 30 years. Nigeria will come into the top 10 in 2100. The countries with large population of younger people have power. On the other hand, elderly people need to work hard in Japan. It would be appreciated to foster many talents who can bridge Japan and the world through iCONM. As for communications I think it is necessary to strengthen the strategy to acquire license partners from all over the world for social implementation from now on.

**ATSUMI:** Going back to the first subject, even when I get older, I imagine I will be working actively. In Tonomachi and the world, I hope that elderly people can maintain their health by "In-Body Hospitals" anytime, anywhere with a small burden, and realize well-being to participate in society.

### ■ Thank you.

(Interviewer: Science Writer KOJIMA Ayumi)



## Create COVID-19 Vaccine Using the Combination of Partially Double-Stranded mRNA and Nanomachines

In 2018, Dr. UCHIDA Satoshi reported that converting parts of messenger RNA (mRNA), which is originally single-stranded, into double-stranded increases its immunostimulatory effect. And when COVID-19 started spreading, he began researching and developing a preventive vaccine using this information. We asked Dr. UCHIDA about the characteristics of this vaccine.

### UCHIDA Satoshi, M.D., Ph.D.

Deputy Principal Research Scientist  
Kawasaki Institute of Industrial Promotion Innovation Center  
of NanoMedicine (ICONM)  
Associate Professor  
Medical Chemistry, Graduate School of Medical Science,  
Kyoto Prefectural University of Medicine

### The World's First mRNA Vaccine Against COVID-19

It has been about a year since the first case of COVID-19 was reported in China. The research and development of vaccines have become a global race. Many types of vaccines prevent virus infections: those that inactivate or attenuate the pathogenic virus, those that genetically modify some of the proteins of the virus, those that express antigen protein genes in another virus such as adenovirus, and plasmid DNA vaccine that expresses antigen protein.

And lastly, a new type of vaccine that is getting a lot of attention—vaccine based on mRNA that expresses antigen proteins. There are safety concerns regarding attenuated vaccines because they use live pathogens, and inactivated vaccines must tackle effectiveness issues. On the other hand, mRNA vaccines pose no risk of infection, proteins can be designed quickly to match the pathogen, and the introduction into antigen-presenting cells is easy as well. Additionally, genotoxicity that can damage the host cell genome may emerge in plasmid DNA vaccines and viral vector vaccines, but there is no risk of this with mRNA vaccines as they do not enter the cell nucleus.

Dr. UCHIDA is a member of Theme 3 of the COINS project and is researching mRNA vaccines. Moreover, this vaccine is unique in that it uses partially double-stranded mRNA, which is originally single-stranded (Fig. 1).

### Adjuvant-Free mRNA Vaccine Born From Partially Double-Stranded mRNA

Dr. UCHIDA wanted to find out what would happen if RNA was converted to double-stranded, so he began his research around 2015. He intended to create a nucleic acid medicine by using RNA to modify mRNA and said, "It is not technically difficult to combine RNA with mRNA and make it double-stranded, but barely anybody researched it because it was predicted that double-stranded mRNA would lose its ability to translate proteins and would not be able to express proteins."

When he changed the mRNA design in practice by converting the entire length or a part of it into double-stranded and conducted experiments using cultured dendritic cells of mice, he found out that the ability to produce antigen proteins was weakened in full-length double-stranded mRNA, whereas the immunostimulatory effect—the

production of cytokines—was higher than that of the single-stranded mRNA.

On the other hand, the partially double-stranded mRNA almost maintained the ability to produce antigen proteins, and the ability to produce cytokines was much higher than that of the single-stranded mRNA. "This mRNA produces antigen proteins, and the double-stranded areas seem to activate the immune system at the same time, so we thought it could be a candidate for vaccines." Subsequently, using chicken egg albumin as antigen proteins, he examined its ability to produce antibodies in mice and its safety and confirmed its immunostimulatory effect in human dendritic cells.

Another major feature of the mRNA vaccine developed by Dr. UCHIDA and his team is that it does not need adjuvants. Adjuvants are usually essential in vaccines because they take in antigens and activate immune cells. However, conventional adjuvants cannot be used in mRNA vaccines. "Vaccines are widely used in healthy people, and because high safety standards are required of adjuvants, its approval for use in new products is difficult to get," said Dr. UCHIDA.

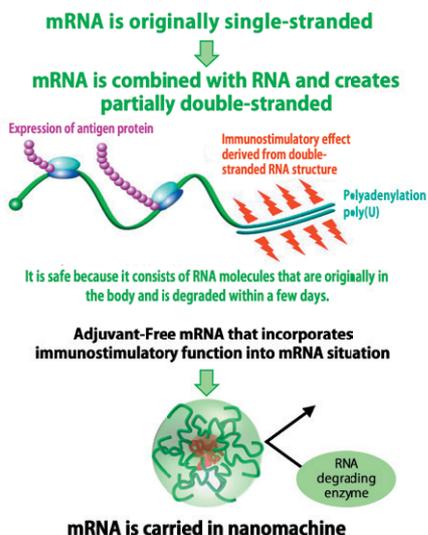
Apart from the moderate immunostimulatory effect that RNA has, this mRNA vaccine is more immunostimulatory than before due to being partially double-stranded, making it adjuvant-free.

This information on partially double-stranded mRNA is applied to the COVID-19 vaccine. COVID-19 is an RNA virus consisting of a single-stranded RNA viral genome. When it infects a cell, it adopts a double-stranded RNA structure (Fig. 2). The activation of the immune system due to this double-stranded RNA structure is an important immune response to the virus. "Our vaccine utilizes this mechanism to induce immunity against COVID-19," said Dr. UCHIDA.

At the same time, to compensate for the drawback of mRNA being unstable in vivo, polymeric micelles are used as nanomachines to house mRNA vaccines. Dr. UCHIDA said, "Research and development on the use of nanomachines for cancer treatment and regenerative medicine are in progress. The idea of using nanomachines for vaccines has been around since COINS started, but as research progresses in practice, various benefits have been revealed." Currently, the mRNA vaccines against COVID-19, with clinical trials being conducted, are all encased in lipid nanoparticles, which have an adjuvant effect.

However, when administered by intramuscular injection, many of them leak out of the muscle, resulting in their distribution throughout the body. Lipid nanoparticles are particularly concentrated in the liver and spleen, and Dr. Uchida said, "Some hypotheses state that this contributes to the effectiveness of vaccines, but the expression of antigen proteins in the liver and spleen and the activation of the immune system throughout the body may give rise to side adverse effects such as damaging

**Fig. 1 Vaccine Using Partially Double-Stranded RNA**



An mRNA vaccine under development. The poly(A) strand is combined with the poly(U) strand, which is the complementary strand. This creates partially double-stranded RNA, which greatly increases the immunostimulatory effect compared to single-stranded mRNA. At the same time, it maintains the ability of single-stranded mRNA in protein expression. To protect the mRNA, which is unstable in vivo, from RNA-degrading enzymes and to enhance its retention in the muscle, it is delivered in nanomachines.

of various organs of the whole body. Our goal is to use nanomachines that stay and express proteins only in the muscle.” In other words, the use of nanomachines will increase safety. “The mRNA is degraded within a few days of administration, so the immunostimulatory effect will not last long. Therefore, we believe that side adverse effects are unlikely to occur,” explained Dr. UCHIDA.

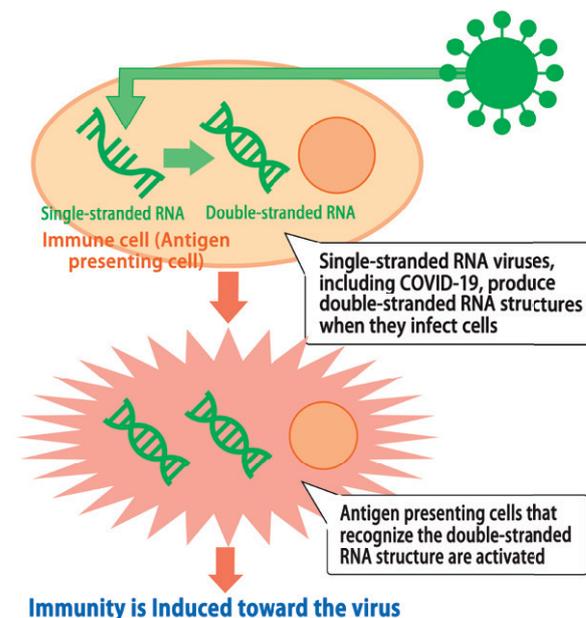
## Acceleration of Research Through iCONM’s Research Support System

Dr. UCHIDA started conducting research at iCONM in 2015, accelerating mRNA and vaccine research. Currently, he is acting as the supervisor for several scientists. “iCONM, the research center of the COINS project which I’m a member of, is well-equipped and has many experimental facilities, creating a research-friendly environment. Normally, a single block functions as a single laboratory, but at iCONM, researchers who share a common theme, such as nanomachines or mRNA, can talk with each other. They can even request someone good at a specific experiment to do it for them. I would often look around for people when I go to iCONM,” said Dr. UCHIDA.

