Newsletter

NanoSky

From KING SKYFRONT to the world - NanoMedical Innovation

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Nanodiagnostic Technology Changes Future Medicine

Contents

Early detection of cancer by miRNA and exosome analyses

The mission of Theme 4 of the "Center of Open Innovation Network for Smart Health (COINS)" is "the development of a use-at-home cancer diagnostic method not involving blood sampling," which has the potential to change the current approach used in medicine. We have Professor Takanori Ichiki (Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo) who is serving as the leader, Hirofumi Shiono (Section Manager, 1st Development Section, 1st Development Department, Medical Business Development Division, Nikon Corporation) who aims to manufacture and market diagnostic devices, and Assistant Professor Ryo Iizuka (Laboratory of Bioanalytical Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo), who will demonstrate the feasibility of miRNA[*1] detection using the method, come together to discuss the purpose and progress of this innovation.

Ryo IIZUKA

Assistant Professor, Laboratory of Bioanalytical Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo; Visiting Scientist, Innovation Center of NanoMedicine (iCONM), Kawasaki Institute of Industrial Promotion

In 2004, he completed the doctoral program in Engineering at the Graduate School of Engineering, Tokyo University of Agriculture and Technology. After working as an Industry-Academia-Government Collaboration Researcher and a Project Assistant Professor at the Graduate School of Engineering, Tokyo University of Agriculture and Technology, a Research Fellow of the Japan Society for the Promotion of Science (PD), and a Project Assistant Professor at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, he has held his current position since 2012. He has also been serving as a Visiting Scientist at the Innovation Center of NanoMedicine since 2016. His expertise lies in protein science, biophysics, and bio-micro-/nanodevices. He aims to understand higher-order biological functions through molecular research.

Takanori ICHIKI

Professor, Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo; Principal Research Scientist, Innovation Center of NanoMedicine (iCONM), Kawasaki Institute of Industrial Promotion

He completed the doctoral program at the Department of Metallic Engineering, Graduate School of Engineering, The University of Tokyo, in 1995. He started his career as a Special Researcher under the Japan Society for the Promotion of Science (JSPS). During 1995–2004, he worked as Assistant Professor, Lecturer, and Associate Professor at the Department of Electric and Electronics Engineering, Toyo University, where he taught LSI microfabrication technology and bioelectronics. In 2004, he moved to the position of Assistant Professor at the Department of Institute of Engineering Innovation, and in 2006, he became the Associate Professor at the Department of Bioengineering, Graduate School of Engineering, The University of Tokyo. He then moved up to his current position. His specialization includes biodevices, microfabrication technology, and plasma engineering.

Hirofumi SHIONO

Section Manager, 1st Development Section, 1st Development Department, Medical Business Development Division, Nikon Corporation

In 1989, he completed the first semester of the doctoral program (MA) in organic synthetic chemistry at the Department of Science and Engineering, Graduate School of Engineering, Aoyama Gakuin University. He then joined Nikon Corporation, was affiliated to the Research Department from 1990 to 2000, and got reassigned to the Laboratory of Molecular Biophotonics from 1994 to 2000. He was involved with Materials R&D related to plastic lenses for use in spectacles and development of optical reagents used in biotechnology. From 2000 to 2003, he was involved in the development of new business in the field of biotechnology. In 2004, he was responsible for planning and developing a cell culture observation apparatus called the BioStation CT, in the Biomicroscope Development Department. He has been involved in medical R&D since 2010, and rose to the position of the R&D Manager with the establishment of the Medical Business Development Division in 2014.

Studying miRNA- and exosome-based devices as well as other analytical instruments

■ First, please introduce the kind of research you are doing now.

Ichiki: We are developing nanotechnology-based biodevices at the Department of Material Sciences, Graduate School of Engineering, The University of Tokyo.
Cell-based methods have been our domain of interest for more than 10 years, but we have recently shifted our focus toward developing miRNA-based diagnostic devices.

Exosome[*2] measurement becomes necessary when studying miRNA-based diagnostic devices; we are also evaluating different methods to study cancer-related exosomes (see pages 6, 8, and 10). Collaborative research with Professor Kazunori Kataoka is also underway because exosome evaluation techniques are thought to be useful in both diagnostics and therapeutics, especially because they can be used to characterize the nanomachines currently being studied at COINS.

Shiono: I am involved in the development of microscopes at Nikon for use in cell-based studies. Also, currently, I am affiliated with the Medical Business Development Division set up in 2014. I am stationed at the NanoMedicine Innovation Center (iCONM) and am responsible for working on new analytical devices and measurement devices for use in medicine.

Iizuka: I am engaged in searching for and creating functional biomolecules, and working on the functional analysis of proteins and supramolecular complexes using single-molecule measurement techniques. As a visiting scientist at iCONM, I am developing an automated microarray system for simple and rapid miRNA profiling in collaboration with Professor Ichiki, Mr. Shiono, and others.

■ Please tell us about the positioning of Theme 4 in COINS.

Ichiki: At present, treatment is administered to a patient. The objective of Theme 4 is to make the detection system smart enough to discover a disease before its onset and allow therapy. This will lower treatment costs.

We choose the methods used in large hospital laboratories and bring them into the clinical settings, while maintaining accuracy, and go ahead to making them available at home. This means that through new devices, we are trying to bring the methods used to monitor "illness" in hospitals closer to "health", before the onset of illness (Figure 1).
Early detection might just allow us to enable treatment outside the hospital premises.

In Japan, medical functions are available only at hospitals and the health insurance system is well in place, and therefore, if you are sick, it is common to go to a hospital to get treated.

However, Florence Nightingale, who laid the foundation of the medical treatment being provided in clinics and hospitals today, said, in a letter addressed to her cousin Henry Bonham Carter in 1867, "while dedicating my life to hospital work, I have reached the conclusion that it is not the best place for patients. .....The ultimate destination of all nursing is the nursing of the sick in their own homes. I look to the abolition of all hospitals and workhouse infirmaries, however it is no use to talk about the year 2000." (Fig. 2). The COINS' concept of an "in-body hospital" is to "bring diagnostics and therapy closer to us, from hospital."

Iizuka: In fact, treatment is so heavily restricted to hospitals that medical treatment might end up becoming unavailable in the event of natural and man-made disasters that can paralyze hospital functions.

Shiono: For example, elderly patients find it difficult to even reach the hospital. This concept of "in-body hospital" will definitely hold great social significance.

Figure 1. "In-Body Hospital" from Sick Care to Health Care

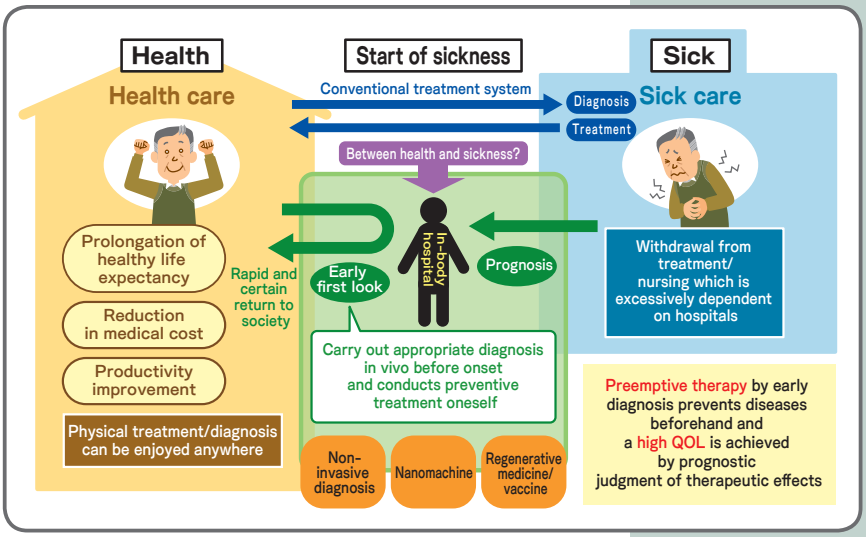


Figure 2

My view is, as you know, that the ultimate destination of all nursing is the nursing of the sick in their own homes. I look to the abolition of all hospitals and workhouse infirmaries. But it is no use to talk about the year 2,000.

