Newsletter
NanoSky
From KING SKYFRONT to the world - NanoMedical Innovation

December 2017 | Vol.4

New Route to Innovative Treatment of Central Nervous System Disease with Nanomachines

Contents

Drug Delivery to Brain via “BBB-Crossing Nanomachines”!

Recently, in COINS Theme 2 “Innovative technology for the treatment of central nervous system diseases”, a paper on BBB-Crossing Nanomachines has been published in English scientific journal “Nature Communications”. Dr. Yasutaka Anraku, Assistant Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, Mr. Hirokazu Iwasaki, Leader of COINS Research Promotion which supports research and social implementation (Vice-Director of Innovation Center of NanoMedicine (iCONM) and Dr. Mariko Tosu, Representative Director & CEO, Braizon Therapeutics, Inc. talked about the prospects of nanomachines.

Yasutaka ANRAKU

**Assistant Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo;
Visiting Scientist,
Innovation Center of NanoMedicine,
Kawasaki Institute of Industrial Promotion**

In 2007, he completed his master’s degree at Graduate School of Science and Engineering for Education, University of Toyama, and in 2010, he finished his PhD. at Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo. He is at current position since 2016. He is also a part-time lecturer at Graduate School of Medical Dental Sciences, Tokyo Medical and Dental University and National Institutes for Quantum and Radiological Science and Technology, and a Scientific Advisor at Braizon Therapeutics Inc. He is engaged in research of polymer chemistry, colloid interface chemistry, and biomaterial chemistry.

Mariko TOSU

**Representative Director & CEO,
Braizon Therapeutics, Inc.**

She graduated Tokyo University of Pharmacy and Life Sciences. She obtained a Doctor of Pharmacy. After working as a researcher at National Cancer Center and The Institute of Medical Science, The University of Tokyo for 12 years, she joined a foreign affiliated firm dealing with research equipment and supplies as a principle investigator of one of the NEDO research projects. She continued her career at another foreign affiliated firm in the same industry as a marketing manager and division manager. From 2013 to February 2017, she took office as representative director at Fluidigm Co., Ltd. In March 2017, she joined Braison Therapeutics, Inc. as a Representative Director & CEO.

Hirokazu IWASAKI

**COINS Research Promotion Leader&Vice-Director,
Innovation Center of NanoMedicine,
Kawasaki Industrial Promotion**

In 1975, he graduated Department of Industrial Chemistry, Faculty of Engineering,The University of Tokyo. Then he joined Showa Denko K.K. In 1979, he became a full-time official of the company's labor union, Chairman of the Central Executive Committee, Chairman of the Chemistry Society, and Union Central Executive Committee. In 1999, he returned to Showa Denko K.K. and served as Corporate Officer; General Manager of Intellectual Property Office, Director; Corporate Officer; Executive Officer of Chemicals Sector and Director; Corporate Officer in charge of factories, etc. He was the first director who has an experience as a chairperson of labor union. In 2014, he joined COINS as a Research Promotion Leader and became iCONM Vice-Director in 2015. He plays a key role in COINS / iCONM management by using broad management know-how such as from labor to intellectual property and business strategy. In June 2015, he became a Director of Kawasaki Institute of Industrial Promotion.

Establish a venture company with a patent on “Drug delivery to brain via BBB-crossing Nanomachines”.

■ Let us know about your work first.

Anraku: I’ve been working on polymer synthesis since my college days, and I specialized in polymer micelles (Fig. 1) as nanomachines in the laboratory of Professor Kazunori Kataoka in the Graduate School of Engineering, The University of Tokyo, to which I belong from the doctoral course (Prof. Kataoka is currently Director General of iCONM , Project Professor of Policy Alternatives Research Institute, The University of Tokyo). We were first targeting cancer but in Theme 2, we are targeting cranial nervous diseases.

Tosu: In March 2017, I assumed the position of Representative Director & CEO of Braizon Therapeutics, Inc., a company that was spun out with the technologies of Dr. Anraku and coworkers. I graduated from Faculty of Pharmaceutical Sciences and worked on research for about 12 years at universities and research institutes. Then, I was engaged in the sales of analytical devices and reagents. When I was offered this position, I recognized the social contribution of this technology if it were to be implemented and the importance of the role of bio-ventures. So, I daringly accepted the offer.

Iwasaki: I’m in charge of Research Promotion Leader in COINS and I am also a Vice-Director of iCONM. In both, I am responsible for facilitating everything from planning to routine operations, as a “Banto” head-clerk or “Joudaigaro” Chief retainer of his lord’s castle.

■ An article on “Drug delivery to brain via BBB-crossing Nanomachines” has recently been published in Nature Communications and is attracting a great deal of attention. Would you please explain the research?

Anraku: The brain has a barrier called the blood-brain barrier (Fig. 2). This barrier protects the brain by blocking substances other than glucose and amino acids essential for the brain. In other words, drugs for brain diseases do not easily reach the brain. As society has aged, brain diseases such as Alzheimer’s disease and stroke have increased, and such diseases elevate the social need for technologies to deliver drugs to the brain. Here we developed a nanomachine with glucose molecules attached to the surface of the polymer micelle to make the nanomachine recognize glucose transporter GLUT1 involved in glucose uptake of the brain (p.8). This nanomachine has a surprisingly higher accumulation in the brain than previous drugs for cranial nervous system diseases. Because the structure of polymer micelle allows for the encapsulation of various substances, if nucleic acid drugs or antibody drugs are contained in it, a more effective drug can be obtained.

Iwasaki: It is generally unknown that drugs cannot reach the brain easily. When we explain that to visitors to iCONM, they present high expectations such as “brain surgery seems terrible, so treatment with drugs is desirable.” After the publication of this paper, we can provide information on our work actively. We think our research can make people around the world happy.

Tosu: This technology is interesting in that a drug for which development was discontinued in phase III or an already marketed drug might be able to have its effect enhanced by carried in a nanomachine. This will have a significant impact on medical economy. Indeed, we received inquiries from various Japanese and foreign pharmaceutical companies even before the article were published. Although research is being advanced in this field around the world, few results have been obtained. So, we think this article had a significant impact.

Figure 1. Polymer micelle

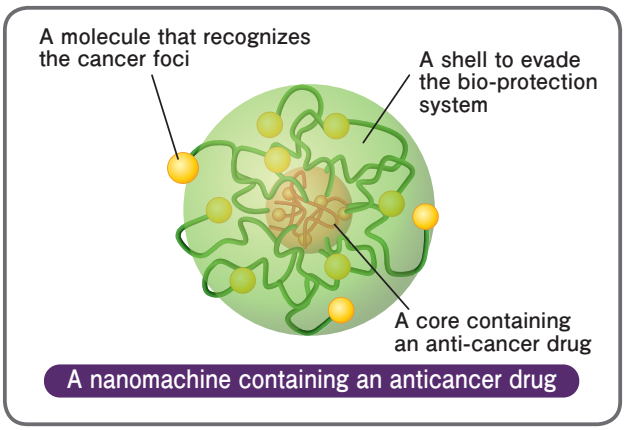
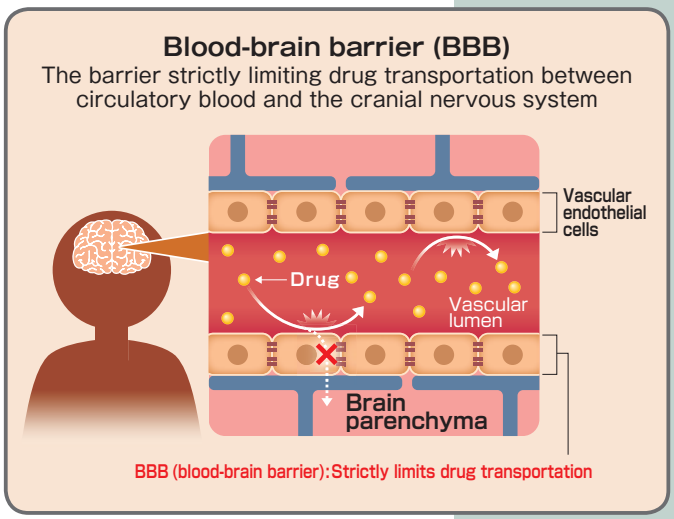


Figure 2. Blood-brain barrier (BBB)



Anraku: The article was so innovative, nobody believed the results and there was difficulty in accepting the article (laughter).

Why was the research successful?