He also said, “Scientists constantly think about publishing papers properly, but we don’t have any intellectual property strategy. It’s nice to have experts who even amateurs can consult with at COINS and iCONM,” indicating that he feels reassured by the fact that COINS and iCONM are strengthening their research support through methods such as intellectual property strategy and public relations. Patents related to partially double-stranded mRNA and polymeric micelles have been applied for, with some of them already granted.

He has benefited from public relations as well. “I don’t know anything about public relations any more than I know about patents. I’ve seen research making progress as a result of publicities, and I’m aware of its power. Being able to consult closely with public relations experts is helpful in terms of promoting not only the research results but also individual researchers,” said Dr. UCHIDA.

**Fig. 2 Double-Stranded RNAs have strong immunostimulatory effects.**



Single-stranded RNA viruses, including COVID-19, produce double-stranded RNA structures when they infect cells.

This April, iCONM partnered with the Tokyo Metropolitan Institute of Medical Science, which oversees the design of mRNA derived from COVID-19 and the experiments on viruses and genetically modified animals, while Dr. UCHIDA and his team focus on the design of polymeric micelles and administration methods. Dr. UCHIDA said, “Now, my job is to advance the research beyond the basic stages and into a more advanced stage for clinical development.”

Social implementation is an important mission of COINS. Dr. UCHIDA is aware of it, and he said, “Many companies that are now researching and developing vaccines have worked on vaccines for emerging infectious diseases such as Ebola virus and Zika virus. Therefore, they were able to act quickly against COVID-19. We also don’t plan on forgetting the threat once it is gone and would like to build a foundation that will allow us to act swiftly if something were to happen in the future.” The use of foreign vaccines also means that a lot of money will flow out of Japan. “Local vaccines are important not only from a business perspective but also because Japanese citizens will be the first to receive them,” stated Dr. UCHIDA. The COVID-19 pandemic has brought about an opportunity to develop vaccines. mRNA vaccines have never been approved before and their efficacy and safety are obscure, so the situation is tough. However, Dr. UCHIDA is going all out with a big team, including COINS and iCONM scientist, research support organizations, and pharmaceutical companies.

(Notes : Science Writer KOJIMA Ayumi )

### PROFILE UCHIDA Satoshi

He graduated from School of Medicine, University of Tokyo in 2007 (M.D.) and completed Internal Medicine, Graduate School of Medicine, The University of Tokyo in 2013 Ph.D. (Medicine). After working as a project assistant professor at the Graduate School of Medicine, The University of Tokyo, he joined Kawasaki Institute of Industrial Promotion Innovation center of NanoMedicine (iCONM) as a visiting scientist, and also became a project assistant professor of Graduate School of Engineering, The University of Tokyo. He has been in his current position since September 2020.

### Reference

\*1 S. Uchida et al., Designing immunostimulatory double stranded messenger RNA with maintained translational activity through hybridization with poly A sequences for effective vaccination. *Biomaterials* 150 162-170 (2018)

# Nano-DDS (Epirubicin-loaded nanomedicines) beat immune checkpoint blockade resistance in Malignant Brain tumors (Glioblastoma).

Chemo-immunotherapy using nano-DDS (Epirubicin-loaded nanomedicine) and immune checkpoint inhibitors (anti-PD1 antibody) deplete inoculated GL261 glioblastoma (GBM) and all mice with transplanted glioblastoma survived for more than four months. Particularly, the combination with nano-DDS even showed a remarkable anti-tumor effect against CT2A GBM (PTEN negative GBM), which is resistant to immune checkpoint inhibitors (ICI)<sup>1</sup> alone. The number of tumor-infiltrating lymphocytes (TILs)<sup>2</sup> has increased greatly and effectively attacked cancer cells, while myeloid-derived suppressor cells (MDSCs)<sup>3</sup>, which interfere with immune responses, have reduced significantly. Furthermore, mice were rejected after glioblastoma rechallenge (re-inoculation).



## KINOHI Hiroaki, Ph.D.

Principal Research Scientist/ Deputy Head  
Kawasaki Institute of Industrial Promotion  
Innovation Center of NanoMedicine

GBM is a brain tumor with an extremely fast progression and poor prognosis (5-year survival rate: 10.1%). Although the clinical development of several compounds as drug candidates is in progress, there is currently no drug therapy that can significantly improve survival. Namely, patients with abnormalities in the PTEN gene<sup>4</sup>, one of the cancer suppressor genes, are highly resistant to immune checkpoint inhibitor (ICI) therapy and have high medical needs.

PTEN gene is known to mutate in GBM as well as endometrial cancer and is believed to be present in nearly 40% of GBM patients. In our study, we also observed that 40% of GBM mouse models with normal PTEN genes survived for more than 70 days after ICI administration (all models in the control group died within one month), while those models with altered PTEN genes showed resistance to ICI therapy (all models administered with ICI also died within one month).

We know that at the cellular level, PTEN-deficient cells (CT2A-luc) expressed about five times more PD-L1 than that of normal cells (GL261-luc), which is thought to be responsible for the resistance to ICI therapy. It is known that anthracycline anticancer drugs suppress PD-L1 expression in breast cancer. We thought that if epirubicin, a common anthracycline anticancer drug, could be effectively delivered to the GBM lesion, the effects of ICI could be enhanced. Therefore, together with ICI, we conducted chemoimmunotherapy<sup>5</sup> using nanomicelles that contain epirubicin in polymeric micelles.

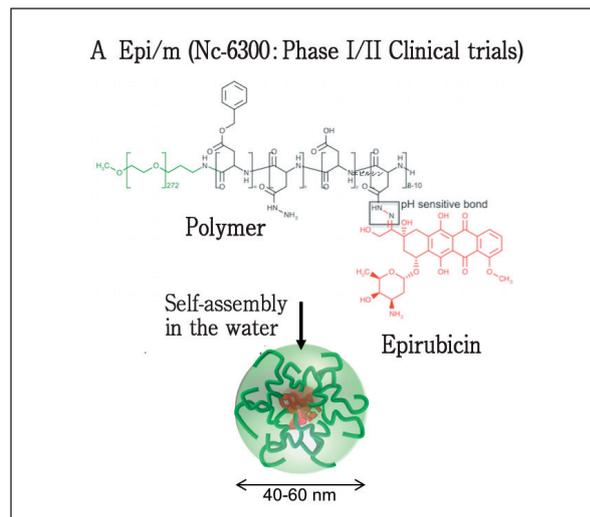
Epirubicin is an anticancer drug that inhibits cell division by directly binding to DNA. It has cytotoxic properties through the inhibition of topoisomerase II and has adverse effects on organs and hematopoietic organs throughout the body. However, when we performed intravenous administration of polymeric micelles containing epirubicin into mice transplanted with CT2A-luc in the brain, it resulted in a 160-fold

increase in the accumulation of epirubicin in tumor tissue as compared to administration of epirubicin alone. Additionally, when the AUC<sup>6</sup> of normal brain tissue and tumor tissue was compared, we found out it was 67 times higher in tumor tissue, indicating that the bioavailability of nanomicelles (Epi/m), in which epirubicin is encapsulated in polymeric micelles, is significantly higher in GBM tissue, and that side effects from epirubicin can be reduced.

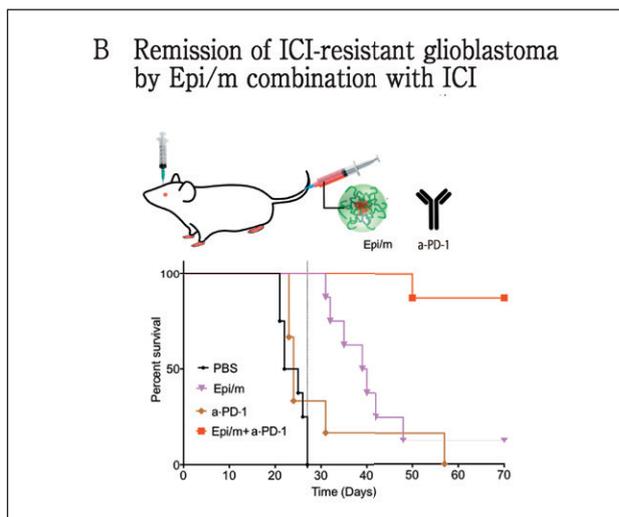
In models with GBM cells of normal PTEN gene (GL261-luc) transplanted, the administration of Epi/m 5mg/kg + anti-PD-1 antibody 5mg/kg resulted in the survival of all models for more than 70 days, showing a remarkable prolongation of survival. (In the control group, all models died within 30 days. The administration of anti-PD-1 5mg/kg alone resulted in 40% surviving for more than 70 days, and Epi/m 5mg/kg alone resulted in 80% surviving for more than 70 days.) In contrast, in models in which GBM cells with altered PTEN (CT2A-luc) were transplanted, only 30% survived for more than 70 days at the same dose, and no clear life-prolonging effect was observed. (In the control group, all models administered with anti-PD-1 antibody 5mg/kg died within 30 days, and 50% of the models administered with Epi/m 5mg/kg survived for more than 35 days.)