From a letter to her cousin Henry Bonham Carter (1867)

Florence Nightingale

How about the progress and outlook of research?

Ichiki: The future prospects of fully automated, packaged cancer diagnostic devices for steps leading up to the separation/purification/detection of exosomal miRNA in blood that are currently being developed with the participation of iCONM, Nikon, The National Cancer Research Center, The University of Tokyo, Riken, and the Tokyo Medical and Dental University look good. Small prototype devices are also being evaluated (Figs. 3 and 4).

Iizuka: Although microarrays are effective tools for comprehensive detection of miRNAs, it takes one whole day to gather results. In combination with our original microarray method, the system being developed allows miRNA detection in 20 min.

Shiono: It is a fairly compact device, but I think that some kind of breakthrough is necessary to make it small enough for doctors to carry around. We believe that *in vitro* diagnosis using body fluids such as urine and saliva is favorable, but hurdles such as those regarding accuracy and safety arise when the general public uses it for themselves rather than healthcare workers.

Iizuka: I hope the diagnostic system is also available in places such as convenience stores. Then, people who buy self-test kits will get results on the site.

Shiono: Pharmacies are also a good option. People would be happy to get quick results.

Ichiki: We believe that preventive diagnosis using this device will not be popular unless health checkups can be conducted at a low cost.

Shiono: Although importance is attached to diagnosis at the site of treatment, it is difficult to judge the effectiveness of the treatment provided. Individual differences in the state of health or effects of treatment are obvious, and the effect of these differences will not be understood if it is not investigated before administration of treatment, when the patient is not unwell.

miRNA may be used as a biomarker[*3] to judge the effectiveness of such therapy.

Ichiki: It is not possible to quantify the effects and side effects of current medical treatment. Even if medicines are prescribed, patients do not consume them as instructed, and neither doctors nor patients are able to verify their effects. Many patients stop taking medicines because they think that they have been cured or give up treatment because they think they will not be cured.

Iizuka: Until now, the time-course of varying biomarker levels has been not examined in detail. Our diagnostic system would allow frequent monitoring of physical conditions by measuring the exosomal miRNA levels. We may be in a position to discuss general diseases, including cancer, if 50 of the 2,500 miRNAs are detected.

Ichiki: Specific cancers might be detected using several miRNAs. Nevertheless, it is noted by researchers in other fields that, because the human body is made up of various molecules, whether it can be judged using no more than several kinds of molecules.

Iizuka: I agree. For example, when the stomach and head hurt at the same time, one can anticipate extremely complex events in the body. In such a situation, it is better to compare the profile of exosomal miRNAs with that observed during normal conditions, because this is likely to yield information about the body. The drive toward personalized medicine was initiated in 2003 when the human genome was completely sequenced, but it is yet to be practiced in reality. I think that our approach would certainly advance personalized medicine in the near future.

Ichiki: Researchers in the US, who led the human genome project, are working on another project to gather samples from healthy individuals over a period of time, to further explore biomarkers that indicate the actual state of health.

This is an indispensable approach in preventive medicine. It is difficult to obtain samples from healthy individuals; such research requires time and money.

In Theme 4, we are developing inexpensive, large-scale, information-gath-

Figure 3. Development of an miRNA Diagnostic Device

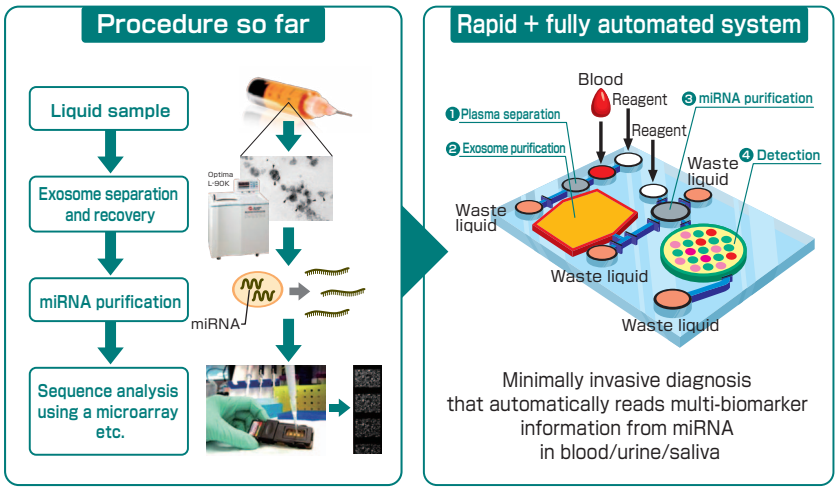


Figure 4.
Nano-Diagnostic Device NDX-2

ering devices, and would like to collaborate with biomarker researchers by sharing a common purpose. Because miRNA has not yet been clinically measured, the evaluation indices of new medical devices are being investigated, with institutes such as the National Institute of Health Sciences being on board.

Iizuka: The current diagnosis and treatment are based on the knowledge and experience accumulated over many years, and therefore, our concept of preventively measuring exosomal miRNAs and using it for use-at-home diagnostics and treatment seems challenging. Whether we can create something that can convince healthcare workers and thus overcome the historical barriers in medicine is, I believe, what we are now challenging.

Research speed and network attracts the attention of COINS

■ What do you feel about the COINS research system and iCONM?

Iizuka: The aim of COINS is clear, and it is good to be able to listen to the opinions of various individuals involved in research. For example, various kinds of microdevices have so far been developed. However, if these are created without understanding the actual need and use, they will remain unused. I feel the quality will differ depending on whether there is a clear way out.

Ichiki: That's right. The most important point about this project is to share the vision of the futuristic technologies. When researchers participate in one major project, they tend to focus primarily on what they want to do, but, in this case, the direction of research is unified while taking advantage of every original idea presented by every scientist.

Shiono: The process of determining vision and mission at retreat camps and the like is rather uncommon in the business sector. This brings about an awareness about the extent of participation in this project, doesn't it?

Iizuka: It is characteristic that research and development are rapid enough to adopt new changes. For example, if I want to try to use the device with a different channel structure, my co-researcher can prepare it quickly. If it succeeds, and this may not be the best example, it feels like assembling a radio-controlled model and exclaiming "It's good! It worked!"–simply because I could not fly radio-controlled models well as a child.

Ichiki: Even if we develop an elementary technology, for example, an miRNA detection method, we need engineers who can work together to take the technology to a point where it is turned into a device, refine it at the site of utilization, and integrate it into a medical system. Here, we have invested research funds and resources over a period of time; universities and businesses have participated, and we are literally bouncing ideas off each other. This would not have been possible based on basic research funds alone.

Iizuka: I think that repeated attempts to create and evaluate cutting-edge innovations are difficult for a single university, research institution, or company.