Anraku: This is because the accurate design of nanomachines such as introducing glucose molecules to the surface of polymer micelle in an appropriate form is tactically combined with physiological blood glucose regulation properties. First, we simply administered this to full-stomach mice or fasting mice, and accumulation increased in such experiments. Some mice ate a lot, and other mice ate a little, resulting in great data variation, because we couldn't force them to eat. In mice, the glucose level was controlled by glucose injection. In humans, it is easier because they eat when they are hungry.

Need for fostering human resources to further refine the technology

Braizon Therapeutics is the first venture company resulting from COINS activities. What do you think about your strategy?

Iwasaki: The Center of Innovation (COI) Program aims at "vision-oriented challenges and high-risk R&D considering the image of society to be realized 10 years in the future" and is looking for research that will significantly change the world. Research becomes valuable only if it is accepted by society. Although many companies participate in COINS, no company has participated in Theme 2 before. Because it was important to develop nanomachines reaching the brain first, setting up a venture company to achieve social implementation was considered to be better taking commercialization into consideration. Setting up a venture company meets the philosophy of COI.

Anraku: Since the start of COI, there has been a policy that Theme 2 accepts no companies but instead creates a venture company, posing pressure to produce results. Dr. Yuzuru Matsuda, Director of the Kato Memorial Bioscience Foundation, is the Visionary Leader of "COI STREAM" Vision 1 "Ensuring Sustainability as an Advanced Low-Birth Rate Aging Country" and stated: "PPP (paper, patent and platform) should be achieved in research." These words remained in my head for a long time. Then we set up the venture company, obtained the patent, and issued the article. It has been five years now since the start and I can eventually proceed with this concept securely.

Tosu: We first obtained the Japanese patent in February 2017, and the U.S. and European patents are now being reviewed. After we obtain the Western patents, it will be easier to negotiate with Western pharmaceutical companies. From now on, we are accelerating its actual utilization by defining target diseases, proceeding with the development, tying up with other companies, and licensing it. I think, if we design the nanomachine, it seems better for us to limit its target diseases to rare diseases such as pediatric brain tumors, seek a partner for this, and proceed with the development.

Iwasaki: The issue of the patent and the publication of the paper have offered the rationale for determining the importance of the theme. More research may be performed in cooperation with iCONM. It is essential for the research and its social implementation to proceed with the triad of R&D strategy, business strategy, and IP strategy.

What are the current issues?

Anraku: In the use of polymer micelle as a nanomachine, solid cancer is easier to target because the cancer cells are concentrated. In brain diseases, on the other hand, the target differs by disease such as the nerve cells and glial cells, and therefore, its selectivity beyond the blood-brain barrier needs to be higher.
In addition, I didn't notice before I joined in COINS that, while "attractive" research is required to issue articles, social implementation requires both high functionalization and simplicity. I feel like these things make me refrain from writing articles. This is a dilemma.

Tosu: The problems of venture companies are entirely human resources, material resources, and financial resources. Now we particularly need human resources. As for material resources, as Dr. Anraku said, research requires brilliant results and actual utilization requires simplicity and high reproducibility. A company must refine technology from a perspective different from that of research. This may be a hurdle that needs to be cleared.

Anraku: A nanomachine itself is very stable and not easily broken down. However, it also needs to be broken down in response only to the brain environment and release the drug there. From now on, we will also research therapeutic effects using disease model mice kept in iCONM. Furthermore, because this is a totally novel technology, unknown potential adverse reactions are also great issues. We will confirm adverse reactions using marmosets in institutes such as the Central Institute for Experimental Animals, a partner institute of COINS.

Tosu: We would also like to cooperate with various research institutes working to overcome brain diseases.

Iwasaki: iCONM, the core institute of COINS, is a new organization. We have improved the system like a venture company, by fostering human resources, looking for management methods, and responding to requests from the outside. The industry-ready staff members have made great efforts since the inauguration, but they will retire some day and the organization needs to change. Young staff members have been fostered. It is important to sustain the current strengths of activeness and flexibility along with removing dependence on individual skills to construct a stable organization. For this goal, I think it is also important to foster young talents through OJT (On the Job Training) and to leave operations to the next generation.

■ Tell us your future resolution

Anraku: I'd also like to deliver nanomachines to sites that are difficult to reach other than the brain, such as the eyes, ears, and muscles. This technology should be required to realize an "in-body hospitals"*. Other Themes define their target diseases and nano-machines are being created for these targets. In Theme 2, I'd like to further proceed with research for the improvement of the performance of the nanomachine itself.

Tosu: If a drug can reach the brain via GLUT1, there may be other candidates of nano-machines and DDS (Drug Delivery System) depending on the drug or purpose in addition to polymer micelle.
Braizon Therapeutics would like to increase the number of employees who sympathize with our mission and set up the business as soon as possible by improving the laboratory set in iCONM.

Iwasaki: COI requires deciding and proceeding with what and how to research and develop through backcasting assuming the desirable form of the future society. We have opportunities to consider what to do now to create and realize "in-body hospitals," the vision for 30 years in the future. We can discuss and learn about research, intellectual properties, and social implementation in the face-to-face meetings and site-visits of the Japan Science and Technology Agency (JST), COINS Retreat Camp and General Meetings. Through these opportunities, I would like to support the further progress of the COINS members proceeding to the realization of in-body hospitals.

■ As the research progresses further and the human resources are being fostered, looking forward to the future. Thank you.

(Interviewer: Science Writer Ayumi KOJIMA)

Terminology

＊in-body hospitals
A research and development concept targeted by COINS: "a smart nanomachine circulates in the body 24 hours a day to detect the signs of a disease, treat it, and immediately transfer the information to the outside of the body, so that serious diseases are detected and treated early on before the person notices them."

References

Y. Anraku, H. Kuwahara, Y. Fukusato, A. Mizoguchi, T. Ishii, K. Nitta, Y. Matsumoto, K. Toh, K. Miyata, S. Uchida, K. Nishina, K. Osada, K. Itaka, N. Nishiyama, H. Mizusawa, T. Yamasoba, T. Yokota, K. Kataoka, Glycaemic control boosts glucosylated nanocarrier crossing the BBB into the brain. Nature Communications 8: 1001 (2017)

Interview with Researcher

Takanori YOKOTA

Professor,Department of Neurology and Neurological Science,
Tokyo Medical and Dental University

Development and Evolution of Hetero-Duplex Oligonucleotide Expected to be an Innovative Nucleic Acid Drug

COINS Theme 2 is developing basic technologies for drugs to handle central nervous system diseases beyond the blood-brain barrier. Professor Takanori Yokota, Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, is participating in Theme 2 and has been creating basic technologies for nucleic acid drugs through novel ideas, such as the development of a hetero-duplex oligonucleotide different from antisense oligonucleotide or siRNA (p. 10). We interviewed Professor Yokota about his previous work and future developments.

Conceives of an artificial nucleic acid through a resolution to create a new molecule by himself

The development of nucleic acid drugs which consists of DNA and/or RNA targeted to messenger RNA (mRNA) or micro RNA (miRNA) to exert its effect is underway around the world. While nucleic acid drugs can target a broader range of molecules than antibody drugs, they have problems such as the stability of nucleic acid, directivity to the target organ/tissue, and adverse reactions of liver disorders etc.

In previous developments of nucleic acid drugs, the first method used was the antisense method where single-stranded DNA complementary to the target gene RNA (antisense oligonucleotide) suppresses gene expression, followed by RNA interference where short double-stranded (small interfering RNA: siRNA) cleaves RNA. Currently, treatment with direct gene modification by genome editing technology using CRISPR/Cas9 is also being focused on.

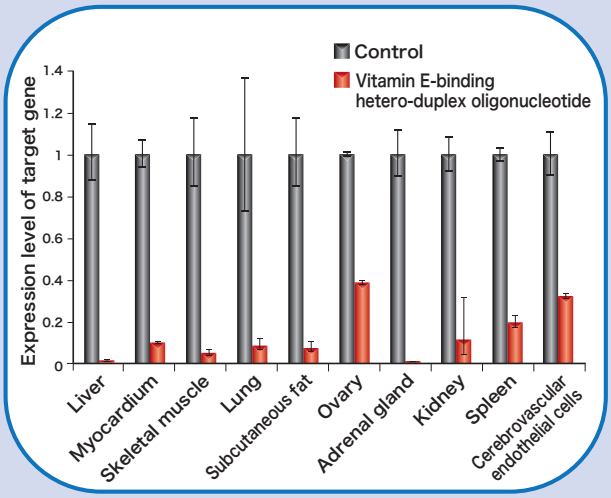
Professor Takanori Yokota, Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, has created a hetero-duplex oligonucleotide that is different from antisense oligonucleotide or siRNA and enhanced its targeting effect by attaching various ligands to it, attracting attention as a novel drug discovery seed (p. 10).