Next, we increased the dose to Epi/m 15mg/kg + anti-PD-1 antibody 5mg/kg, and when we assessed the survival rate, we found out that 90% of the models survived for more than 70 days, confirming a remarkable life-prolonging effect. (In the control group, all models died within 30 days, while 90% of those administered with antibody 5mg/kg died within 30 days, and 50% of those administered with Epi/m 15mg/kg survived for more than 40 days.) Moreover, we observed significant viable rejection of PTEN-deficient GBM cells when we re-transplanted them into the long-lived mice. (Reference 1)

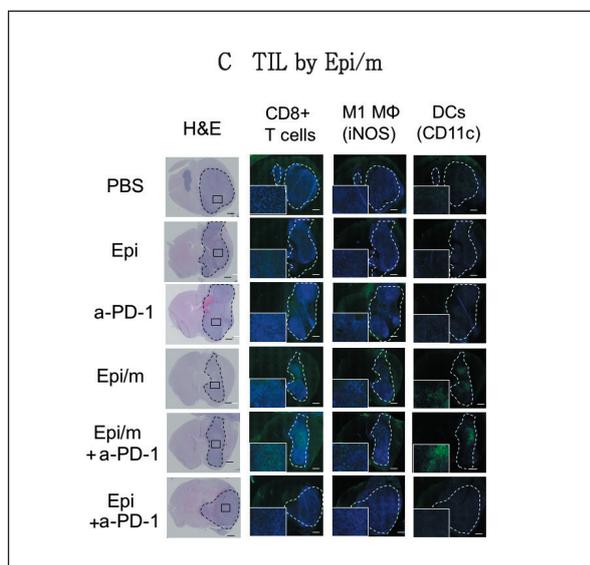
**Fig. ICD7 Polymeric Micelles Encapsulated with Induced Epirubicin Overcome Anti-PD-1 Antibody Resistance in PTEN-Negative Glioblastoma Respective Captions of ABCD**



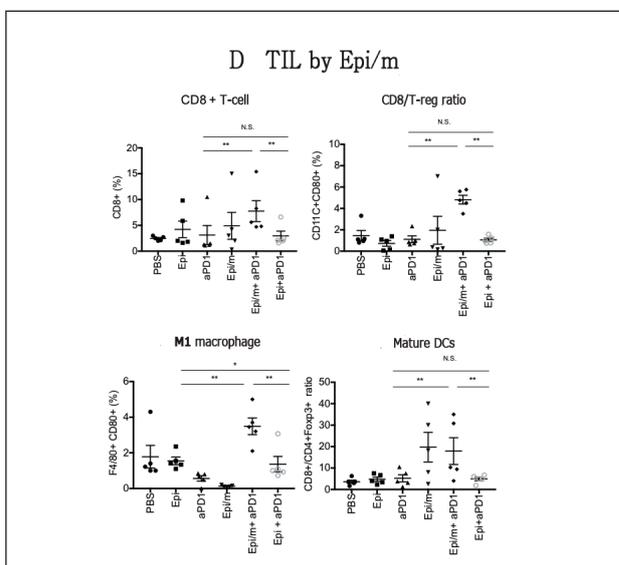
The scheme of polymeric micelles encapsulated with pH-sensitive (Epi/m). These micelles are in Phase I and II clinical trials.



The effects of Epi/m, anti-PD-1 antibody (a-PD-1), and antitumor activities of Epi/m and PD-1 against PTEN-negative orthotopic CT2A-luc tumors were presented in the form of the mice's survival. The combination of Epi/m and a-PD-1 eradicates the tumor and provides long-term immunological memory.



Immunofluorescence microscopy images of CD8+ T cells, M1-like macrophages, and dendritic cell infiltration in CT2A tumors after treatment with Epi/m, anti-PD-1 antibody (a-PD-1), and Epi/m and anti-PD-1 antibody (a-PD-1).



Evaluation by flow cytometry. CD8+ T cells, CD8+ T/Treg ratio, M1-like macrophages, and mature dendritic cells after treatment with Epi/m, anti-PD-1 antibody (a-PD-1), and Epi/m+a-PD-1. The combined administration of Epi/m and a-PD-1 increased the level of anti-tumor immune cells in the tumor.

## Glossary of Terms

### \*1 Immune checkpoint inhibitor (ICI)

When T cells infiltrating cancer tissues approach cancer cells, they express a ligand called PD-L1 on the surface of the cancer cells. It is known that when this PD-L1 binds to the PD-1 receptor on the surface of T cells, T cells lose their ability to attack cancer cells. Drugs that inhibit the binding of PD-L1 are called immune checkpoint inhibitors. In this study, we used the anti-PD-1 antibody in mice.

### \*2 Tumor-infiltrating lymphocytes (TILs)

For T cells, a type of lymphocyte, to be able to recognize and attack specific cancer cells, they must infiltrate cancer tissues and encounter the cancer cells. In refractory cancers, however, some mechanisms can prevent T cell infiltration.

For immune checkpoint inhibitors to work successfully, T cell activation and a sufficient number of TILs to induce it are essential.

### \*3 Myeloid-Derived Suppressor Cells (MDSCs)

Cancer cells secrete immunosuppressive substances and induce the production of immunosuppressive cells in the bone marrow. As a result, cells that attack cancer cells, such as T cells and dendritic cells, are inactivated, and cancer cells can avoid the immune system. For immune checkpoint inhibitors to be effective, T cell activation is essential. To this end, the number of MDSCs needs to be reduced.

## Reference

1. H. Kinoh, S. Quader, H. Shibasaki, X. Liu, A. Maity, T. Yamasoba, H. Cabral, K. Kataoka, Translational nanomedicine boosts anti-PD-1 therapy to eradicate orthotopic PTENnegative glioblastoma. *ACS Nano* 14 Issue 8 10127-10140 (2020)

### \*4 PTEN (Phosphatase and Tensin homologue deleted on chromosome 10)

A tumor suppressor gene that negatively regulates the PI3K/Akt signaling pathway, which promotes the proliferation of genes and cells. Abnormal expression of this gene, such as mutations, frequently promotes malignant transformation of cells and creates an environment where disease progression is likely to occur in cancer tissues.

### \*5 Chemoimmunotherapy (CIT)

A combination of chemotherapy and immunotherapy for cancer. It is a cancer treatment method that attacks cancer cells by improving the attacking power of T cells that attack cancer cells and weakening cancer's defense response to reduce its attacking power.

### \*6 AUC (area under the concentration-time curve)

It refers to the area bounded by the curve representing the change in drug concentration over time (drug concentration in blood-time curve) and the horizontal axis (time axis). Since we cannot directly measure the amount of drug that has entered the bloodstream, we use AUC.

### \*7 Immunogenic Cell Death (ICD)

Certain types of anticancer drugs and agents, such as epirubicin, kill cancer cells in a manner that has a higher chance of eliciting an immune response than normal necrosis or apoptosis. This cell death is known as immunogenic cell death. Several mechanisms have been reported, including the exposure of molecules on the cell membrane surface, which makes them the targets of the immune system.

# Heart to Heart Talk by iCONM Foreign Scientists



## The anxiety we had before coming to Japan disappeared because of the people around us

**Theo :** At the beginning, I struggled with the language. There are formal and informal forms in Japanese language. Trying to learn these two forms simultaneously and choosing when and to who to use them with had been particularly hard for me.

**Saed :** The problem I had was the cultural barrier in communication. I first came to Japan as a student. It was not that easy to communicate well with people around me at the beginning.

**Sabina :** I was very lucky to have beautiful people around me. My daughter's friend's mum translated school-related communications in English and every week she gave it to me. Everyone was so helpful and did it selflessly. That is the reason may be why I have been living here for so long.

**Theo :** That's wonderful. In my case, I continue to study the language and keep the motivation alive by reading books. Japanese is one of the most difficult languages in the world, but I figure that it really helps living here and immersed with the culture. It's not easy, but it may be a fruitful endeavor.

## There is a full support system for both research and life aspect

**Saed :** When I first arrived in Japan in 2013, Japanese universities were not yet ready to accept international students, but my experience was completely different when I came to iCONM in 2018. I was amazed because there was a strong facilitation and support system for foreign researchers.