Shiono: I think it is characterized that we could work whole-heartedly toward it as a national project. The iCONM has assembled related areas such as biochemistry, organic chemistry, and nanofabrication, and has the necessary infrastructure and laboratory to safely undertake biological experiments. Thus, an environment consistent with its objectives is in place. It is also good to have so many exchange meetings and study meetings. You end up meeting new people within the company.

Ichiki: We usually never get to meet people from the medical industry. However, here, we are always able to communicate with each other and understand the varying thought processes prevalent in the industry.

Iizuka: In general, young academic researchers, including undergraduate and graduate students, have little chance to interact with people from different research communities. However, it will be possible here. I think iCONM is a great place to nurture people.

■ With COINS and iCONM systemizing and linking elemental technologies, this collaboration can achieve things, which neither a university nor an enterprise can, by incorporating cutting-edge research into innovative products and give rise to a new networking place. The yet-to-be-generated results of this research are already garnering a lot of interest, and we are all waiting in anticipation. Thank you very much.

(Interviewer: Science Writer Ayumi KOJIMA)

Terminology

＊1 miRNA (microRNA)
miRNAs are approximately 22 nucleotides in length, which post-transcriptionally regulate gene expression. The existence of miRNAs was first discovered in nematodes in 1993, and they are found in various organisms, including plants, and animals and viruses. miRNAs are involved in various biological events and diseases, and expected to be used as nucleic acid drugs and diagnostic markers. Most of extracellular miRNAs are encapsulated in exosomes.

＊2 Exosome
A lipid bilayer vesicle, ～100 nm in diameter that is secreted by many cells and encapsulates various molecules. Exosomes have recently been found to function as a communication tool between cells. They are actively being studied in detail.

＊3 Biomarker
An entity characterized by objective measurement to be an indicator of conventional biological processes, pathological processes, or pharmacological responses to therapeutic intervention. A biomarker is a living body-derived marker for understanding the physiological condition and disease state. The so-called tumor markers are examples of biomarkers.

Interview with Researcher

Takahiro OCHIYA

Chief, Division of Molecular and Cellular Medicine
Advanced Medical Biology Research, Treatment Development Group
National Cancer Center Research Institute

Connecting Exosomes and miRNA research to an understanding of Biological phenomenon and Healthcare

The diagnostic device being developed in Theme 4 in COINS aims to analyze miRNAs encapsulated in exosomes secreted from cancer cells. Takahiro Ochiya, Chief in the Division of Molecular and Cellular Medicine, National Cancer Center Research Institute is supporting basic research in this project. I asked Chief Field Manager Dr. Ochiya, who leads world exosome research, about current exosome research and the spread of exosome research.

To deepen our understanding of exosomes and elucidate mechanisms of disease

Once looked upon as the "cell trash can", exosomes have been studied on a smaller scale. Exosomes have been a major global topic in biology and medicine over the last 10 years since 2007 when it was first reported that exosomes contain miRNA (Figure 1).

Exosomes are nano-sized vesicles having a diameter of about 100 nm that encapsulate miRNAs as well as mRNAs and carry proteins and DNA information (Figure 2). Exosomes are conformed by a lipid bilayer similar to the one of the cell membrane, they have molecules such as proteins present on their surface and these are thought to be involved in exosome secretion and cellular uptake.

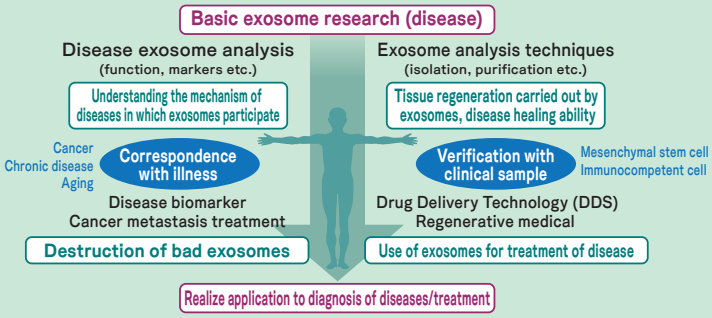
A function of exosomes that is currently drawing attention is their relationship with cancer malignant transformation including metastasis.

Chief Ochiya says "Many cancers metastasize to specific organs. In terms of which organ cancer metastasizes to, a new finding has been shown that this depends on the type of surface integrin on exosomes secreted from cancer cells. Integrin is a protein known to be a cell adhesion substance. It is speculated that exosomes are taken up into cells in organs that are metastatic targets guided by the exosome integrin, and various molecules in exosomes create an environment to draw in cancer cells." Furthermore, he explained that "our research results also clarified that specific exosomes are involved in brain metastasis of breast cancer. Exosomes destroying the brain blood barrier were secreted from breast cancer cells that are easily metastasized to the brain." (Figure 3).

Thus, secretion of exosome that conveys the signal of disease onset and deterioration, and inhibiting efforts on target cells may lead to the prevention of disease which is the subject of drug discovery.

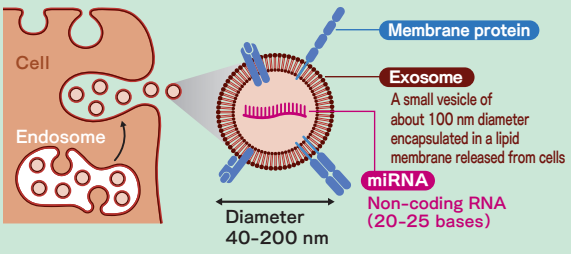
On the other hand, so to say "good exosomes" that do a good job has been studied. "In the field of regenerative medicine, for example, the use of mesenchymal stem cell exosomes and miRNAs that have the ability to differentiate into bone, blood vessels, and myocardial cells is being investigated". That is, strengthening the exosome working physiologically within the body helps maintain health. Originally exosomes were a communication tool secreted in response to the physiological status of the body and it is thought that the miRNA encapsulated therein is important. One reason is that there are two types of miRNA, one that emerges from dead cells into bodily fluid and circulates unchanged and one that circulates within the exosome, and it is speculated that the latter is a "spontaneous" message. Chief Ochiya *et al* calculate that about 37 % of the total RNA amount in the blood is contained in exosomes in the form of secretory miRNA. "I think that about 40 % of this miRNA is specifically encapsulated in exosomes and I believe this has meaning and has an important role. It is possible to understand the complexity of the body by understanding the important role carried out by exosomes. I also expect that it' ll lead to an understanding of diseases for which effective medicines have not been developed, for example, mental disease like depression and autism, and lead to the development of therapeutic agents." This seems to be a world apart from the image of exosomes which was once said to be a "cell's trash bin".

Figure 1. Basic Research into Exosomes and Scope of Application



The development of diagnostic/therapeutic methods targeting exosomes (bad exosomes) from cancer cells and the therapeutic application of exosomes (good exosomes) from mesenchymal stem cells in regenerative medicine are anticipated. DDS development of exosomes is also an important subject.

Figure 2. miRNA Secreted from an Exosome



miRNA is encapsulated by exosome and is stable over a long period even in blood. The presence of more than 700 miRNAs has been confirmed and it is possible to identify the primary cancer organs with relatively high accuracy only by analyzing a relatively few expression patterns.