Professor Yokota engaged in research on gene therapy in the U.S.A. from 1998 to 2000, in Burnham Medical Research Institute, San Diego and Bach Neurodegenerative Disease Institute, San Francisco. There, he was working on the synthesis of RNA with enzymatic activity capable of cleaving RNA strands (ribozyme). Just in this period, the mechanism of RNA interference was discovered enhancing the expectation that artificially introduced siRNA would achieve gene therapy. However, although a Nobel Prize in Physiology or Medicine was awarded for the discovery of RNA interference in 2006, major Western pharmaceutical companies withdrew from siRNA research one after another. Professor Yokota returned to Japan and continued research on RNA interference. However, the Budget Screening Process under the cabinet of the Democratic Party of Japan in 2009 significantly affected his research funding. At this time, he resolved "If researching the application of a technology developed by someone, I would suffer from such events. I will create a novel nucleic acid by myself."

Then he the conceived of the cleavage of RNA by artificial hetero-duplex oligonucleotide formed by combining an antisense

Figure 1

High-dose (50 mg/kg) hetero-duplex oligonucleotide suppresses target genes in various organs and tissues

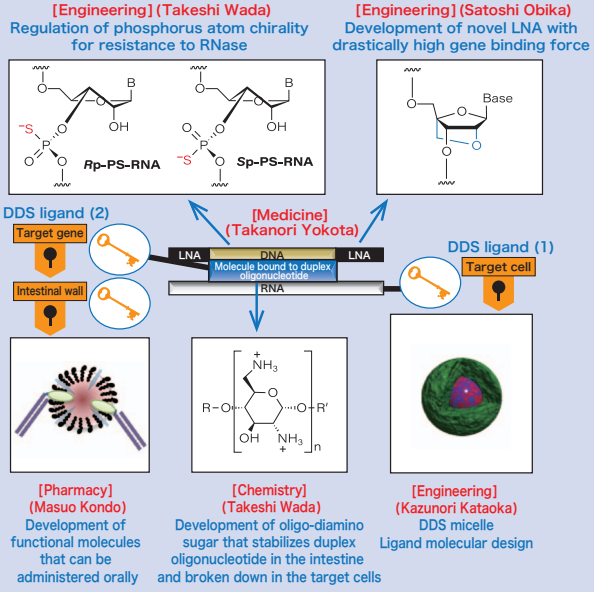


Enables gene regulation in various organs other than the liver!

Figure 2

Core hetero-duplex oligonucleotide technology with 5 coordinated component technologies

Nucleic acid drug contained in DDS



oligonucleotide to its complementary RNA strand. "I conceived of it in the airplane on my way to see one of my coworkers Professor Satoshi Obika, Osaka University. I told Dr. Obika about it and he said that he had never seen such a substance. Then we started development."

Professor Yokota said with laughter, "It's cherry picking, an idea like putting a square peg in a round hole." However, after the hetero-duplex oligonucleotide was created, experiments revealed that it has an accumulation in the cells that is about several dozen times higher than that of antisense oligonucleotide or siRNA, respectively. It was later found that the mechanisms of action are totally different among them.

Strengthen DDS by attaching ligands to hetero-duplex oligonucleotide

Professor Yokota has further enhanced its targetability by attaching ligands to the hetero-duplex oligonucleotide.

The first hetero-duplex oligonucleotide that exerted its effect was one with vitamin E attached to it as a ligand (Fig. 1). Drugs are recognized as foreign substances in the body and either broken down in the liver or excreted through the kidneys. Nucleic acid drugs are characterized by being readily accumulated in the liver in general, and hetero-duplex oligonucleotide accumulated in the liver as well.

Vitamin E was selected because it was a substance familiar to Professor Yokota. In 1997, when Professor Yokota was in his second year as a doctor, he reported a patient with spinocerebellar degeneration where motor dysfunction occurs because vitamin E cannot be taken up by the body, for the first time in the world. Then he discovered that this disease is due to an abnormality in the gene responsible for producing vitamin E transfer protein. "In this way, the source of my ideas is seeing patients and examining questions generated in practice," said Professor Yokota.

In the collaborative research with Director General, Dr. Kataoka of iCONM and Dr. Anraku Project Assistant Professor of Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, Professor Yokota's group proposed the idea that the uptake of polymer micelle into the brain may be improved by administering polymer micelle with glucose attached to it in a fasting condition followed by glucose administration. (p. 2, p. 8.) This was inspired by a PET to examine the occurrence of cancer and the presence of metastasis. PET utilizes the characteristics of cancer cells of taking up more glucose than normal cells, and it depicts where glucose labelled with positron nuclear species is taken up after it is administered. "Since glucose is the only energy source of the brain, the brain takes up glucose and represented in black in PET, even if the brain is intact. Because PET is performed in a fasting condition, we thought polymer micelle would reach the brain more easily if administered in a fasting condition followed by glucose." After this idea was proposed, the accumulation of glucose-attached macromolecular micelle increased in several months.

"In the blood-brain barrier, GLUT1 may migrate from the vessel side to the brain side at a certain probability as necessary and glucose-bound macromolecular micelle may be carried away at the same time, we think. Currently, we are developing a seed for nucleic acid drugs with its ability to deliver to the brain further enhanced by inserting hetero-duplex oligonucleotide in the inner space of the glucose-bound macromolecular micelle."

In addition, hetero-duplex oligonucleotide with ligands attached is being developed as indicated in Fig. 2. "The cells recognize hetero-duplex oligonucleotide itself as a totally new substance. Here, a new molecular biology is present. Although hetero-duplex oligonucleotide can be used alone, if its targetability is enhanced by ligands, the dose can be reduced while maintaining its effect, and adverse reactions can be reduced as well." Currently commercialized nucleic acid drugs use nucleic acid only and none of them have ligands attached.

In January 2015, Professor Yokota and his coworkers established Rena Therapeutics, a venture company originating from Tokyo Medical and Dental University, which has already signed contracts with pharmaceutical companies for technology provision.

In 2017, the antisense oligonucleotide drug nusinersen (trade name: Spinraza) was approved in Japan as a drug for spinal muscular atrophy, where systemic muscle power decreases. "Although the number of patients with the target disease is not large and the treatment cost exceeds 100 million yen per patient in the first fiscal year, it is markedly effective compared with previous therapies. There have been few diseases that can be cured in the neurological field, and doctors have sought to support patients rather than treat them. In this regard, the launch of a nucleic acid drug is very meaningful in the neurological field."

In this way, there is a favorable trend for nucleic acid drugs, while practical research should move forward in cooperation with pharmaceutical companies, such as toxicity, pharmacology, and dosage form, to make a pharmaceutical product from the hetero-duplex oligonucleotide. "To make a pharmaceutical product, we further need several steps of breakthroughs. I think this is my role, as a doctor who attends patients," said Professor Yokota. "Although doctors cannot create things that will be seeds for drug discovery, we can dig into the need or think of for what existing things could be used, in cooperation with excellent scientists. Japanese are not good at creating a comprehensive concept, which is essential to create novel and globally useful drugs. For example, although many parts of Japanese patents are used in global products such as the iPhone and Boeing airplanes, but nobody knows these are Japanese products. Now we have created hetero-duplex oligonucleotide, and I wish we could create the concept of its use and the framework to produce products.

Professor Yokota said that he did not think the research could proceed to the current level in 6 years. There are various diseases in the neurology field each with different pathologies, such as dementia, cerebrovascular disorder, headache, epilepsy, Parkinson's disease, and ALS. "I would like to engage in research that is favorable for patients. It is tough to think of novel things, but research is fun. Our research is progressing steadily but more work will be needed from now on."

(Notes: science writer Ayumi KOJIMA)

PROFILE

Takanori YOKOTA

In 1984, he graduated Tokyo Medical and Dental University Faculty of Medicine. After training at Department of Internal Medicine, Musashino Red Cross Hospital, he completed Graduate School of Medicine Tokyo Medical and Dental University in 1990. After working at Department of Neurology, Tokyo Metropolitan Neurological Hospital, he moved to the Burnham Medical Research Institute, San Diego, and Bach Neurodegenerative Disease Institute, San Francisco in 1998. In 2000, he returned to his old school, and in 2004, took position of Associate Professor of Department of Neurology and Neurological Science, Tokyo Medical and Dental University and has been in present position since 2009.