**Sabina :** Yes, that's right. I came to iCONM first at the time of establishment. There were many foreign scientists in the laboratory, and I could always speak English about my research, so I

had no communication problems but on the administrative side, the staff in the iCONM management office were not very accustomed to foreigners at first, but now they are able to talk little by little and they are fully supportive of us. They will help us with all sort of things such as housing, family, and visa application, etc. The administration office also helped me apply for "Kakenhi" (Grants in Aid for Scientific research).

**Saed :** Kawasaki City, where King SkyFront and iCONM are located, has one of the fastest population growth rate among other Japanese cities. Also, there are progressive aspects such as the early enforcement of hate crime laws.

## iCONM is a melting pot of diversity that is inspiring

**Saed :** All three of us are the same in that we

The world's best R & D hub "Innovation Center of NanoMedicine (iCONM)" in life science field. As COINS members, young scientists from all over the world genuinely talked about their research and prospects.



joined iCONM to do research with Professor Kazunori Kataoka. The great thing about working here is the diversity of people and the fact that all the instrumentation I need for my research is in this building. For us as scientists, having state-of-the-art equipment and facilities is very attractive.

**Sabina :** Yes, I agree. The King SkyFront has many unique research institutions and facilities and is very inspiring. The iCONM is a paradise for scientists in the nanomedical science field.

**Theo :** iCONM is undoubtedly diverse. We have scientist from India, Belgium, Mexico, China, Jordan, Bangladesh, and Indonesia to name a few. It's also great to have a summer internship student program. Personally, it is a very good learning experience. You can also get powerful research support here. At the press conference, I had a great support from the staff of the COINS Research Promotion Support office in making slides for my presentation, seeing me struggling with the various technical Japanese terminologies



**Theo**

**Tockary, Theofilus A., Ph.D.**

Born in Indonesia. He came to Japan in 2008. Received a PhD from the University of Tokyo in 2013. After participating in Kataoka Lab, he came to iCONM. Previously working on DNA nanostructures, he now focuses on mRNA vaccine for cancer and infectious diseases.



**Sabina**

**Quader, Sabina, Ph.D.**

Born in Bangladesh. She came to Japan in 2010. Received a PhD from Griffith University, Australia in 2007. After working in Kataoka Lab, at the University of Tokyo, she moved to iCONM. Currently developing nanomedicine based drug for malignant glioblastoma and pediatric brain tumors.



**Saed**

**Abbasi, Saed, Ph.D.**

Born in Jordan. He came to Japan in 2013. After obtaining a PhD from Hokkaido University in 2018, he joined iCONM. Researching one-shot and permeant treatments based on genome editing. He is also developing a vaccine for COVID-19.

to use. Thanks to that, I was able to make a very successful presentation.

**Saed :** I had experience in applying for patent here and process was very fast and very smooth. We have a specialized team here at iCONM to bridge between the patent application authority and the researchers.

**Theo :** Unlike other research institutions, iCONM has facilities related to organic synthesis, cell culture, pharmacological experiments, etc. all these under one roof, so we can learn about fields other than our own. We also have medical doctors who may share with us on what's really expected of our research from patients. This is important for advancing research.

**Saed :** It is very multidisciplinary research team of pharmacists, chemists, engineers, and medical doctors. It is like a melting pot of different expertise, all working to develop the same goal.

**Theo :** It is very diverse not only terms of nationality but also in terms of the research background, skills.

### **iCONM makes a push to scientists' dreams and passions**

**Saed :** iCONM is going to set a new strategy for attracting incubation and start-ups. It is wonderful that the results of the basic research we are currently conducting will lead to startups here. The facility itself was built based on this idea, half of the building is for academic research and the other half is for social implementation.

**Sabina :** So in this case, we can expect that our innovation, also has a chance to make a start-up, isn't it? It is wonderful that the results of the basic research we are currently conducting will lead to start-ups here. The facility itself was built based on this idea, half of the building is for academic research and the other half is for social implementation. Bangladesh is a relatively young country, only 40 years old. We have very little basic innovation, so what we are doing now is may be taking the technology from

developed countries. We do not have established nanomedicine research in Bangladesh, drug delivery field is quite new.

Recently, I made a proposal with a Bangladesh professor who actually wants to visit iCONM for research. If everything goes well, my expertise could be used for both countries.

**Saed :** iCONM provides us with funds and good opportunities to collaborate or to expand our network and one example is the COINS Seminar. It is a good opportunity to expand our networks with well-known researchers from all over the world.

**Theo :** I have so much expectation for the business incubation in iCONM. Such activity requires support on patent issues. iCONM's patent support team will provide this support for patent applications not only in Japan, but also Europe and the United States. In the future, I foresee that this patent support can be easily extended to countries where growth is expected, such as Asia and ASEAN countries.

**Sabina :** We innovate something here and at the same place, we have an opportunity to make it reality. I think this is maybe the dreams of the people who are in this field.





TSUCHIYA Chieko

Head of CEO's Office  
NanoCarrier Co., Ltd.

I transmit the appeal of DDS drugs to investors, a new concept that combines engineering and medical science invented by Dr. KATAOKA Kazunori, Director General of iCONM, and create the value of bio-ventures.

## Create corporate value by transmitting new technologies created by iCONM to investors

I joined NanoCarrier in 2000 and was involved in the early stages of research, including studying the manufacturing methods of micelle formulations. At NanoCarrier, we never lack people who are passionate about creating and delivering innovative drugs. Since micelle formulation is a new concept, we encounter many issues during its development. Nonetheless, we have made steady progress by integrating the knowledge of members with rich experience in pharmaceutical companies, and now, several late phase clinical trials are being conducted.

I also feel a high level of expectation as we have been contacted by patients who want to take part in clinical trials. Furthermore, we have integrated with AccuRna, which aims to complete the nucleic

acid medicine created by iCONM, and have absorbed new values. Through drugs that efficiently transport mRNA—which is also getting a lot of attention as a vaccine—and other nucleic acids that are expected to lead the future of medicine into cells, we promote the development of innovative therapeutic drugs for targets that could not be targeted before. Although the members of the clinical development team feel a sense of mission to put the drugs to practical use as soon as possible using the experience gained in the development of micelle formulations, they also feel excited about this challenge.

I believe the products I have researched will reach patients and contribute to their health and well-being.

Currently, I'm in charge of IR, which is expected to create corporate values through the transmission of the appeals of a company to investors. Support from investors is essential for drug development ventures to be proactive. I will continue to take in new values created at iCONM and promote activities that communicate the appeal of innovative technologies to not only scientist but also investors.



When I was studying the manufacturing method and evaluation method of NC-6004

DIRISALA Anjaneyulu, Ph.D. iCONM Research Scientist

## Think Big to Engineer Nano

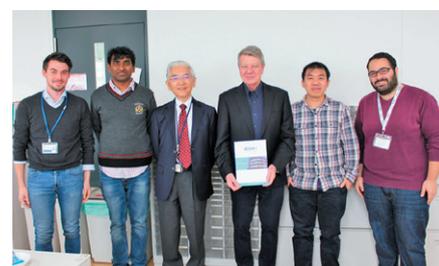
The legendary Einstein once said: "imagination is the highest form of research". One recent example of scientific imagination is the visionary concept of Prof. KATAOKA's "In-Body Hospitals", which constantly ignites my inspiration to think big to engineer nanomachines that aid the realization of the "In-Body Hospitals". I was born and raised in India and received double Master's degree in Biochemistry and Medical Biotechnology. Next, I went onto obtain Ph.D. in Bioengineering from the University of Tokyo. Later, I had an opportunity to continue my research on engineering nanomachines. After spending 5 years at the iCONM, I can unequivocally say that iCONM is a unique research institute wherein researchers can experience a) the multidisciplinary science with the multicultural background; b) not only a

scientific thrust but also leadership qualities; c) revolutionary solutions to health problems such as predictive, preventive, and personalized medicine which aid the realization of a disease-free society; d) cutting-edge research with world-class state-of-the-art instrumentation. India has emerged as the world's fifth-largest economy and is projected to become the second-largest economy by 2050, with a majority of the population under the age of 25. This encourages us to invite Indian students via youth exchange programs. I had an opportunity to streamline the partnership between iCONM and the Department of Science and Technology, Government of India, via S&T partnership initiatives organized by the Embassy of India, Tokyo. Followed by this partnership, the Minister of Economy and Commerce participated in roundtable networking of the 6th COINS

Based on the concept of "In-Body Hospitals", we are conducting research on incorporating specific genes using smart supramolecular nanomachines designed according to the purpose.



symposium. Later, Prof. Kataoka was invited to deliver keynote lecture on "Engineering In-Body Hospitals" in the India-Japan S&T webinar series. Also, I delivered a presentation on core research themes of iCONM to Indian university students. I am thankful for the opportunity to meet many world-renowned experts and listen to their success stories through the COINS seminar series.