Front-line Research for miRNAs and exosomes

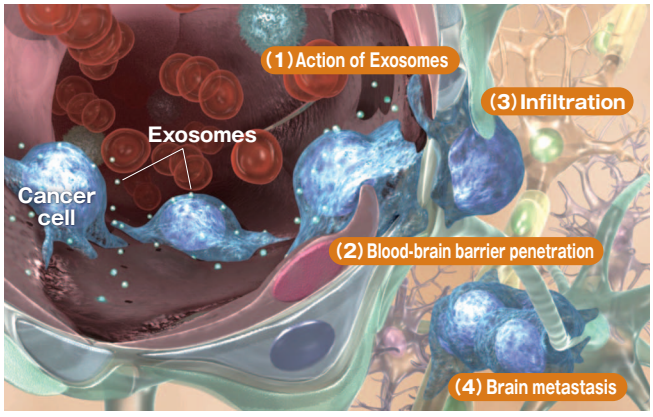
Chief Ochiya's research in this field began with a view to exploring the relationship between miRNA and cancer and applying it to therapy. From the latter half of the 2000s to around 2010, he examined miRNAs whose expression change in cancer cells and proved the therapeutic effect by replenishing those miRNAs to cancer cells in a mouse model that caused cancer and suppressing by administering nucleic acids of complementary sequence. After that, he analyzes the function of miRNAs whose expression is altered in cancer cells, and studied the relationship between drug resistance ability and miRNA and the relationship with cancer stem cells.

From 2007 onwards the scope of research has also expanded to exosomes. In 2010 he clarified, for the first time in the world, that exosomes envelop miRNA and function as an information transmitter, that mother's milk contains maternal miRNA and works in children's cells. Apart from studying the relationship between cancer malignancy and exosomes, he is also currently creating a database of exosomes and miRNAs from samples held in The National Cancer Research Center, searching for proteins in specific exosomes from cancers, and is developing early diagnosis methods using these samples. One of them is the method of early diagnosis of about 140 kinds of miRNAs with high sensitivity microarray chip on examination site for 13 kinds of cancer and dementia, and industrialization has come to be seen. "We will calculate combinations and detection frequencies of miRNAs with artificial intelligence, and will further give sensitivity and specificity. Anyhow, I would like to have the ability to investigate all 2500 miRNAs even at home."

Chief Ochiya expects that in the future new knowledge will be forthcoming from a combination of transcriptomes to analyze epigenetic DNA changes and mRNA and other biological information and, in doing so, thinks that the use of artificial intelligence in analysis is essential.

In COINS, he is developing technology for the detection and analysis of exosomes and miRNA for participation in Theme 4 and, using exosome surface molecules as clues, he is in the process of developing methods to find and measure exosomes (see p. 2, 8, and 10). "In COINS, natural nanoparticles such as exosomes and artificial nanoparticles such as polymeric micelles are studied at the same time. I am applying them to prevention and from ultra-early diagnosis to treatment and am focusing on their industrialization. Measurement methods cannot be developed nor can they be industrialized with only researchers working in basic research centered on biology such as ourselves. COINS has gathered researchers in engineering, pharmaceutical science and medicine and experts in many different fields such as business and intellectual property to form a particularly unique and useful project. If smart life care in daily life is achieved while unconsciously monitoring changes occurring within our bodies, we will be able to make a contribution to Japan which will have an aging society and increased medical expenses."

Figure 3. Novel Mechanism of Breast Cancer Metastasis to the Brain by Exosomes



(1) Exosomes secreted by breast cancer cells act on cells making up the blood-brain barrier, and (2) destroy the blood-brain barrier. (3) Cancer cells infiltrate the damaged blood-brain barrier and eventually (4) brain metastasis is established.

Exosomes may also be related to the evolution of living organisms

Chief, Ochiya is currently mainly studying cancer as a target but, of course, other diseases too as well as broadening his field of vision relating to the maintenance of homeostasis in humans and other living organisms, environmental factors and exosomes.

"Exosomes and miRNAs are present in many biological organisms regardless of their species. Moreover, the possibility that exosomes and miRNAs can transfer between different species began to be reported. Although it is known that miRNA inhibits bacterial invasion and promotes growth in plants, plant-derived miRNAs may act similarly in our bodies so exosome and miRNA research may lead to the development of supplements and superfoods that will make our bodies healthier."

Furthermore, Chief, Ochiya also predicts the involvement of species differentiation, the evolution of living things such as spontaneous mutations, and extracellular vesicles such as exosomes. "As I mentioned earlier, exosomes are conserved in many biological species. Exosomes also contain DNA fragments as well as transposases. It would be interesting to think of using them as a tool to create diverse evolution by incorporating a specific genomic unit into the genome of another person."

Although listening to the details of "cells chatting to each other" through studies of exosomes and miRNAs then elucidating the physiology of living organisms and making use of them in medical care and health broadens our interests, "I would like to put more emphasis on fundamental research as this is a research field where applications are expected" says Ochiya Chief expressing his ambitions.

(Notes: science writer Ayumi KOJIMA)

PROFILE

Takahiro OCHIYA

In 1988, he obtained PhD after completing the doctorial course at Graduate School of Medicine, Osaka University. After working as an assistant professor at Osaka University Institute for Molecular and Cellular Biology, he became a researcher at La Jolla Cancer Research Foundation in the United States in 1991 and chief researcher at the National Cancer Center Research Institute in 1992. In 1993 he was a director of the Laboratory of Molecular Oncology at the same institute and in 1998 he took on his present position as Head of the Cancer Metastasis Laboratory of the same institute. He has been serving both as a visiting professor in the Department of Advanced Science and Engineering at Waseda University since 2004 and a visiting professor at the School of Life Science and Technology, Tokyo Institute of Technology since 2008.

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New light on cancer diagnosis! Success in capturing nanoparticles released from cancer cells

"Cancer" was discovered. However, it was detected early so it can be treated."
The biggest therapeutic agent for cancer may actually be early diagnosis. It has recently been found that exosome secreted by cancer cells are useful in early diagnosis and this has attracted attention. In this study, a novel method to capture and detect exosomes secreted by cancer cells into the blood using an antibody was developed and possibility of early cancer detection was demonstrated. I hope that the number of people suffering from cancer will decrease in the future with early diagnosis using exosomes.

Yusuke YOSHIOKA
Researcher,
Division of Molecular and Cellular Medicine,
National Cancer Center Research Institute

Currently, cancer is treatable if found early so the development of diagnostic methods aiming at early diagnosis and the search for biomarkers are being actively conducted. Nanoparticles of around 100 nm in diameter secreted by various cells have recently attracted attention as new biomarkers. This nanoparticles are called exosomes and contain nucleic acids such as mRNA and miRNA and various proteins and circulates in body fluids[1]. Since exosomes secreted by cancer cells envelop specific molecules, attempts have been made worldwide to use these specific molecules in diagnosis by detecting exosomes secreted by cancer cells in body fluids such as blood and urine.

We focused on the protein present on the lipid bilayer membrane of exosomes and worked on the development of a new exosome detection method[2]. Conventional exosome detection methods mainly focused on Western blotting*1 so it was necessary to purify and concentrate exosomes using an ultracentrifuge. However, purification of exosomes by ultracentrifuge is time consuming, labor intensive and has a low throughput. When clinical application is intended, a high throughput method that eliminates the need for purification of exosomes, a highly sensitive detection system and multi-sample treatment are required. We developed a method to detect exosomes in a short period of time using an antibody that specifically recognizes proteins present on the exosome membrane and two types of beads (Figure 1 ExoScreen). As it was possible to detect exosomes using this method by simply mixing an exosome-containing solution (body fluid), antibody, and beads on a 96-well plate, high throughput was achieved and exosomes were extracted from 5 μL of healthy serum*2.