Reference

K. Nishina, W. Piao, K. Yoshida-Tanaka, Y. Sujino, T. Nishina, T. Yamamoto, K. Nitta, K. Yoshioka, H. Kuwahara, H. Yasuhara, T. Baba, F. Ono, K. Miyata, K. Miyake, PP. Seth, A. Low, M. Yoshida, CF. Bennett, K. Kataoka, H. Mizusawa, S. Obika, T. Yokota, DNA/RNA heteroduplex oligonucleotide for highly efficient gene silencing. Nature Communications 6: 7969 (2015)

Light to Treatment/Diagnosis of Central Nervous System Disease!! Development of Nanomachine to Deliver Drugs from the Blood to the Brain

The blood-brain barrier (BBB) inhibits drug transportation from circulatory blood to the cranial nervous system, serving as the greatest bottleneck in the treatment of cranial nervous system diseases. Here we have successfully developed a nanomachine that crosses the BBB efficiently in response to external stimuli (glucose) and accumulates in the brain several orders of magnitude more efficiently than previous technologies. This is a basic technology to deliver various drugs to the brain. It is expected to evolve into the development of innovative drugs for cranial nervous system diseases, for which no truly effective treatments have been established, such as Alzheimer's disease.

Yasutaka ANRAKU

Project Assistant Professor,
Department of Bioengineering, Graduate School of Engineering,
The University of Tokyo

The aging of society has been progressing significantly in developed countries, and refractory cranial nervous system diseases such as Alzheimer's disease pose serious social problems. Furthermore, the prevalence of such diseases is also expected to increase significantly in association with the ongoing increase in the aging population. The greatest bottleneck that inhibits the treatment of cranial nervous system diseases is the in vivo barrier system called the blood-brain barrier (BBB). The BBB is responsible of regulating the transportation of substances between circulatory blood and the cranial nervous system. It selectively takes up nutrients essential for the brain to function, while it significantly limits the delivery of drugs to the brain. Indeed, even drugs currently used in the symptomatic treatment of Alzheimer's disease in clinical settings accumulate at less than 0.1% by dose in the brain. Thus, development of technology that allows drugs to cross the BBB efficiently is being conducted around the world. In this context, we successfully developed a "BBB-crossing nanomachine"[*1] that crosses the BBB at a markedly higher efficiency than that of existing technology, in response to a simple stimuli of blood glucose change and further accumulates in the nerve cells in the brain.

The cerebrovascular endothelial cells that construct the BBB have several orders of magnitude more glucose transporter 1 (GLUT1) to transport glucose, the energy source for the brain, than other transporters. Therefore, the delivery of drugs to the brain by binding glucose to the drug or its carrier has been attempted around the world, resulting in insufficient delivery. We focused on the site in which GLUT1 is localized in the cerebrovascular endothelial cells which varies in association with blood glucose change, and proposed that drug delivery while smoothly crossing the BBB may be achieved by introducing a biological approach of administering glucose as an external stimulus.

Then, we appropriately introduced glucose in the superficial layer of nanomachines with polymer ensured for their in vivo safety as component molecules, and constructed a nanomachine of 30 nm in diameter that accurately recognizes GLUT1 localized in the cerebrovascular endothelial cells (Fig. 1). By intravenously administering the nano-machines to fasting mice, then subsequently administering glucose solution 30 minutes later, it was confirmed that a maximum of about 6% of the dose was accumulated in the brain. This accumulation is over 100-times higher than that of non-glucose-binding nano-machines (Fig. 2). The behavior of the nanomachines in the brain was microscopically observed, confirming that it has a smart function of crossing the BBB in response to glucose (Fig. 2) and that it is evenly distributed up to the deep regions of the brain (Fig. 3). Furthermore, we revealed that the nanomachines cross the BBB and are then taken up into the nerve cells in the brain (Fig .3). Drug delivery to the nerve cells is very important to achieve the treatment of many cranial nervous system diseases.

In previous development of drugs for cranial nervous system diseases, polymer drugs could not cross the BBB, and low molecular drugs crossed the BBB inefficiently in many cases, resulting in insufficient therapeutic effects that are significantly limited in the development of drugs. Nanomachines significantly enhance the ability to cross the BBB of any drugs and facilitate the enclosure of biological drugs that assume future advanced medicines such as antibody drugs and nucleic acid drugs. Nanomachines are expected to have an inestimable impact on scientific disciplines, medical practice and society as a great innovation in the development of drugs for cranial nervous system diseases.

Figure 1. Structure of glucose-bound nano-machine

Nano-machines are constructed through self-organization of macromolecules ensured for their in vivo safety in aqueous solutions. More than one glucose molecule is mounted on the surface layer for the recognition of GLUT1 and the diameter is about 30 nm.

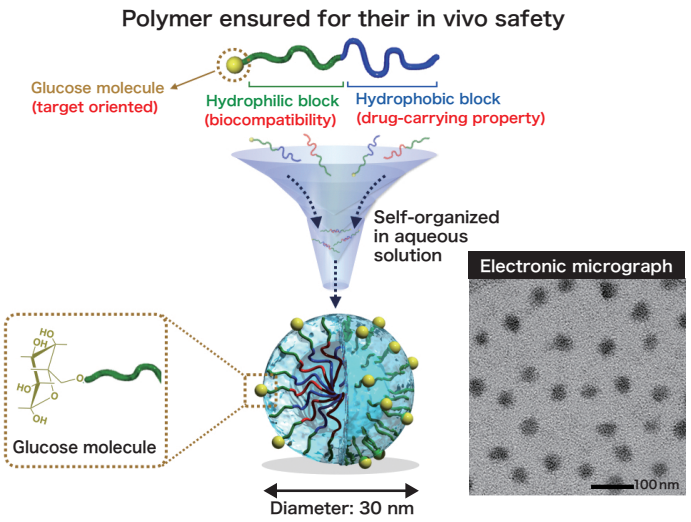


Figure 2. Nanomachines accumulate in the brain in response to external stimuli (glucose administration)

Glucose-bound nanomachines were confirmed to accumulate in response to external stimuli in an amount over 100 times as high as that of a non-glucose bound nanomachine. This results in an efficacy about 100 times as high as that of the drugs currently used in symptomatic therapy for Alzheimer's disease. Real-time behavior of the nanomachines in the brain (red) was successfully observed indicating the nanomachines that crossed the BBB in response to external stimuli and were diffused in the brain parenchyma.

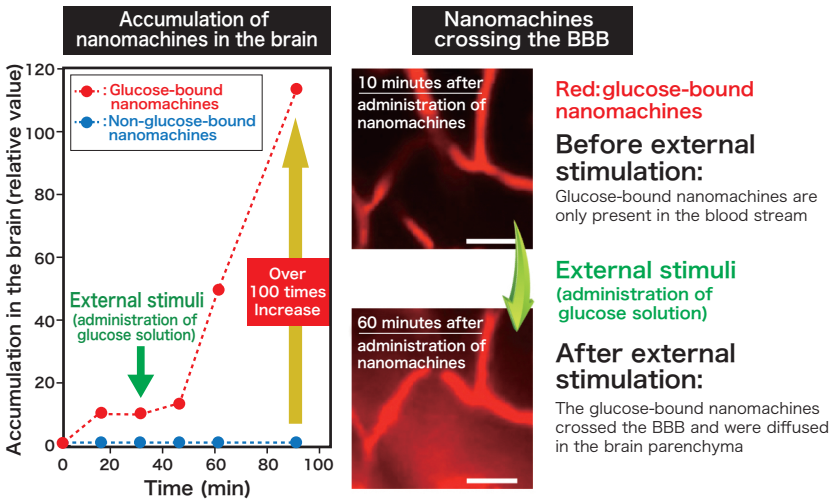
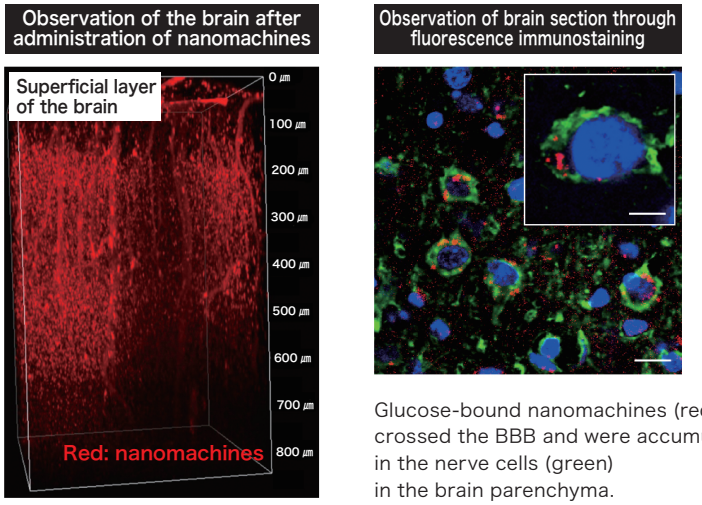


Figure 3. Behavior of glucose-bound nanomachines in the brain

The glucose-bound nanomachines (red) were confirmed to cross the BBB and then be evenly distributed up to the deep regions of the brain. It was revealed that the nanomachines are taken up particularly in the nerve cells in the brain parenchyma.