With Prof. MATYJASZEWSKI, Prof. KATAOKA, and colleagues after the COINS seminar

## OHTAKE Tomoyuki

Research & Technology Development Group Leader  
Corporate R&D Division, I&S Department  
NOF CORPORATION



We are developing new polymers for DDS, regenerative medicine and tissue engineering. I hope the high-purity materials will contribute to the progression of advanced medicine

## Supporting Advanced Research and Development Through High-Purity Polymers and Collaborative Creations

**N**OF Corporation pursues business development in the pharmaceutical and medical industry by providing high-quality polyethylene glycol (PEG) derivatives and lipid derivatives for DDS and methacryloyloxyethyl phosphorylcholine (MPC) polymer derivatives for diagnostic reagents and medical devices. Until now, the DDS Laboratory has participated in COINS on developing and supplying block polymers for various polymer micelles, and starting from this year, as our new department for the new business development, of which I'm a member, we have also set up a laboratory in iCONM and joined COINS. The new department is an organization that aims

to create and nurture new businesses without being bound by existing our businesses. Its first target is on the advanced pharmaceutical and medical industry fields. Located in the King SkyFront area, where many life sciences companies have gathered, and with leading researchers of this industry, iCONM is truly at the forefront of development. As a chemical manufacturer, we would like to support all forms of development by making polymers purer, improving them, and providing samples. We are afraid that we have not been able to introduce ourselves due to COVID-19, but please feel free to contact us if you have any problems related to polymers.

We would like to contribute to the progress of the advanced medical and pharmaceutical industry through collaborative creations with everyone on providing new polymers as well, on top of PEG and MPC derivatives.



With members of the New Business Development Office, NOF Corporation at iCONM Room



I support research activities at iCONM through the management of common laboratories, common equipment, and laboratory animals of iCONM.

## KARIYA Yuko

Innovation Center of NanoMedicine (iCONM)  
Management Department, Innovation Support Group  
Laboratory Management Team

## Support research with accumulated know-how

**I**t has been already more than 10 years since I got involved in the establishment of an animal facility for the first time in the project of Dr. KATAOKA Kazunori, Director General of iCONM.

In the beginning, I was only engaged in looking after animals as a veterinarian, but after the establishment of iCONM, I became in charge of managing experimental equipment, and here I got still managed to be here with the help of our scientist though struggling to handle unfamiliar analysis equipment.

At iCONM, where various companies, universities, and research institutes conduct research under the one roof, all kinds of effort are input to obtain the maximum outcome for everyone to use laboratories and equipment

smoothly and safely. In addition to receiving legal training on safety and health, animal experiment ethics, and biosafety, the newly appointed scientists also attend workshop on how to use the laboratory. Compliance is guaranteed by conducting research activities in accordance with these contents.

When using the equipment, it is possible to use it smoothly and systematically by using the online reservation system and borrowing the key of the equipment with an ID card.

Furthermore, since who, when, and which equipment was used is accumulated as data, it can easily grasp the situation if a trouble occurs and charge the usage fee. At the animal facility, staff with specialized skills in care of laboratory animals, and in order to notify scientists immediately when there is an

abnormality in an animal, appropriate animal experiments can be done from the viewpoint of animal welfare.

I will continue to support the scientist with my utmost for their greater results.



I check condition of every single animal every day.