We then searched for proteins specifically contained in exosomes secreted by cancer cells in order to detect exosomes secreted by cancer cells. It was consequently found that a membrane protein called CD147 was common in exosomes secreted by colon cancer. As a result of attempting to detect serum exosomes from 194 colorectal cancer patients and 191 healthy volunteers using CD147 as a marker, it was shown that CD147-positive exosomes are extremely common in the sera of colorectal cancer patients. It is thought that colon cancer cells secrete this protein as CD147-positive exosomes decrease when tumor tissue is removed by surgery. Furthermore, as CD147-positive exosomes are detected in early colon cancer, which cannot be detected using the conventional biomarkers of CEA and CA19-9*3, new diagnostic methods using exosomes have demonstrated utility in early diagnosis (Figure 2).

If this is limited to colorectal cancer alone and if early cancer (stage I) can be diagnosed, then the 5-year survival rate will be almost 100%. However, as discovery is delayed because there are few subjective symptoms in the early stage, it is desirable that cancer can be accurately discovered by a less invasive blood test such as this method. By advancing our research results in the future, it is thought that it can be applied not just to colorectal cancer but also to pancreatic cancer which is said to be difficult to detect early. Day to day we are working on the development of diagnostic methods using exosomes aiming at "early diagnosis is the best treatment".

Figure 1. Summary Figure of ExoScreen Method

Exosomes secreted from cells bind to 2 kinds of bead (donor bead and acceptor bead) via an antibody. The oxygen molecules around the donor beads are converted to singlet oxygen ($^1O_2$) when irradiated with light at 680 nm. When this singlet oxygen reaches the acceptor beads, the acceptor beads emit light. The amount of exosomes present in body fluids can be measured from the intensity of this emission. In this case, the amount of exosomes from cancer cells can be measured by using antibodies against specific molecules present in the exosomes secreted by cancer cells and this is usable in diagnosis.

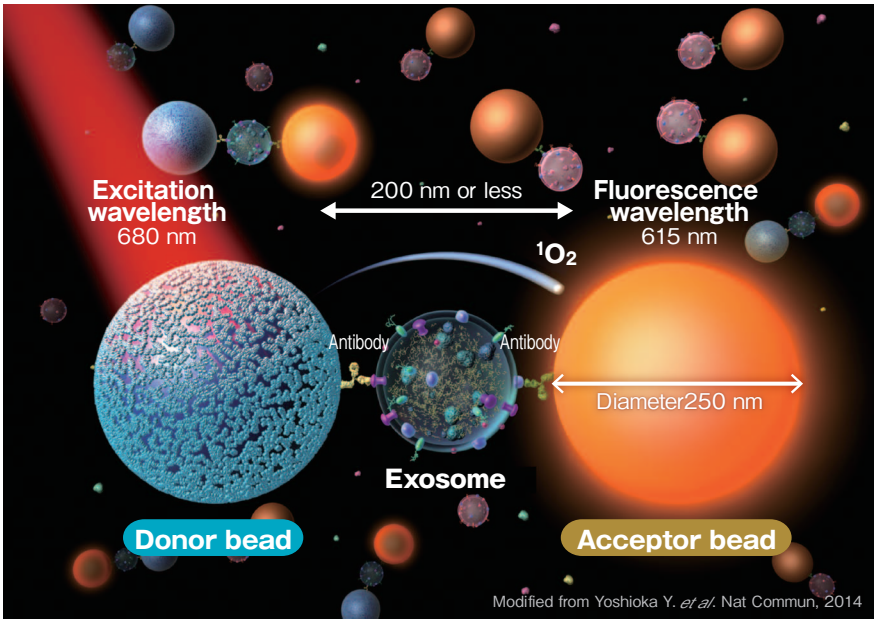
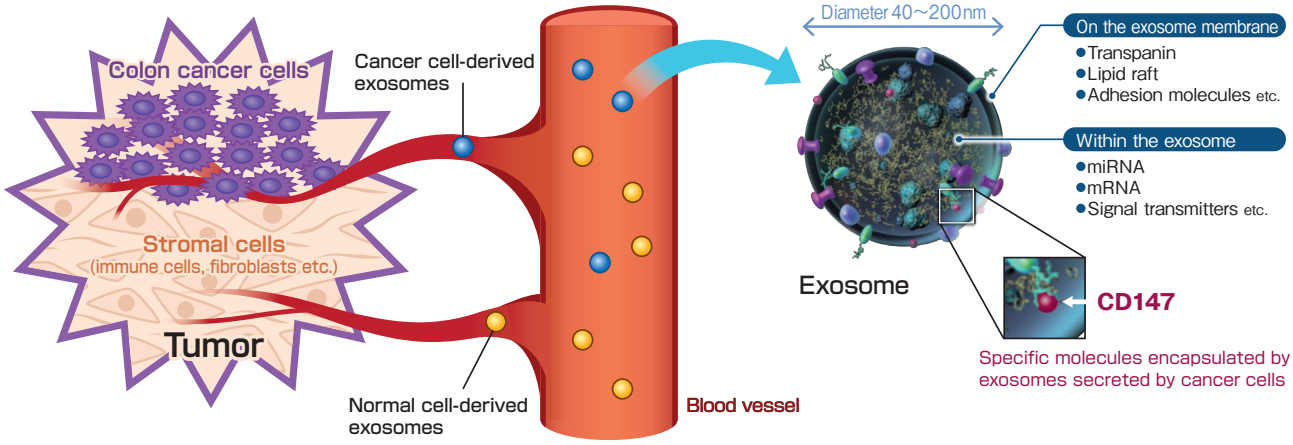


Figure 2. Specific Exosomes Secreted by Cancer Cells



Exosomes are secreted not only from cancer cells but also from normal cells and circulate in human body fluids. The exosomes secreted by cancer cells, however, contain specific molecules and, as an example, exosomes secreted by colon cancer cells contain CD147. Early colon cancer can be discovered by detecting exosomes in blood using this molecule as a marker.

Terminology

＊1 Western blotting (immunoblotting)
A typical method to detect specific proteins. Proteins are separated according to molecular weight by electrophoresis using polyacrylamide gel and are then transferred onto a membrane. The target protein is detected on this membrane by immunostaining using an antibody that recognizes the protein.

＊2 Serum
The liquid component of blood after the cellular component has been removed. It contains no coagulation factors since blood cell components coagulate and clots precipitate upon centrifugation. It is used in many biochemical blood tests.

＊3 CEA, CA19-9
Both are used as tumor markers of gastrointestinal carcinoma. However, since they are difficult to detect in early patient blood, they are often used in the evaluation of therapeutic effect by treatment intervention, and are not used in blood tests such as examinations.

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Starry sky observations in microspaces? Development of a revolutionary nanoparticle analysis system

The development of diagnosis and treatment using particles (nanoparticles) having a diameter of about 100 nm such as exosomes and polymer micelles is advancing. The importance of analyzing individual particles is increasing in the development of nanoparticle applied technology. Nevertheless, in conventional instruments it was not easy to measure these particles individually. In our research, we have developed a system that tracks and analyzes the movement of nanoparticles in microchannels using scattered light. This system is expected to speed up research and development of nanomedicine and contribute to the realization of new diagnostic methods and treatments.