Glucose-bound nanomachines (red) crossed the BBB and were accumulated in the nerve cells (green) in the brain parenchyma.

Terminology

＊1 BBB-crossing nanomachine

BBB-crossing nanomachines are produced by introducing glucose into the surface layer of nano-particles with component molecules ensured for their in vivo safety. They have smart functions of accurately recognizing glucose transporter 1 (GLUT1) localized in the cerebrovascular endothelial cells and crossing the BBB in response to external stimuli (glucose). Due to the fact that this nanomachine is covered by a shell made of polymer material with excellent biocompatibility, it can circulate in the blood stably without being recognized as foreign material. Change in structure of the polymer constituting the nanomachines enables the encapsulation of various drugs. Thus, this technology is expected to provide highly-versatile nanomachines that can be developed for the treatment of various cranial nervous system diseases.

References

Y. Anraku, H. Kuwahara, Y. Fukusato, A. Mizoguchi, T. Ishii, K. Nitta, Y. Matsumoto, K. Toh, K. Miyata, S. Uchida, K. Nishina, K. Osada, K. Itaka, N. Nishiyama, H. Mizusawa, T. Yamasoba, T. Yokota, K. Kataoka, Glycaemic control boosts glucosylated nanocarrier crossing the BBB into the brain. Nature Communications 8: 1001(2017)

Development of Hetero-Duplex Oligonucleotide to Regulate a Specific Gene far more Efficiently than Previous Nucleic Acid Drugs

While antisense oligonucleotide and siRNA are known as major nucleic acid drugs that treat by regulating a specific gene, we are developing hetero-duplex oligonucleotide with a different molecular structure and mechanism of action. Hetero-duplex oligonucleotide has far higher effects than those of previous nucleic acid drugs. It is a molecular technology with versatility that can strengthen the effects of existing antisense oligonucleotides. I am making every effort in the research with my coworkers in the hope of enabling hetero-duplex oligonucleotide to be used as an innovative therapy for intractable diseases without effective treatments.

Hiroya KUWAHARA
Research Assistant Professor,
Department of Neurology and Neurological Science, Tokyo Medical and Dental University

Nucleic acid drugs such as antisense oligonucleotide[*1] and siRNA (small interfering RNA)[*2] are expected to be developed as innovative drugs for refractory diseases such as cancers or genetic diseases. While antibody drugs, the mainstream of current molecular targeted therapy, have their target molecules limited on the cellular surface, nucleic acid drugs can also target intracellular molecules. Therefore, as promising candidates for the next generation core molecular targeted therapy, the development of nucleic acid drugs is broadly promoted by from academic basic research to clinical development by companies.

Antisense oligonucleotide is the most developed nucleic acid drug. In 1998, a drug for cytomegalovirus retinitis in patients with AIDS (fomivirsen, intraocular) was approved for marketing and manufacturing, as were drugs for familial hypercholesteremia (mipomersen, subcutaneous) in 2013, and for Duchenne muscular dystrophy (eteplirsen, intravenous) and spinal muscular atrophy (nusinersen, intrathecal) in 2016. In this way, while antisense oligonucleotide is developed energetically, further improvement is required in the chemical modification of nucleic acid and in vivo delivery, which significantly affect safety and efficacy.

We have developed a double-stranded artificial functional oligonucleotide hetero-duplex oligonucleotide (HDO) that consists of a DNA strand with about 12 to 20 bases (primary strand) and its complementary RNA (Fig. 1). Taking a gapmer form where locked nucleic acids (LNA) are allocated at both ends of the DNA strand, the central part of the double-stranded strands forms hetero DNA/RNA oligonucleotide, which is recognized by an intracellular ribonuclease RNase H and the complementary RNA strand and the delivery ligand bound to it is cleaved (Fig. 2). As a result, the primary DNA strand becomes single-stranded and is bound to the target RNA strand, and again RNase H cleaves the target RNA to exert a gene-suppressing effect (Fig. 2). The characteristic of our molecular technology is that RNase H plays dual roles of cleaving the complementary RNA strand and the target RNA strand, and the ligand can therefore be attached to the complementary RNA strand without affecting binding affinity of the primary DNA strand.

Hetero-duplex oligonucleotide with vitamin E (α-tocopherol) bound to it as a ligand has an effect about 20 times as high as that of antisense oligonucleotide. In intravenous injection research in disease model mice for familial amyloid polyneuropathy[*3] to examine the suppression of the target gene in the liver (transthyretin), the antisense oligonucleotide suppressed the gene by about 50%, while the hetero-duplex oligonucleotide suppressed it by about 99% (Fig. 3). Hetero-duplex oligonucleotide is also characterized by the versatility that significantly enhances the efficacy of existing antisense oligonucleotides like this. In addition, molecules such as lipids, antibodies, peptides, or sugar chains that regulate/enhance drug delivery can be bound to the end of the complementary RNA strand. Therefore, hetero-duplex oligonucleotide can be considered to be a novel nucleic acid drug with a built-in drug delivery system.

For the development of hetero-duplex oligonucleotide, Rena Therapeutics Inc., a venture company originating from Tokyo Medical and Dental University, was established in January 2015. Hetero-duplex oligonucleotide is expected to be used practically for various intractable diseases in clinical settings as the first novel nucleic acid drug from Japan.

Figure 1. Molecular structure of hetero-duplex oligonucleotide

Major nucleic acid drugs

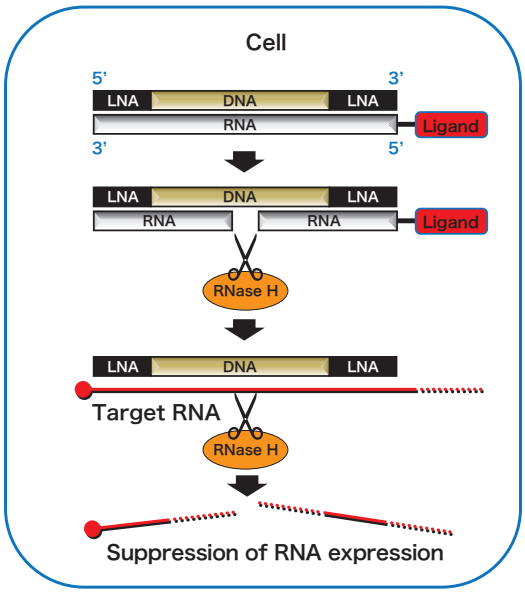
1. Antisense oligonucleotide
⇒ Single-stranded DNA

2. siRNA (small interfering RNA)
⇒ Double-stranded RNA

3. Hetero-duplex oligonucleotide (HDO)
⇒ Double-stranded DNA/RNA

Hetero-duplex oligonucleotide (3) has a structure of double-stranded DNA/RNA, contrary to antisense oligonucleotide (1) or siRNA (2).

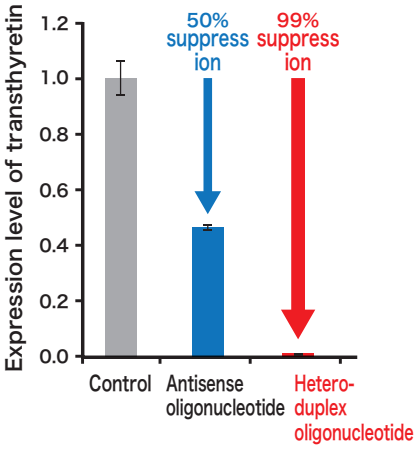
Figure 2. Mechanism of action of hetero-duplex oligonucleotide



For hetero-duplex oligonucleotide, RNase H is assumed to play dual roles of cleaving both the complementary RNA strand and the target RNA strand in the cell.