- 6.14.2019 [Activity] 12th General Meeting was held.
- 6.24.2019 [Press release] "J-Startup" by public and private! The Ministry of Economy, Trade and Industry has newly identified 49 companies as startup support companies and announced their press. COINS's venture company Braizon Therapeutics is among the 49 companies.
- 6.25.2019 [Activity] COINS Seminar #45 was held at iCONM.  
Speaker: Dr. MIYAGISHI Makoto, Group Leader, Molecular Composite Medicine Research Group, Biomedical Research Institute, Advanced Industrial Science and Technology (AIST)  
Title: "Development of screening method of nucleic acid aptamer, and its application to finding of DNA/RNA catalyst"
- 6.28.2019 [Information] "Nanomachines that carry nucleic acid medicine for fundamental treatment of hereditary intractable disease. Launched crowdfunding for R&D and disease enlightenment."
- 7.1.2019 [Activity] Deputy Director-General Mr. YAMAWAKI of the MEXT and participants of the Japan-China OTC exchange meeting visited COINS, iCONM.
- 7.4.2019 [Press release] Tokyo Medical and Dental University has made a press release that a manuscript "Enhancement of Motor Function Recovery After Spinal Cord Injury in Mice by Delivery of Brain Derived Neurotrophic Factor mRNA" by Dr. ITAKA Keiji, COINS Theme 3 leader, Professor, Tokyo Medical and Dental University, et al. has been published online in "Molecular Therapy-Nucleic Acids" on June 28, 2019.
- 7.8.2019 [Coverage] The article about the research team of Dr. ITAKA Keiji (Professor, Tokyo Medical and Dental University), was appeared in Qlife Pro.
- 7.15.2019 [Coverage] The article about the research team of Dr. ITAKA Keiji, was appeared in Nikkei Shimbun Electronic version and Nihon Keizai Shimbun.  
The research theme was "Recovery by spinal cord injury mouse RNA administration".
- 7.15.2019 [Coverage] An interview article "From DDS to 'In-Body Hospitals' practitioner of medical-industrial collaboration" of Dr. KATAOKA Kazunori, Director General of iCONM has been published in the magazine Pharmaceutical Economics.
- 7.15-17.2019 [Activity] Dr. KATAOKA Kazunori, Director General of iCONM gave a keynote speech at "Symposium on Innovative Polymers for the Nanomedicine of the 21st Century" held at Jena in Germany.
- 7.17-19 [Activity] Mr. IWASAKI, Vice-Director gave a lecture at "International Modern Hospital Show 2019".
- 7.26 – 27.2019 [Coverage] An article about Dr. MATSUMURA Yasuhiro (Chief, Division of Developmental Therapeutics, EPOC, National Cancer Research Center), member of our center's COINS project, was published in the evening paper Fuiji.  
28th: A new treatment "DDS" that strikes cancer cells and breaks through barriers  
27th: Interstitial Targeting Therapy to Challenge High-grade Cancer
- 7.31.2019 [Activity] The COINS Seminar #46 was held.  
Speaker: Dr. Nuno M. NEVES, Associate Professor, University of Minho / Vice Director of 3B's.  
Title: Nanoparticles and Nanofibrous Scaffolds Combined with Stem Cells for Advanced Therapies
- 7.31.2019 [Coverage] An interview articles about Dr. OCHIYA Takahiro (Professor, Tokyo Medical University, Visiting Researcher, National Cancer Center Research Institute) who is a member of COINS was published in Nihon Keizai Shimbun Electronic Edition and Nihon Keizai Shimbun (date of July 31, 2019). The interview title was "Early cancer test in blood, 'garbage' breaks through (report), can cancer be overcome (3)".
- 7.31.2019 [Activity] Participants in industrial location practical workshops, President of the Darma Persada University, Indonesia, and second-year students of science department, Kawasaki city Hight School for Science and Technology visited iCONM.
- 8.1.2019 [Activity] "King SkyFront Summer Science Event 2019," organized by Kawasaki City, was held
- 8.5.2019 [Coverage] An article "Aiming for cells and tissues that interfere with the efficacy of "Cancer allies" commented by Dr. MATSUMURA Yasuhiro (Chief, Division of Developmental Therapeutics, EPOC, National Cancer Research Center) who is a member of COINS was published in Nihon Keizai Shimbun Electronic Edition and Nihon Keizai Shimbun.
- 8.5.2019 [Coverage] An article about Dr. ITAKA Keiji (Professor, Tokyo Medical and Dental University), was appeared in Daily pharmaceutical industry. A title of the article was "mRNA medicine" breaks or attention strain following nucleic acid medicine".
- 8.6.2019 [Coverage] An article "Discovering the phenomenon of drugs gathering in cancer, maintaining the effectiveness of anticancer drugs (trajectory of innovation)" commented by Dr. MATSUMURA Yasuhiro (Chief, Division of Developmental Therapeutics, EPOC, National Cancer Research Center) who is a member of COINS was published in Nikkei Business Daily Electronic Edition and Nikkei Business Daily.
- 8.8.2019 [Coverage] An Interview article with Dr. TOSU Mariko, President of COINS venture companies Blazon Therapeutics, Inc. was published in Nikkei Beyond Health.
- 8.8.2019 [Information] COINS' venture company Braizon Therapeutics, Inc. was selected as one of the ten startups as the recipients of support measures under the first round of a call for applicants for the FY2019 IP. They will be able to receive support of an "IP Mentoring Team" consisting of selected experts in the fields of business and IP for help to develop IP strategies for accelerating their businesses.
- 8.15.2019 [Coverage] An article about Dr. SOGA Kouhei (Professor, Tokyo University of Science) who is a member of s COINS published in the magazine Pharmaceutical Economics. A title of the article was "In-vivo imaging with near-infrared. Practitioner of medical-industrial collaboration".
- 8.19-22.2019 [Award] Dr. Junjie Li, a JSPS Postdoctoral Fellow for Research in Japan received CASNN Best Poster Award at Chinese-American Society of Nanomedicine and Nanobiotechnology 2019 Annual Conference held on August 19 – 22 in Hangzhou, China.
- 8.20.2019 [Information] AccuRna Inc. announced that the company enters into a Feasibility Study Agreement with Astellas Innovation Management LLC subsidiary of Astellas Pharma Inc for the use of delivery system of polymer micelle1 loaded with messenger RNA (mRNA) under pre-clinical development by AccuRna.
- 8.21.2019 [Activity] Mr. HIRAI Takuya (Minister in charge of Information Technology Policy, "Cool Japan" Strategy, the Intellectual Property Strategy, Science and Technology Policy, Space Policy) visited King SkyFront.
- 8.28.2019 [Activity] COINS Seminar #47 was held.  
Part1: Speaker Dr. IWATA Hiroo, Eng. / Manager, Strategy Research Support Section of Center of Innovation Program, Kyoto U. Title: "Cell Lego"  
Part2: Speaker: Dr. Peilin CHEN, Professor / Research Fellow, Research Center for Applied Sciences, Academia Sinica, Taiwan. Title: "Isolation of Rare Cells: Toward Noninvasive Diagnostic"
- 8.31.2019 [Activity] The members of Kawasaki City Elementary School Japan Social Study Research Association, Foundation for Biomedical Research and Innovation at Kobe, Ministry of Finance, Japan Budget Bureau and the students of Seiritsu Gakuen High School visited iCONM.
- 9.5.2019 [Activity] COINS Seminar #48 was held at iCONM.  
Speaker: Dr. TANIGUCHI Hiroaki, Project Associate Professor, Keio Cancer Center & Clinical and Translational Research Center, Keio University School of Medicine.  
Title: "PRDM14 silencing by siRNA combined with an innovative nanoparticle reduced tumor formation and metastasis"
- 9.11.2019 [Award] Dr. MATSUMOTO Akira, (Associate Professor, Tokyo Medical and Dental University), received 68th SPSJ Annual Meeting of the Publicity Award.  
Title: Microneedle type "just stick" artificial pancreas: dramatically improved invasiveness, stability, economy and aesthetics
- 9.13.2019 [Coverage] An interview with Dr. AKINAGA Shiro, President of AccuRna, Inc. the main project COINS, was published in the Nikkei Business Daily. A title of the article was "Dr. AKINAGA Shiro, President of AccuRna, Inc. "NuclAeic acid medicine in clinical settings".
- 9.15.2019 [Coverage] An articles about Dr. Masamune Ken (Professor, Tokyo Women's Medical University) published in the magazine Pharmaceutical Economics. A title of the article was "Integrate information to predict postoperative. Practitioner of medical-industrial collaboration".
- 9.26.2019 [Activity] iCONM decided October 2019 to be "Compliance Awareness Month" and conduct activities to promote compliance with research ethics and use of public research expenses.
- 9.28.2019 [Coverage] The TV program "Seimeiji no Kaname Exosome" which Dr. OCHIYA Takahiro (Professor, Tokyo Medical University, Visiting Researcher, National Cancer Center Research Institute), Tokyo Medical University appeared was released on NHK E-TV "Science ZERO".
- 9.30.2019 [Activity] The members of Kawasaki Saginuma Rotary Club visited iCONM.
- 10.9-11.2019 [Activity] iCONM had an exhibition booth at "BioJapan 2019".
- 10.10.2019 [Coverage] An article about Dr. ANRAKU Yasutaka (Project Professor, The University of Tokyo), was appeared in JSTnews. A title of the article was "Pioneer scientist —Opens up his own way keeping his teacher's words as spiritual nourishment."
- 10.16.2019 [Coverage] An interview with Deputy Director, Mr. IWASAKI was broadcasted on BS TV Tokyo "Nikkei Plus 10".
- 10.16.2019 [Coverage] An article of the COINS' venture companies Braizon Therapeutics, Inc. was published in Chemical Daily. The title was "Braizon develops childhood brain tumor drugs in-house, applying DDS to known anticancer drugs".
- 10.18-19.2019 [Activity] COINS Retreat Camp 2019 "Looking ahead to globalization and the arrival of the AI era" was held at the Shonan Village Center.
- 10.21.2019 [Coverage] An interview article "Research goal is In-Body Hospital" with Dr. KIMURA Hiromichi (Project Leader of COINS) was published in The Chemical Daily.
- 10.24.2019 [Activity] COINS seminar #49 was held. Lecturer: Dr. Rainer HAAG (Chair, Professor of Organic and Micromolecular Chemistry, Department of Chemistry and Biochemistry, Freie Universität Berlin, Germany) Title: Multivalent Nanosystems and Supramolecular Dendritic Architectures.
- 10.25.2019 [Press release] A press conference was held by Dr. KATAOKA Kazunori, Director General of iCONM, Dr. OSADA Kensuke (Senior Scientist of QST) and Dr. TOCKARY Theofilus A. (Research Scientist of iCONM). A novel technology has been developed to convert the double helix structure of DNA into a single strand of DNA (ssDNA), roll it into a compact form, and encapsulate it inside a smart nanomachine. This research result was published in "ACS Nano". This article was introduced in the Chemical Daily, Nikkei Biotech ONLINE and Nikkei Beyond Health, etc.
- 10.28.2019 [Coverage] An interview article "Brain tumor treatment with nanomachine" of Dr. QUADER Sabina, Senior Research Scientist of iCONM, was published in The Chemical Daily.
- 10.31.2019 [Activity] CEA France, Hong Kong Trade Development Council, participants of National Association of science and mathematics research meeting and high school students from Philippines visited iCONM.
- 11.2.2019 [Activity] A public talk session was held at Miraikan.
- 11.8.2019 [Coverage] An article about "Analysis of exosomes one by one" Dr. ICHIKI Takanori, Professor, The University of Tokyo, a leader of COINS Theme 4, was appeared in The Nikkei Business Daily.
- 11.11.2019 [Coverage] An article about "Nanomachine is the growth engine" of Dr. KATAOKA Kazunori, Director General of iCONM, was published in The Chemical Daily.
- 11.15.2019 [Coverage] An interview article of Dr. KATAOKA Kazunori, Director General and Mr. IWASAKI Hirokazu, Deputy Director was published in the magazine "Pharmaceutical Economy". A title was "Don't let technology dying in large companies medical-engineering practitioners®".
- 11.21.2019 [Information] Dr. KATAOKA Kazunori, Director General of iCONM, has been selected to 2019 Highly Cited Researcher in Clarivate Analytics (Web of Science).
- 11.21.2019 [Coverage] Yomiuri Shimbun covered the matters that we presented at the press conference held on October 25. The article entitled as "A New Carrier for Gene Therapy – Development of An Artificial Vector Capable of Also Encapsulating Larger-Sized Genes"
- 11.22.2019 [Coverage] An article of interview with Mr. TAKAHASHI Tomohiro, Director of Kawasaki City Waterfront International Strategy Department, about the past, present and future of King SkyFront where iCONM is located was published in Nikkei Beyond Health.
- 11.25.2019 [Activity] iCONM and Braizon Therapeutics, Inc. held a luncheon seminar at the 41st Annual Meeting of The Japanese Society for Biomaterials.
- 11.25.2019 [Award] Ms. NAKAMURA Noriko (2nd year doctoral course, Graduate School of Engineering, The University of Tokyo) received the Outstanding Poster Award 2019 at the 41st Annual Meeting of The Japanese Society for Biomaterials (11 / 24-26 @ Tsukuba).  
Title: Interaction analysis between target membrane proteins and ligand molecules attached to the polymeric micelle with different molecular weight of hydrophilic shell
- 11.30.2019 [Activity] A Principals Association of Kanagawa Prefectural Senior High School and participants of Ministry of Foreign Affairs Japan-German Young Professional Exchange Program visited King SkyFront.
- 12.1-6.2019 [Information] The iCONM introduction video was broadcasted by digital signage at MRS Autumn meeting in Boston.
- 12.6.2019 [Activity] COINS Seminar #50 was held at iCONM.  
Speaker: Dr. Kris MATYJASZEWSKI / J.C. Warner University Professor of Natural Sciences, Carnegie Mellon University Title: "Bio-related ATRP".
- 12.9.2019 [Coverage] An interview article "People and topics' Have a transparent relationship with the institution that further expand" of Mr. MIURA Atsushi, Director of the Kawasaki Institute of Industrial Promotion was published in the Chemical Daily.
- 12.13.2019 [Activity] The 6th COINS Symposium was held. Theme: King SkyFront Bridges the World.