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Department of Bioengineering, Graduate School of Engineering,
The University of Tokyo

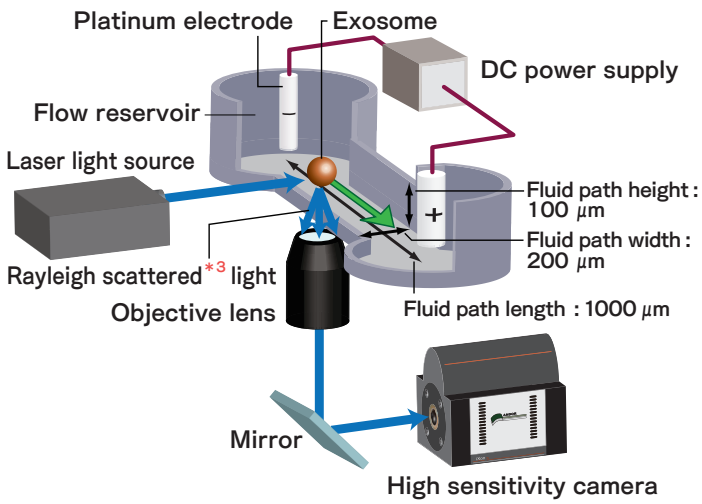
The development of medical technology using 100 nm diameter particles such as exosomes and polymer micelles has been actively conducted recently. For example, if it is possible to detect exosomes secreted from abnormal cells such as cancer cells among the exosomes present in blood, the presence of abnormal cells in the body can be determined. Moreover, in drug delivery systems (DDS) using polymer micelles, drugs can be delivered to specific sites only, so effective drug treatment can be carried out. In the development of technologies for medical applications of these nanoparticles, the importance of single particle measurement technology in analyzing various nanoparticle clusters is increasing. It was, however, not easy to measure nanoparticles individually using conventional apparatus so I have developed a single-particle detection system for nanoparticles that uses a microfluidic chip by combining laser dark-field illumination with high-sensitivity imaging. This system consists of a polydimethylsiloxane (PDMS) polymer microfluidic chip and a platinum electrode, a high voltage power supply, a laser light source, and a high sensitivity camera. The equipment configuration and a prototype system are shown in Figure 1.

After introducing the nanoparticle sample into the flow path, scattered light is generated by the particles when an incident laser beam is shone from the side of the chip. When this scattered light is focused with an objective lens and imaged with a high sensitivity camera, the bright spots of twinkling and flickering nanoparticles are observed in microspace as shown in Fig. 2a.

Quantitative information on particle concentration, particle diameter distribution, surface potential (zeta potential[*1]), and surface molecules (surface markers) can be obtained for each particle by tracking and analyzing these bright spots.

Figure 2b shows an example of exosome analysis carried out as a model experiment. The exosome sample was prepared from a cultured human breast cancer-derived cell line (Sk-Br-3 cells) by purification from culture supernatant with density gradient centrifugation using fraction ultracentrifugation and a density gradient centrifugation medium (OptiPrep). The exosome sample was allowed to react with an anti-CD9[*2] antibody or a control antibody (IgG) not bound to CD9, and this was then introduced into a microfluidic chip for measurement. There was no significant difference in particle diameter distribution between exosomes reacted with anti-CD9 antibody or control antibody. A significant difference was, however, observed for the zeta potential of exosomes that reacted with the control antibody having negative potential and exosomes that reacted with the anti-CD9 antibody having a positive potential. The difference in zeta potential is thought to be because of the positive charge of the anti-CD9 antibody bound to the exosome surface. It was demonstrated in this experiment that a small amount of CD9 protein present on the exosome surface can be evaluated using a change in zeta potential as an index. This system will accelerate the research and development of medical technology using nanoparticles, and it is anticipated that new diagnostic methods and treatments will materialize.

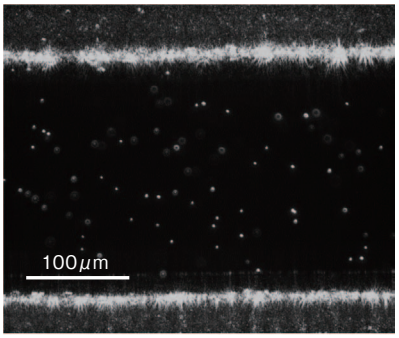
Figure 1. Device Configuration of a Microfluidic Chip-type Nanoparticle Analysis System



This is composed of a laser dark-field microscope optical system and a microfluidic chip made of PDMS. The laser beam that forms a sheet-like shape is shone from the side of the flow path, the scattered light generated by particles in the flow path is focused by an objective lens below the flow path, an image is formed with a high sensitivity camera and a high contrast dark-field image results. In dark field imaging*4, it is possible to individually detect nanoparticles with a size less than the diffraction limit of light that cannot be detected by illumination using general transmitted light.

Figure 2. Example of Analysis of Exosomes Derived from Human Breast Cancer Sk-Br-3 Cells

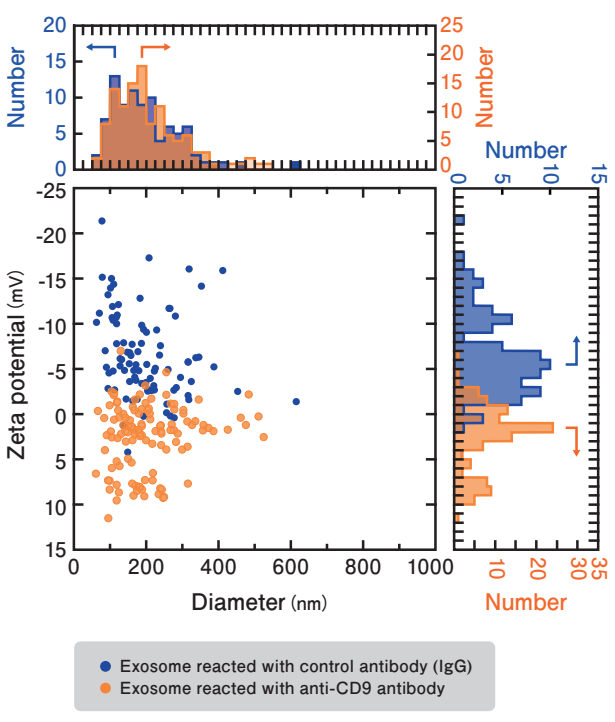
a



a. When a sample having exosomes dispersed within it is introduced and positioned in a dedicated measurement device, the exosomes can be detected and it is possible to see an image which is like a starry sky.

b. Particle diameter measurement by Brownian motion analysis and zeta potential measurement by electrophoretic analysis are performed consecutively for individual exosomes so that the measured values of particle diameter and zeta potential are associated with individual particles. This shows an example of analysis of exosomes derived from the culture supernatant of human breast cancer Sk-Br-3 cells. Measurement is carried out after treatment with the exosome markers, anti-human CD9 antibody and control antibody, and a change in zeta potential caused by binding of antibody to the marker protein on the exosome surface is observed.

b



Terminology

＊1 Zeta potential
An electric potential that attracts and fixes ions with opposite charges in an electrolyte due to the charge generated on the surface of the substance. The zeta potential of an exosome can be understood from measurement of the speed of exosome migration when a voltage is applied to a solution in an electric field in which exosomes are suspended.

＊2 CD9
A type of tetraspanin protein assumed to mark exosomes.

＊3 Rayleigh scattering
Light scattering by tiny particles smaller than the wavelength of light.

＊4 Dark-field imaging
A method of observing high contrast and microstructures in observations using a microscope by observing scattered light generated in a sample being observed.

References

Akagi T, *et al.,* PLoS ONE, 10, e0123603 (2015)

Listen to COINS' Members

What w

Analysis of miRNA and DNA in body fluids is thought to be useful in the diagnosis of cancer and the like. We are developing a microfluidic chip to simply conduct such analysis.