Figure 3. Effect of hetero-duplex oligonucleotide

Suppressive effect on target gene in the liver by intravenous administration to disease model mice for familial amyloid polyneuropathy



Use of hetero-duplex oligonucleotide markedly potentiates the suppressive effect of antisense oligonucleotide on the target gene

Terminology

＊1 Antisense oligonucleotide
Antisense oligonucleotide is a single-stranded DNA with a length of 12 to 30 bases with a sequence complementary to a specific messenger RNA (mRNA), and in a more limited sense, it has an inhibitory effect on translation to protein by binding to the mRNA of the target gene. In a broader sense, its effects include the regulation of splicing targeting pre-mRNA (e.g., exon-skipping) and the regulation of gene expression targeting micro RNA (miRNA).

＊2 siRNA (small interfering RNA)
siRNA consists of about 20 to 25 base pairs and has a structure of double-stranded RNA with 2 extruding bases at the 3' ends. It causes the phenomenon of RNA interference (RNAi) where gene expression is suppressed by the specific cleavage of the target mRNA, resulting in a strong suppressive effect on gene expression and high specificity to the target gene.

＊3 Familial amyloid polyneuropathy
Familial amyloid polyneuropathy is a sort of amyloidosis where amyloid (a protein with a fibrous structure) deposits in the general organs resulting in dysfunction. It is an intractable disease significantly presenting peripheral or autonomic neuropathy, mostly caused by transthyretin gene mutation.

References

K. Nishina, W. Piao, K. Yoshida-Tanaka, Y. Sujino, T. Nishina, T. Yamamoto, K. Nitta, K. Yoshioka, H. Kuwahara, H. Yasuhara, T. Baba, F. Ono, K. Miyata, K. Miyake, PP. Seth, A. Low, M. Yoshida, CF. Bennett, K. Kataoka, H. Mizusawa, S. Obika, T. Yokota, DNA/RNA heteroduplex oligonucleotide for highly-efficient gene silencing. Nature Communications 6: 7969 (2015)

iCONM Trainees Talk about their Activities

Innovation Center of NanoMedicine (hereinafter referred to as iCONM), the core institution of COINS, is not only a research institute but also offers training opportunities for students. It is our mission to give students a chance to personally develop through research activities at iCONM as a trainee as well. On this occasion, we asked the trainees to talk about what they had learnt through the activities at iCONM, what they felt was important, and are where they expect iCONM to work more actively in the future.

Facilitator / Shigehito Osawa
Participants / Ai Kohata, Noriko Nakamura, Akitsugu Matsui, Takamasa Majima (Japanese alphabetical order)

Shigehito OSAWA

Research Scientist,
Kawasaki Institute of Industrial Promotion Innovation Center of NanoMedicine
Earned a doctorate at Kataoka Kazunori laboratory of Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo. At the time of Professor Kazunori Kataoka's retirement, he joined iCONM as a postdoctoral fellow. He is the youngest research scientist at iCONM. His research field is polymer synthesis; researching DDS micelles.

It is nice that we are able to openly consult with many people about the research.

Osawa: Do you feel any difference between university and iCONM as a research institute?

Matsui: The rules for using the facilities are stricter here than university, but still it is not as strict as companies. We can flexibly make our own schedule for experiments. I think iCONM has both good points of university and companies.

Kohata: I was surprised to see so many open spaces. Unlike university labs that are partitioned, iCONM has multiple labs in the same space and the common spaces are also substantial, so I feel that the discussion is easy to create.

Majima: Sharing results is also active compared to universities, and I get a feeling that I am a member of a big project.

Matsui: It is friendly atmosphere and we can discuss casually. We can get and share idea on points and tasks of the experiment frequently and easily.

Nakamura: Compared to universities, the ratio of postdoctoral fellows is high, and so it is very good to be able to talk about experiments at any time.

Osawa: I agree. iCONM style that everyone is in one large room gives us advantages. For example, when discussions start around me, various people gather, and I learn a lot from them. I sometimes feel pressure that I can' t say the wrong thing, haha. But I think this tension-filled discussion is a good training. Kohata san and Majima san have joined iCONM lately. Could you tell me what kind of impression you have for iCONM?

Kohata: I was nervous to enter iCONM at first because there are a diversity of people.That is too different from traditional Japanese universities. Moreover, I feel the security and professionalism are excellent here. We need a license card for entering and leaving the building.

Majima: I am learning techniques for using the *in vivo* confocal laser microscope at iCONM and this started to benefit works in our institute, too. There are many open spaces in iCONM like the magnet area where we are talking now. It is easy to come, isn't it?

When physicians who worked in a hospital or a clinic like me want to obtain phD., their motivation may be getting good results in lab research and completing a dissertation to acquire the degree, but they may not think well how their research will contribute to society. In contrast, researches at iCONM have a clear objective of implementing "in-body hospitals". By joining iCONM research, I think we are motivated well because purpose of research, our attitude and what we should do are clarified without the singular purpose of acquisition of a degree.

It became easier to image a carrier after the graduate school

Osawa: Nakamura san and Matsui san, you have the desks in iCONM and you are engaged in research as a full-time trainee. Could you tell me your first impression, and current impression of iCONM?

Nakamura: I came to iCONM only to use experimental equipment at first. At that time, my impression of iCONM is excellent facility having great equipment, that all. Now, I feel iCONM activities expand my research by collaborating with other research groups working on similar nanomachines to my research topic. We are sharing results and establishing new experiments through demonstration of novel machines together, etc.

Osawa: You have good impression on hardware of iCONM good, and you have gradually got good impression on software of iCONM. Matsui san, you have been helping us to set up laboratories.

Matsui: When I came first, I thought I could conduct experiment immediately, but actually I couldn't because the environment was immature. Currently, I have an impression that it finally became well-organized experimental place by our effort of maintaining and adjusting the equipment and all kinds of advice about environments from other researchers. In order to further improve usability, I would like people coming from outside to give a comment on our institute; it is really a progressive learning environment!

Osawa: At iCONM, we ask trainees to do work such as management of experimental equipment. We believe that having a job with responsibility is also good training for students. Now, do you actually feel that doing research at iCONM would be useful for your future carrier?

Kohata: Most of the people here have higher position than post-doctoral fellows. This is excellent for me to look for a role model and/or mentor as a researcher. There are diverse teams with many female researchers and I can talk with them about balancing family, research, and my future carrier. It is very helpful for me.

Nakamura: For example, it is not easy to imagine how our research could be translated and profitably applied to product in the market when we only think about our research from the narrow student's standpoint. But when I am in iCONM, it will become easier to draw out the future vision of my work through learning many stories about how companies are advancing concretely towards commercialization.

Ai KOHATA

Trainee
M1 Takuzo Aida Laboratory, Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo
She is engaged in DDS research that has target direction by producing polymer coating the surface of siRNA. For evaluating the polymer made by herself *in vitro* and *in vivo*, Prof. Takuzo Aida recommended her to collaborate with Prof. Kazunori Kataoka's group .She has just started her research at iCONM.

Noriko NAKAMURA

Trainee
M2 Horacio Cabral Laboratory, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo
She is engaged in research looking to improve the function of the nanomachine targeting the brain. She attends iCONM as a trainee from this fiscal year, and conducts various experiments from polymer synthesis *in vitro* and *in vivo*.

Akitsugu MATSUI

Trainee
D4 Internal Medicine, Graduate School of Medicine, The University of Tokyo
He has been studying therapeutic nucleic acid at Prof. Keiji Itaka Group. He got master degree at Prof. Kazunori Kataoka's group. When the Prof. Kataoka lab. moved to iCONM, he moved to Prof. Itaka lab. at iCONM and he is continuing his research as a trainee.

Takamasa MAJIMA

Trainee
D2 Department of Neurology and Neurological Science, Tokyo Medical and Dental University
He entered the graduate school after working as a neurologist for five years. Now he is engaged in research of therapeutic nucleic acid delivery system and vascular endothelial imaging., He is acquiring the *in vivo* confocal laser microscope skills at iCONM, which is necessary for DDS research of the nucleic acid delivery.