# Activity Report

- 12.17.2019 [Activity] COINS Seminar #51 was held.
  - ◆Part 1: Speaker: Dr. Michael BAUER/Director, Jena University Hospital, Dep. Anesthesiology & Intensive Care Medicine Title: Nano on ICU: Overcoming limitations for the treatment of organ failure
  - ◆Part 2: Speaker: Dr. Adrian T. PRESS/Group leader, Jena University Hospital, Nanophysiology Group Title: Raman spectroscopic imaging reveals changes in the micellar conformation dictating pharmacokinetic properties
- 12.17.2019 [Coverage] An article of President & CEO of LabCentral Dr. Fruehauf, who gave a talk at the 6th COINS Symposium, was published in the Chemical Daily.
- 12.28.2019 [Coverage] An interview for TV TOKYO "Admatic". The program will be on air on Saturday, January 4, 2020.
- 1.1.2020 [Coverage] TV Kanagawa "Love Kawasaki" broadcasted the scene that Mr. IWASAKI Hirokazu, Vice-Director of iCONM and Dr. Saed Abbasi, Research Scientist from iCONM introducing iCONM to Mr. Fukuda, the Mayor of Kawasaki.
- 1.10.2020 [Coverage] Content of the 6th COINS Symposium was covered by Nikkei Beyond Health focusing on mRNA medicine. Title: Focus on the potential of mRNA medicine.
- 1.21.2020 [Coverage] Lectures by Dr. NISHIYAMA, Professor, Tokyo Institute of Technology and Dr. Muragaki, Professor, Tokyo Women's Medical University at the 6th COINS Symposium were covered by Nikkei Beyond Health focusing on "medicine X device".
- 1.23.2020 [Coverage] Dr. NOMOTO Takahiro, Assistance Professor and Dr. NISHIYAMA Nobuhiro, Professor, Tokyo Institute of Technology (iCONM Principal Research Scientist) and their research group succeeded in nearly eliminating mouse tumors by adding poly(vinyl alcohol), the main component of liquid glue, to a p-boronophenylalanine (BPA) and using it for Boron neutron capture therapy (BNCT) in collaborative research with iCONM, Kyoto University and STELLA PHARMA. The results were published in the US science journal "Science Advances" Many articles on this subject were published in the media such as Asahi Shimbun Digital, Nihon Keizai Shimbun, Nikkei Beyond Health and Jiji Press.
- 1.28.2020 [Activity] 13th COINS General meeting was held.
- 2.3.2020 [Coverage] An article of Dr. KIMURA Hiromichi, Project Leader of COINS, "King SkyFront providing networking opportunities to create a new industry" was covered by Yakuji Nippo.
- 2.5.2020 [Coverage] Contents of the presentations of Dr. KATAOKA Kazunori and Dr. MIYATA Kanji at the 3rd Link-J/UCSD Life Science Symposium "Engineered Nanomedicine: Drug Delivery Systems and Platforms" were covered by Answers News.
- 2.19.2020 [Coverage] An interview article of Dr. ATSUMI Hiroshi, Head of business development and the social implementation of research at iCONM was covered by Yahoo Japan's special issue.
- 3.1.2020 [Coverage] Dr. NISHIYAMA Nobuhiro, Senior Researcher, Prof. Institute of Innovative Research, Tokyo Institute of Technology has been introduced in a medical industry magazine "Iyaku-Keizai".
- 3.4.2020 [Coverage] NOF Corporation which announced that its open innovation base for the life science business will be open in iCONM this spring, was introduced in The Chemical Daily as "NOF Corporation to iCONM: Open innovation base focusing on advanced and regenerative medicine will be open in Kawasaki".
- 3.23.2020 [Coverage] Dr. MURAYAMA Atsushi, Professor, Tokyo Institute of Technology, Life Science and Engineering was featured in "Nikkei Business" magazine.
- 3.26.2020 [Activity] Mr. KOMINE, Executive Director of Yokohama Bank and the course students of Leading Graduate School, Chiba University visited iCONM in February.
- 3.26.2020 [Coverage] Research for overcoming intractable cancer using nanomachines in combination with ultrasound for intractable cancer, effective in experiments was featured in Nikkei Sangyo Shimbun.
- 4.1.2020 [Press conference] Kawasaki City and the Kawasaki Institute of Industrial Promotion launched a press release regarding the start of cluster operation of Tomomachi King SkyFront.
- 4.1.2020 [Coverage] The research of Dr. TOCKARY Theofilus A., iCONM research scientist was introduced in RikeLab. The research title was "The world's first established technology to convert double-helical DNA into a single strand, compactly round it, and encapsulate in a smart nanomachine".
- 4.2.2020 [Coverage] Dr. Kazuko TOH (Research scientist)'s collaborative research group of iCONM including Dr. UEKI Ryosuke, Assistant Professor, Dr. UCHIDA Satoshi, Project Associate Professor, Dr. CABRAL Horacio, Associate Professor, Dr. SANDO Shinsuke, Professor, the Graduate School of Engineering, The University of Tokyo have developed a cell growth factor replacement compound that shows high biological activity in living organisms. The results were published in the US science journal "Science Advances".
- 4.8.2020 [Coverage] An interview article of Dr. ITAKA Keiji, Professor, Tokyo Medical and Dental University was published. The title of the article was "mRNA drug: Promising for novel corona virus / Ask Dr. ITAKA Keiji, The Chemical Daily".
- 4.22.2020 [Activity] An inner-communication event was held using a web conference system.
- 4.28.2020 [Coverage] An article about smart Nanomachines and "In-Body Hospitals was introduced in Deutsche Well, a state news agency in Germany. A title of the article was "COVID-19: Nanomachines to be deployed to fight next viral pandemic".
- 5.1.2020 [Award] Dr. TAKEMOTO Hiroyasu, Assistant Professor, Tokyo Institute of Technology, a visiting scientist, COINS Theme 5, received the 2019 Award for Encouragement of Research in Polymer Science, the Society of Polymer Science, Japan.
- 5.7.2020 [Coverage] A comment by Dr. MORIMOTO Takuya, iCONM Theme Leader, Kao Institute of technology was posted in Asahi Shimbun. A title was "Discover new type coronavirus antibody Expected to apply to diagnostic agents and test agents".
- 5.12.2020 [Award] Dr. KATAOKA Kazunori, Director General, iCONM including Dr. MIYAZAKI Takuya from Kanagawa Institute of Industrial Science and Technology (KISTEC), Dr. CABRAL Horacio Associate Professor, Dr. NAGAMATSU Takeshi, Associate Professor, Dr. SUUKI Kensuke from The University of Tokyo, have developed nanomedicine for chemotherapy during pregnancy. With this nanomedicine, we can treat intractable diseases like preeclampsia and preterm birth without drug distribution in fetus. This press release received the Publicity Award from the Public Relations Committee of the Polymer Society of Japan.
- 5.20.2020 [Press conference] Dr. KATAOKA Kazunori, Director General, iCONM, Dr. TSUMOTO Kouhei, Professor, University of Tokyo, Dr. ANRAKU Yasutaka, Visiting Scientist, iCONM / Project Associate Professor, The University of Tokyo, Dr. YOKOTA Takanori, Professor, Tokyo Medical and Dental University and their research group designed and synthesized smart nanomachine that efficiently deliver antibody drugs into the brain and succeeded in demonstrating the suppression of amyloid  $\beta$  aggregation in brain parenchyma at low doses in Alzheimer-type dementia model mice, and a joint press conference was held. This research result was published in "ACS Nano" Paper title: Dual-Sensitive Nanomicelles Enhancing Systemic Delivery of Therapeutically Active Antibodies Specifically into the Brain.
- 5.22.2020 [Activity] COINS Seminar #52 was held online. Speaker: Dr. NISHIYAMA Nobuhiro, Professor, for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology Title: Development of Medical Nanomachines Based on Fine Design of Functional Polymers.
- 5.29.2020 [Coverage] The contents of the COINS seminar # 52 held online on 5/22 was published in "Iyaku-tsushin".
- 6.4.2020 [Coverage] iCONM started collaborative research with the Tokyo Metropolitan Institute of Medical Science on April 1st 2020. It aims to create technology for the rapid development of mRNA vaccine integrated with an adjuvant function to be prepared for the recurrence of the new coronavirus (COVID-19), and /or further mutated species of "coronavirus". Articles regarding this research was published in numerous media such as Nikkei Biotech, Jiji Press, and Yakuji Nippo, and were broadcast on TV Kanagawa.
- 6.11.2020 [Activity] 14th COINS General meeting was held online.
- 6.17.2020 [Coverage] An article about the press release announced jointly with Graduate School of Engineering, The University of Tokyo on 4/2 was published in the Yakuji Nippo.
- 6.18.2020 [Coverage] iCONM and AccuRna Inc. were introduced in the special feature of Nikkei Beyond Health. A title was Closely watch mRNA drugs for the development of a novel coronavirus vaccine.
- 6.26.2020 [Coverage] The research group of Dr. MATSUMOTO Akira, Associate Professor and Dr. MIYAHARA Yuji, Professor, Institute of Biomaterials, Tokyo Medical and Dental University (COINS Theme 4) developed a closed-loop artificial pancreas device, which was combined with glucose-responsive gel and hollow fiber for hemodialysis. Their research was introduced as "Fully synthetic artificial pancreas device, Tokyo Medical and Dental University, Nagoya University, etc. developed" in The Science News.
- 6.26.2020 [Coverage] For the first time in the world, iCONM has succeeded in controlling the clearance of gene therapy drugs at the liver sinusoidal wall by developing a reagent for the selective and transient coating of the liver sinusoidal walls. This was collaborative research with the National Institute for Quantum Science and Technology and Department of Bioengineering, Graduate School of Engineering, The University of Tokyo. A press conference was held. This research result was published in "Science Advances" Articles on this research have been published in numerous media such as Jiji Press, Oncology Tribune, and Nikkan Kogyo Shimbun.
- 7.10.2020 [Coverage] iCONM was introduced in "Case Study of Unique Lab Design(3/4)" by MEXT. iCONM is Chapter 2, Case No.15.
- 7.17.2020 [Coverage] Dr. UCHIDA Satoshi, iCONM Visiting Scientist (Project Assistant Professor, Graduate School of Engineering, The University of Tokyo) was interviewed by German media Ruptly and the interview was delivered online.†
- 7.19-20, 2020 [Coverage] An interview article of Dr. KATAOKA Kazunori, Director General, iCONM on "Smart Nanomachines and mRNA" was carried in Tokyo Shimbun and Chunichi Shimbun.
- 7.20.2020 [Coverage] Dr. UCHIDA Satoshi, iCONM Visiting Scientist was introduced in TV Tokyo "Stars of Quest".
- 7.27.2020 [Coverage] iCONM collaborating with the Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, developed the world's first drug delivery system that suppresses accumulation in peripheral tissues and delivers drugs only to brain tissues. This has been published in many media such as PHARM TECH JAPAN ONLINE.
- 7.27.2020 [Information] A paper published in PNAS on July 23, which was first authored by Dr. CARTER Daniel Gonzalez of iCONM Kataoka-Kino Lab, was selected as "Editor's Choice" by an US medical media "BioWorld Science".
- 7.27.2020 [Coverage] An article of AccuRna Inc. one of the participating organizations of the main project COINS, was published in the Nikkei Shimbun.
- 8.4.2020 [Coverage] iCONM demonstrated a new therapeutic option for glioblastoma (GBM), which is a type of brain tumors, in mice in a collaboration study with the Department of Bioengineering, Graduate School of Engineering, The University of Tokyo and held a press conference. This research result was published in ACS Nano and the related article was carried in many medias such as Nihon Keizai Shimbun, Nikkei BioTech and Iyaku Keizai.
- 8.12.2020 [Coverage] An article of a press release jointly announced by The University of Tokyo and Tokyo Medical and Dental University was carried in Kouruisha Jutaku Shimbun.
- 8.14.2020 [Coverage] An article about Dr. MATSUMURA Yasuhiro, Chief, Division of Developmental Therapeutics, EPOC, National Cancer Center, who is a member of COINS, was published in Katei Gaho.
- 8.14.2020 [Coverage] For an information on coronavirus, an interview article of Dr. KATAOKA Kazunori, iCONM Director General published in the Chunichi Shimbun on July 20 was published in "MYTTLINE", a town magazine in Tajimi City, Gifu Prefecture.
- 8.18.2020 [Activity] Dr. DIRISALA Anjaneyulu, who is a research scientist of iCONM gave a lecture to the undergraduate and graduate students, majoring biochemistry, biotechnology, and pharmaceutical sciences at KL University in India.
- 8.19.2020 [Award] Dr. MIYATA Kanjiro, leader of COINS Theme 1 (Associate Professor, Graduate School of Engineering, The University of Tokyo) and Dr. NISHIYAMA Nobuhiro (Professor, Institute of Chemistry and Life Sciences, Tokyo Institute of Technology) won the "2020 2nd Materials and Devices Joint Research Award" from the Network Joint Research Center (NJRC) for Materials and Devices with researchers of Graduate School of Medicine, The University of Tokyo and the researchers of Nishiyama Lab.
- 8.20.2020 [Information] iCONM LinkedIn page was launched for English speakers and released the introduction and movie of iCONM.
- 8.21.2020 [Coverage] The article of the press briefing jointly announced with The University of Tokyo on 8/4 was published in Nikkei beyond Health and The Science News. "The effect of cancer immunotherapy provides a dramatic improvement with Nanomachines | Nikkei Beyond Health 8/19/2020". "Effective in combination with immune checkpoint inhibitor and nano-DDS | The Science News (8/21/2020)".
- 9.1.2020 [Award] Dr. MATSUMOTO Akira, Associate Professor, Tokyo Medical and Dental University, won the Asahi Kasei Award 2020 on July 14.
- 9.2.2020 [Coverage] Cancer Institute Hospital for the Japanese Foundation for Cancer Research (JFCR) has started an investigator initiated clinical trial (First In Human study) on September 2, 2020 with anti-breast cancer therapy (SRN-14/GL2-800) containing siRNA. An article relating this was carried in many medias such as Nikkei Medical and Iyaku Tsushinsha.
- 9.2.2020 [Coverage] Regarding the review "An overview of nanomedicines for neuron targeting" published by Dr. QUADER Sabina, Senior Research Scientists of Nanomedicine, Vol. 15 (6) on July 3rd, was published as an interview article in the scientific media Neuro-Central with co-responsible author Dr. RODRIGES Rosalia, Associate Professor, Faculty of Science, University of Catalonia, Spain.
- 9.3.2020 [Activity] Kawasaki City Council Members visited iCONM.
- 9.8.2020 [Coverage] A report on the technology that efficiently delivers antibody drugs into the brain by "Brazon Therapeutics, Inc. was appeared in Nikkan Kogyo Shimbun.