Kazuo HOSOKAWA

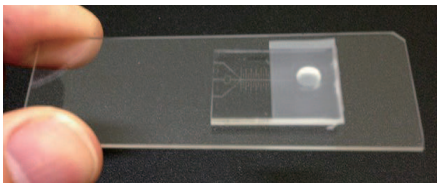
Senior Research Scientist
RIKEN
Maeda Bioengineering Laboratory

Analysis of a nucleic acid biomarker using an original microfluidic chip

miRNA is an RNA which is not translated into protein, contains about 22 bases, and regulates gene expression in cells. It has recently been found that miRNA is also present in body fluids such as blood and it is thought possible to diagnose cancers by analyzing specific miRNAs in blood. Conventionally, quantitative PCR has been used for this purpose but requires a complex procedure taking 2-3 hours and this is difficult to conduct in the clinic or at home.

We are developing microfluidic chips where miRNA analysis takes about 20 minutes by simply introducing samples and reagents. The chip is made of rubber and glass known as PDMS and there is a Y-shaped microchannel on the bonded surface. PDMS takes in air so samples and reagents placed by the entrance of the channel automatically flow into the chip. The specific miRNA present in the sample binds to DNA immobilized on the glass surface and then binds a fluorescently labeled reagent molecule for detection.

Recently however, we have tried to apply microfluidic chips not only to the analysis of miRNA but to DNA methylation as well. DNA derived from cancer cells is also present in blood and it has been found that it has a characteristic methylation abnormality that is related to the type of cancer and malignancy. When the methylation of DNA is analyzed using a microfluidic chip, a specific sequence of DNA is bound to the DNA on the glass surface and the methylated cytosine base binds to antibody. We are aiming at practical application of this chip as soon as possible and we are pushing our research forward every day.



Microfluidic chip under development.

We are developing *in vitro* diagnostic devices for POCT (Point of Care Testing) that can process a sample and return the results in a short time.

Ryo KOBAYASHI

NIKON Corporation
R&D Department, Medical Business Promotion

The appeal of cutting a way through without a road

Do you know the sport of orienteering? This competition is a sport of navigation around successive check points drawn on a map and competing on a time basis to the goal. In Japan, the image of camping school recreation is deeply rooted but it is, in fact, a very tough competition competing for even a 1 second advantage by running practically from the start to the goal. The areas where the competition takes place are often in forests near villages but recently competitions have also been held in parks and on university campuses. I came across this sport when I was a student and I have been enthusiastic in travelling overseas to represent Japan. Even after becoming an adult, I frequently find a nearby race and take part. Although roads are also shown on orienteering maps they are not necessarily the fastest route. I often you go over a mountain ridge, go through thickets, and jump over streams. The real thrill of this sport is instantaneously reading topography and aiming at the goal by cutting a way through by oneself, and this is the thing I'm addicted to.

In my company, I am in charge of developments in the medical field, which is a new business for us, and we are collaborating with the Ichiki Laboratory which is my old laboratory. While using cutting-edge equipment at iCONM, we open new paths and push research and development forwards day by day in order to realize "rapid diagnosis". The more you research, the more the things you don't know emerge on a daily basis and, although this is serious, I'm filled with excitement, I really enjoy it and I feel fulfilled every day.

The situation at Yatsugatake's race. I run hard without a road.

e treasure

Akira MATSUMOTO

Associate Professor
Tokyo Medical and Dental University Institute of Biomaterials and Bioengineering

When the molecular recognition ability of boronic acid is skillfully combined with materials, it is possible to achieve multi-level environmental responsiveness and functionality. We are conducting biological measurement and DDS research which cleverly utilizes this system.

Aiming to develop "boronic acid engineering" having outstanding compatibility with biomolecules

Boronic acid interacts with various biomolecules, and its selectivity is synthetically chemically variable. It is also known as “boronolectin” because of its binding to carbohydrate. Molecular recognition involving boronic acid causes changes in physical properties synchronous with its dissociation equilibrium and this can lead to various functionalities by incorporating them into material design.

I am fascinated by this characteristic and conducting medical engineering research by paying a lot of attention to "making it readily available". We have recently focused on the development of an artificial pancreas by application of boronate gel in particular. An existing artificial pancreas for the treatment of diabetes comprises a machine equipped with a power supply, a motor, a microcomputer etc. but we have created an artificial pancreas-like, blood sugar-dependent insulin supply mechanism using only boronate gel and have already demonstrated its safety and therapeutic efficacy in small animals. It is inexpensive and robust and, because it has high affinity for existing medical devices such as needles and catheters, it is possible to create a “just pierce and paste artificial pancreas”. It is expected to form the next-generation technology to solve unmet medical needs in diabetes (long-term blood sugar control, avoidance of hypoglycemia, reduction in patient burden). I feel strongly about the potential of "boronic acid engineering" which involves superb affinity to biomolecules and creates dynamic function. I would like to contribute to the realization of an 'in-body hospital' while proposing a unique method of use for them.

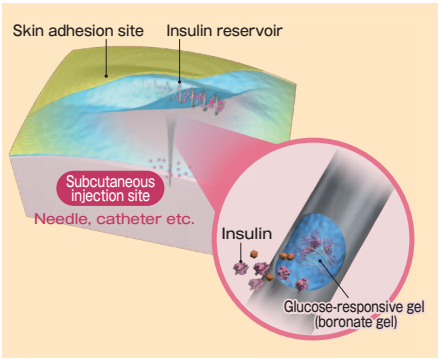
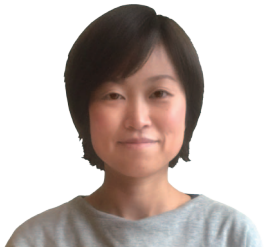


Image of a “just paste artificial pancreas" which combines boronate gel and minimally invasive subcutaneous injection technology.



I have been affiliated with the Ichiki Laboratory since April 2016 and am carrying out research into diagnostic devices aiming at achieving minimally invasive cancer diagnosis using miRNA testing.

Fumi TOSHIOKA

Research Assistant
Ichiki Laboratory
Innovation Center of NanoMedicine, Kawasaki Institute of Industrial Promotion

As a working mother, I want to respond to my daughter's smile

I have been engaged in research into cancer diagnostic markers and improved drugs for lifestyle diseases in the area of biochemistry such as protein analysis using cultured cells. When I heard about the COINS project, I initially wondered what diagnostic devices, which were in a completely different field of engineering research from mine, were? It was a starting point. When I went to visit the Innovation Center of NanoMedicine, I didn’t know what some of the instruments measured although I’d heard the names from familiar devices, and I was curious about this interesting place. Researchers from many institutions are conducting research all under one roof and it was extremely open and I felt the closeness of the gap with society. When I worked in a clinical investigation company, conventional cancer diagnosis was made by biopsy of a pathology sample and diagnosis took 2-3 days with cytodiagnosis by a pathologist. Furthermore, it is likely that mistakes with samples occur as samples pass through the hands of many people in preparing them. It was actually a chilling moment. If diagnostic devices linked to research are placed in hospitals, accurate and rapid diagnosis may be possible.

I have a 5-year-old daughter who has been to nursery school since she was less than one year old. Although I am anxious about working while trusting small children, each morning she send me on with a smile and say, “Good luck with your work today!” I want to cherish the time spent with my child and one day I can say that “Your mother helped create this diagnostic device”.

My 5-year-old daughter full of energy.