Matsui: Furthermore, I think it will become an even better environment for us to study if we are able to build up collaboration and cooperation with neighboring other research institutes such as National Institute of Health Sciences and Central Institute for Experimental Animals. It is practically useful if we, students can learn about social regulations and use it for our future research.

Osawa: Social regulations may delay translation of your research into practical use. With knowledge that some specific chemicals cannot use for medicines, you may be able to set up a research plan more effectively.

Matsui: Majima san, from the point of view of a physician, do you think that students and postdoctoral researchers should have a mind to conduct research aimed at clinical trials?

Majima: Well, I think that it is necessary to grasp the situation from a broader perspective of which stage the research is in now.

Kohata: When I was engaged in research of chemical synthesis, I was only concentrating on short-term experiments and I had never thought about whether it could be used clinically. However, after discussing with Prof. Kataoka, Director-General of iCONM, my way of thinking has changed to make something to advance to clinical use. I felt that there was a large gap between disciplines.

Nakamura: When I was undergraduate, my purpose were studying towards graduation and writing a thesis. When I was asked how useful my research was, I could answer but I did not think so deeply. Here I can learn about research that is close to practical use, and with this knowledge, I can easily assume potential benefits of my research and which stage my research is in now.

Osawa: Since iCONM is the core institution of COINS and can collaborate with many universities / research institutes and companies, I hope everyone also shares information and develops broad research networks to accumulate the necessary context and knowledge for future innovation.

Students can also work in a place where companies and universities are mixed- "Under the one roof"

Osawa: Finally, do you have any requests to iCONM?

Matsui: May be rent subsidy? It takes 15 mins from Kojimashinden station on foot, I am doing my best though….

Osawa: I agree. Usually, universities are located with good access, aren't they? I heard there are plans to improve public transportation around the iCONM. I think it will be improved soon.

Nakamura: I work in iCONM everyday. So I know what devices are available and what I can do, but outside people do not know such information. If the information was more readily available, students can be more motivated and actively come to iCONM.

Kohata: I didn't know anything about iCONM either. I happened to know about iCONM when I was searching Prof. Kataoka on the internet, but I couldn't understand the relationship with Kawasaki city and the COI program, and detailed formations etc.

Matsui: I think that it will be difficult for students to come up with ideas to work in places where enterprises and universities are mixed without opening more information on iCONM and its concept.

Osawa: I see. People do not know iCONM well and this is a psychological barrier in addition to the physical distance problem. This makes it difficult for students to travel to iCONM.

For more students to use iCONM as a place for research and study, it is necessary to transmit information on, for example, what kind of experiment we can do on the webpage in an easy-to-understand manner in addition to the concept and goal of research.

Thank you for your comments.

8th General Meeting

The 8th General Meeting was held in the main conference room at the Life Science & Environment Research Center (LiSE) on Friday, June 2, 2017. This meeting is held semi-annually with all participating institutions. COINS entered the second year of Phase 2 (Fiscal year 2016 - 2018) and Tokyo Science University, AccuRna, Inc. and Brazison Therapeutics Inc. newly joined and a system for accelerating R&D and social implementation has been in place. This time, under the theme of selection and concentration for realizing COINS' vision "Realization of in-body hospitals", we aimed to take the opportunity to review all efforts from the viewpoint of differentiation and advantage from the existing technology. Thus, both theme leaders and participating organizations gave presentation on research outcome and afterwards there was a panel discussion with presenters.

In the panel, they discussed on the theme of "Future development of R&D for realization of in-body hospitals" and "How to connect outcome to social implementation", and we discussed future guidelines and issues to overcome. Further, regarding utilization of researcher information filing tool "Pure" system, Ms. Yoshiko Kakita from Elsevier B.V. gave presentation and confirmed the effectiveness of using filing tool.

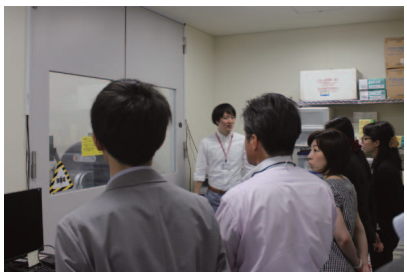
In poster session, active discussion and exchange of information were carried out among researchers with 35 posters.

Finally, we had valuable advice from Dr. Tatsuro Irimura, COINS Advisor and Project Professor of Juntendo University, Mr. Toshio Asano, Standing Counsellor of Asahi Kasei Co., Ltd. such as "For using a completely new viewpoint and approach to the project, we expect especially young researchers to raise antenna to daily tasks", the meeting became very meaningful to strengthen further unity towards "Realization of in-body hospitals". You need to prepare that innovation inevitable takes long time, it is important to deepen collaboration between companies and academia, but also to fulfill each one of respective roles firmly along the way. As the first attempt at this time, under the cooperation of the Central Institute for Experimental Animals (CIEA) of the participating institution, CIEA lab. tour was conducted for those who were interested. Visitors seemed to be thinking about the next step of research while looking around valuable animal laboratory and experimental equipment such as marmosets that are not usually seen.

The meeting was a very meaningful which could foster an atmosphere to further strengthen unity and accelerate toward realization of in-body hospitals.

Lively panel discussion

Lecture by Ms. Yoshiko Kakita from Elsevier B.V.



Lab. Tour of the Central Institute for Experimental Animals (CIEA)

Tatsuro Irimura
Project Professor, Juntendo University

Toshio Asano
Standing Counsellor, Asahi Kasei Co., Ltd.

Topics December 2016 – June 2017

- 12.14.2016【Activity】Newsletter「NanoSky vol.2」was published.
- 12.15.2016【Activity】The 3rd COINS International Symposium was held at Kawasaki City Industrial Promotion Hall.
- 12.24.2016【News】The article about Prof. Nobuhiro Nishiyama, Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology (COINS Theme 5 leader) was appeared in Nikkei Science 2017 Feb. issue under the title of "Drug delivery with high function nanomachines"
- 1.13.2017【News】Introduction of Innovation Center of NanoMedicine (iCONM) which is a core research center of COINS and interview of Prof. Kazunori Kataoka, iCONM Director General (COINS Research leader) was appeared in life style magazine "My way" commemorative Issue vol. 100 (Published by Hamagin Institute of Industrial Promotion). The title is "No side effect from targeting a cancer and practical use is at hand".
- 1.16.2017【News】Special Issue: Macromolecular Bioscience (Volume 17, Issue 1, 2017) was published under the title on "Special Issue: Dedicated to Kazunori Kataoka on the Occasion of his 65th Birthday".
- 1.17.2017【Activity】COINS Seminar #23 was held at iCONM. Lecturer: Prof. Ulrich S. Schubert (Laboratory of Organic and Macromo-

lecular Chemistry, Jena Center for Soft Matter, Friedrich Schiller University Jena)
Title : “Engineering pharmaceutical polymers and nanoparticle libraries”

- 1.19.2017 【Activity】 COINS Seminar #24 was held at iCONM.
Lecturer: Prof. Mark E. Davis (Chemical Engineering, California Institute of Technology)
Title : “Nanoparticle Therapeutics: From Concept to Clinic”

- 1.26.2017 【Activity】 The 7th COINS General Meeting was held.

- 1.31.2017 【News】 Interview of Dr. Takanori Ichiki, Professor, Dept. of Materials Engineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 4 leader) was introduced in Tokyo Electron web Magazine "TELESCOPE Magazine" No.13 under the title of “Downsize complete examination function of major hospital and detect diseases at early stage”

- 2.8.2017 【Appoint】 National Academy of Engineering (NAE) announced newly elected members this year on February 8, and Kazunori Kataoka (Director General of iCONM, Kawasaki Institute of Industrial Promotion, the Research Leader of COINS, Professor Emeritus, The University of Tokyo) was elected as a foreign member (NAE) for his pioneering contributions to the design of supramolecular nanostructures and their application to drug and gene delivery. Appointment ceremony will be held at the National Academy's Headquarters in Washington DC, USA on October 8 this year.

- 2.15.2017 【Activity】 ASEAN Young Officers from Invitation Program of JST visited iCONM.

- 2.22.2017 【News】 Prof. Kataoka Kazunori, COINS research leader's interview video was delivered on 10MTV Opinion. The delivery will be 5 times in total from 2/22 (Wednesday) every other week.

- 2.27 - 2.28. 2017 【Activity】 11th Annual Symposium on Nanobiotechnology organized by Kawasaki Institute of Industrial Promotion was held.