- 9.10.2020 [Activity] India-Japan Webinar on Nanotechnology was held.
- 9.15.2020 [Coverage] A paper by Dr. MIYAZAKI Takuya, a visiting scientist of iCONM (Kataoka / Kinoh Lab) et al. was published in the issue on August 19 of Advanced Healthcare Materials and his design was utilized for the cover page.
- 9.15.2020 [Coverage] The newsletter "KAWASAKI Coastal Area News" Vol.25 has been published by Kawasaki City. As a cover story, there was a roundtable talk on the importance of industry-academia-government collaboration and its synergies by Dr. KATAOKA Kazunori, Director General, iCONM, Mr. OKABE Nobuhiko, Director General, Kawasaki City Institute for Public Health and FUKUDA Norihiko, Mayor of Kawasaki city.

## Turn adversity into chance! Establish a new online communication way

Under the coronavirus pandemic in 2020, many changes were required in the operation of COINS. In a situation where people could not gather, we quickly established an operating system for smooth online meetings and held many events. Starting with the "Online tea party" that was held to rebuild the connection that had been fading due to continuous remote work, the "Online General meeting" in which all participating organizations participated to report on progress and exchange opinions, "Online workshop" that aiming human resource development and communication, we were able to promote cooperation and cross-cultural exchange within and between institutions. In addition, we actively developed outreach activities, such as holding COINS seminars in which Dr. NISHIYAMA Nobuhiro was a lecturer, and a press briefing session in which researchers took the stage.

In the age of New Normal, we will try to utilize the know-how cultivated through these activities to work on the COINS management in addition to face-to-face communication.



Online workshop that various members participated (September 2020)



Stretching exercise in front of the PC during a break! @General meeting (June 2020)



Press release for thesis presentation (June 2020)

## Editor's Note

The NanoSky Vol.1 – Vol.7 have introduced six themes of COINS project. This issue introduces a new approach to develop COINS' "Mono and services that change the future", "Development of the new coronavirus infectious disease preventive vaccine", "Future medicine from COINS", and "Roundtable talk with foreign scientists". The COI program will end in end of March 2022, however, iCONM is working to establish an ecosystem that gathers resources from all over the world and to become independent while adhering to COINS' vision and mission toward the realization of "In-Body Hospitals" in 2045. We hope that this issue will convey the passion of COINS members and let more people know about iCONM. The COINS will reborn and we will continue to push forward as it goes. We sincerely hope that everyone will overcome this new coronavirus pandemic.

A next NanoSky will be the last issue. Please don't miss it.

(Editor-in-chief YOKOYAMA Miyako)