- 3.10.2017 【Award】 Mr. Daiki Sueyoshi, Cabral Lab. Dept. of Bioengineering, Graduate School of Engineering, The University of Tokyo, received Dean's Award from Graduate School of Engineering.

- 3.13.2017 【News】 Articles related to the research of Professor Yoshihiro Muragaki, Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University (COINS Theme 5) were posted on the Nihon Keizai Shimbun electronic version and the Nihon Keizai Shimbun Morning edition p. 11. The title was "Development of Pancreatic cancer therapy with molecules and ultrasonic wave.

- 3.20.2017 【Activity】 COINS Newsletter Vol.3 was published.

- 3.28.2017 【News】 Dr. Kazunori Kataoka, Director General, iCONM appeared in 'Front-Line Medicine' of "Flood of appointments! Amazing doctors at special outpatient!!" on TBS.

- 3.29.2017 【News】 Articles related to the research of Professor Yoshihiro Muragaki, Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University (COINS Theme 5) were appeared in Nikkei online and p.11 in Nikkei Morning paper. The title is "Anticancer agent × ultrasound clinical study”.

- 4.7.2017 【News】 Article related to research of Prof. Takahiro Ochiya, Head, Section for Studies on Metastases Cancer Center Research Institute (COINS Theme 4) was published in Nikkei online and p.31 in Nikkei Morning paper. The title was "Let's search the criminal who is causing a recurrence of cancer".

- 4.12.2017 【Award】 Dr. Yasutaka Anraku, Assistant Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 2 Leader) was awarded The Young Scientist' s Prize for The Commendation for Science and Technology 2017 by the Minister of Education, Culture, Sports, Science and Technology.

- 4.14.2017 【Award】 Director General, Dr. Kazunori Kataoka was awarded to the 34th H. C. Brown Lecturer at Purdue University, USA.

- 4.21.2017 【Activity】 The COINS Seminar #25 was held at iCONM at 16:00 – 17:00.
Speaker: Dr. Yuji Tanaka (Researcher, Riken)
"An Engineering trial for eyes disease."

- 5.17.2017 【News】 Article related to research of Dr. Shuhei Murayama, Dept. of Molecular Imaging and Theranostics, National Institute of Radiological Sciences was published in Nikkan Kogyo Shimbun p.29 and Nikkan Kogyo online. The title is "Researcher who open the way".

- 5.17.2017 【News】 Articles related to research of Dr. Takahiro Ochiya, National Cancer Center were published in Nikkei online and p.3&p.26 in Nikkei Morning paper. The title was "Cancer treatment Kaitai Shinsho (3) Cell garbage bag - actually a cause".

- 5.26.2017 【Award】 Dr. Chika Sato, Dr. Ichio Aoki and others, NIRS, QST (COINS Theme 5) were selected for The Best Poster Presentation Award from 12th Japanese Society for Molecular Imaging.

- 5.28.2017 【News】 Article related to research conducting at COINS and interview with Dr. Kazunori Kataoka, COINS Research Leader, Dr. Yasuhiro Matsumura, Chief, Investigative Treatment Division, Research Center for Innovative Oncology, National Cancer Center Hospital East (COINS Theme 1) and Dr. Nobuhiro Nishiyama, Professor, Institute of Innovative Research, Tokyo Institute of Technology were published in Yomiuri Shimbun p.34. The title is "Drug delivery directly to cancer cells".

- 5.29.2017 【News】 Articles related to development plan of KING SKYFRONT and iCONM were published in Kanagawa Shimbun p. 1 and Kanakoro Kanagawa Shimbun Web. The title was “Life Science Center heading for new stage Kawasaki Tonomachi - Town will be completed within this fiscal year”.

- 5.31.2017 【Award】 Mr. Sotaro Kuroyanagi, D1, Tokyo Institute of Technology (COINS Theme5), Mr. Naoto Nakamura, M2, The University of Tokyo (COINS Theme1) and Mr. Naoto Yoshinaga, M2, The University of Tokyo (COINS Theme1) receive Poster Awards from 66th SPSJ Annual Meeting.

- 6.1.2017 【Award】 Dr. Kanjiro Miyata, Visiting Research Scientist (Associate Professor, The University of Tokyo) received The Nucleic Acids Therapeutics Society of Japan (NatsJ) Award for Young Scientists.

- 6.2.2017 【Activity】 The 8th COINS General meeting was held. (p. 14 in this issue)

- 6.14.2017 【Activity】 Mr. Yoichi Ito, Chief, The Science and Technology Policy Bureau of Ministry of Education, Culture, Sports, Science and Technology (MEXT) and 7 others visited iCONM and COINS.

- 6.26.2017 【News】 Angewandte Chemie International Edition (Published by German Chemical Society) carries an article about selection of Prof. Kazunori Kataoka, Director General of iCONM, to foreign member of United States National Academy of Engineering. The title is “News: New Members and Foreign Members of the National Academy of Engineering”.

- 6.26.2017 【Activity】 The iCONM information delivery system was ready. The information of events of COINS or/and iCONM and related projects (seminars, symposium etc.) were sent by email. Please register on line via COINS or iCONM homepage.

- 6.29.2017 【Award】 Mr. Naoto Nakamura (Trainee of iCONM, The University of Tokyo, Cabral Lab.) received Poster Awards from the 70th Annual Meeting of Society for Free Radical Research Japan.

Editor's Note

The "in-body hospitals" that COINS seeks is a future vision of medical care that enables the support of health without mental and physical burden. The key to achieving this is the creation of "smart nanomachines" that circulate in the body 24 hours a day to detect, diagnose and treat disease autonomously. In the present issue, Theme 2 significantly handles the technical development of nanomachines to allow them to run through the body.

Our bodies have various barrier systems to protect us from external enemies and foreign bodies and sustain homeostasis. Among these biological barriers, the most difficult one for substances to pass is the blood-brain barrier (BBB) in the brain. So, in Theme 2, treatments effective for cranial nervous system diseases are being developed under the mission of "deliver drugs into the brain beyond the BBB" and venture companies have been established in order to proceed to social implementation. For details, see the Talk about Theme 2 (p. 2) and Research topics 1 (p. 8).

In Theme 2, the research and development of a novel nucleic acid drug "hetero-duplex oligonucleotide" has also been advanced. As hetero-duplex oligonucleotide has a higher therapeutic effect than previous antisense nucleic acids and siRNA, it is expected to be applied to treatment for cranial nervous system diseases by being mounted in the nanomachine. For details, see Researcher' s interview (p. 6) and Research topics 2 (p. 10).

It is said that innovative drug discovery requires a period as long as several dozen years. Where and how human resources for the future are fostered is an issue. In the iCONM Round-table talk (p. 12), we asked the future researchers engaging in research at the Innovation Center of NanoMedicine (iCONM) to talk casually about activities and human resource development in iCONM. You may see the cheerful and positive young researchers.

Dr. Kazunori Kataoka, Research Leader of COINS, was appointed as a foreign associate of the U.S. National Academy of Engineering. Being selected as an associate is the greatest honor in the field of engineering. This is a result of the appreciation of his life-long performance. Congratulations! In addition, iCONM is holding COINS seminars, inviting Professor Mark E. Davis, California Institute of Technology and other eminent researchers as speakers (topics p. 14). For the details of the seminars, sign up at Information or Information Provision pages on the COINS website.

The subject in the next issue is "the development of medical care-machine combination device for single day treatment of cancer" in Theme 5 and will be published in March 2018. I hope you look forward to this.

Finally, we are most grateful to those who were willing to cooperate in the publication of this newsletter despite their busy schedules.

Chief Editor: Takashi Sugimoto

Published by Center of Open Innovation Network for Smart Health (COINS),
Innovation Center of NanoMedicine (iCONM),
KAWASAKI INSTITUTE OF INDUSTRIAL PROMOTION,
3-25-14, Tonomachi, Kawasaki-ku, Kawasaki City, Kanagawa Pref. JAPAN
TEL: +81 44 589 5785 / FAX: +81 44 589 5789
http://coins.kawasaki-net.ne.jp/

Edited by NanoSky Editorial Board (Takashi SUGIMOTO, Yasutaka ANRAKU, Hiroya KUWAHARA, Shigehito OSAWA, Yuki MOCHIDA)
Writer : Ayumi KOJIMA
Camera: Aki TANAKA
Design: Studio L Co., Ltd.