3rd COINS International Symposium

Towards Smart Health Society
～Challenge of Kawasaki based Medical Innovation～

The first international symposium in Kawasaki was held on Thursday, December 15 with the theme of "Towards Smart Health Society～Challenge of Kawasaki based Medical Innovation～" at Kawasaki City Industrial Promotion Hall. The number of the participants has reached nearly 300, and it was a great success to open up the spare second floor seats. Unlike the past two symposiums, the proportion of visitors from industries and general was higher than that of universities and research institutions. We could see that the interest in COINS efforts was very high.

The symposium started with opening remarks of Dr. Yuzuru Matsuda, Vision 1 Visionary Leader, JST Center of Innovation (COI) program (Former president of Kyowa Hakko Kirin Co., Ltd.). After introducing COI program, he expressed high expectation to COINS and Kawasaki city.

In session 1 「Medical Innovation/Forefront of Technology」, after introducing COINS' major research outcome, Dr. Xiaoyuan Chen, Senior Investigator and Lab. Chief (NIH) and Professor Wim Hennink, Department of Pharmaceutics, Utrecht University gave talk on "Albumin-Binding Evans Blue Derivatives as Theranostics" and "Polymeric Micelles for Targeted Drug Delivery".

In session 2 「Forefront of Medical Innovation Eco-System」, after COINS effort being introduced, Mr. Peter Takizawa, Senior commercial officer of Life Science, Danish Embassy gave talk on "Medicon Valley – A Danish-Swedish Life Science Cluster".He explained that 60% of the employment in the life sciences field in Denmark and Sweden is in Medicon Valley, that 99% of the markets targeted by companies in Medicon Valley are overseas markets, and it is easy to change job or start up new business because the move between the companies is flat. This indeed impressed the audience.

In poster session, 28 posters were presented by COINS participating researchers, organizations and local government and there were active discussions and exchanges between the participants with coffee in hands.

Yuzuru Matsuda
Visionary Leader,
COI Program Vision 1

Xiaoyuan Chen
Senior Investigator and
Lab Chief,NIH

Wim Hennink
Professer, Department of
Pharmaceutics, Utrecht University

Peter Takizawa
Senior commercial officer,
Life Science, Danish Embassy

Ryuta Nomura
Chairman of the Board and chief executive officer, Central Institute for Experimental Animals (CIEA)

Osamitsu Yamada
Chairman, Kawasaki Chamber of Commerce and Industry (Kawasaki CCI)

In final panel discussion, as theme of Innovation through community collaboration, the session started with greetings by Mr. Ryuta Nomura, Chairman of the Board and chief executive officer, Central Institute for Experimental Animals (CIEA) and Mr. Osamitsu Yamada, Chairman, Kawasaki Chamber of Commerce and Industry (Kawasaki CCI) and followed with short presentations by Mr. Kazuhiko Tamai, Department Director, Headquarters International Strategy Promotion Department, Kawasaki City Coastal Area International Strategy, Mr. Hideki Kaji, Vice Chairman, Kawasaki Chamber of Commerce and Industry (Kawasaki CCI) Senior Adviser, Mr. Toru Kawanishi, Director General, National Institute of Health Sciences (NIHS) and Mr. Keitaro Takebayashi, Division Director, DaiwaHouse Industry Co., ltd. After short presentation, there was a panel discussion, having Dr. Hiromichi Kimura as a moderator, with Mr. Hideki Kaji, Mr. Toru Kawanishi, Mr. Keitaro Takebayashi, Mr. Peter Takizawa Ahlenius and Prof. Kazunori Kataoka as panelists. There was a real intention discussion on future of King SkyFront and the task was shared with all including the audience.

In the questionnaire, almost 90% of participants said they were satisfied with the symposium, and there were many positive feedback such as "I'm expecting the activities of COINS based in Kawasaki" "I want to have some kind of relationship" "I want you to hold a symposium in Kawasaki from now on". COINS is in the stage of advancing social implementation of the research outcome of Phase 2, and the contact with society is more important than ever.

This symposium was a great opportunity for people and companies to be interested in research of COINS and it was a meaningful time to further strengthen determination towards the realization of a smart life care society that departed from Kawasaki.

(Report by Takashi SUGIMOTO)

Panelist
Kazunori Kataoka
Director General &
COINS Research Leader,
Kawasaki Institute of Industrial Promotion
Innovation Center of NanoMedicine

Panelist
Peter Takizawa
Senior commercial officer,
Life Science section,
Danish Embassy

Panelist
Keitaro Takebayashi,
Division Director,
Building division, Tokyo Head office
Daiwa House Industry Co., ltd

Panelist
Toru Kawanishi
Director General,
National Institute of
Health Sciences

Panelist
Hideki Kaji
Vice Chairman,
Kawasaki Chamber of Commerce
and Industry (Kawasaki CCI)

Moderator
Hiromichi Kimura
COINS Project Leader,
Kawasaki Institute of Industrial Promotion
Innovation Center of NanoMedicine

Panel discussion

Topics June 2016 – December 2016

- 6.30 – 7.1.2016【Award】Mitsuru Naito, Visiting Researcher, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo received an Excellence Presentation Award (oral) at the 32nd Annual Meeting of the Japan Society of Drug Delivery System on June 30 – July 1. Award title: 「Organic/inorganic hybrid multilayered nanocarriers with controllable ligand density for targeted siRNA delivery」(Co-author: Ryota Azuma、Hiroyasu Takemoto, Mao Hori, Shigehito Osawa, Kim Hyun-Jin, Takehiko Ishii, Nobuhiro Nishiyama, Kanjiro Miyata, Kazunori Kataoka).

- 7.5.2016【Activity】 14 members of OSONG Medical Innovation Foundation from Korea visited iCONM.

- 7.19.2016【News】 The paper "Nanomedicines Eradicating Cancer Stem-like Cells in Vivo by pH-Triggered Intracellular Cooperative Action of Loaded Drugs" of Dr. Hiroaki Kinoh, Principal Research Scientist (Deputy Head, Kataoka Kinoh Lab./ Visiting Scientist, The University of Tokyo) and Dr. Horacio Cabal, Associate Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (Visiting Scientist, iCONM) et al. which was published online of ACS Nano, one of the top journal within Nanotechnology field was introduced as most read article in one month in "Most Read Articles" column.

- 7.29.2016【News】The research outcome of iCONM was carried in "Research highlight corner" of WEB newsletter Kawasaki SkyFront i-Newsletter Vol.7 which is run by Kawasaki city.

- 7.29.2016【Activity】 Students from Kawasaki city high school for Science and Technology visited iCONM.

- 7.31.2016【News】 The related article of Joint Press Conference that took place in 5.16 was published in Kanagawa Shimbun. Title: New contrast agents with Nanotechnology - Cancer tissue structure clearly visible

- 8.9.2016【Activity】 "King SkyFront Summer Science Event 2016" was organized by Kawasaki city. 300 primary students visited iCONM.

- 8.13.2016【News】 The article of research that Dr. Kazunori Kataoka, Professor, The University of Tokyo (COINS Research Leader) and Dr. Yasutake Anraku, Assistant Professor, Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 2 Leader) are pursuing as playing a central role was published in Nikkei Shimbun.

- 8.17.2016【News】 The article of development of anticancer agent by one of the COINS' participating companies Nanocarrier Co. Ltd. was published in Nikken Shimbun.

- 8.23.2016【Activity】Mr. Katsuaki Watanabe, Advisor of Toyota Motor Corporation and Mr. Sadayuki Tsuchiya, former Deputy Minister of MEXT visited iCONM.

- 8.25 – 8.26.2016【Activity】"JST Fair 2016 – Creation of Future Industries by Science and Techology" organized by JST was held in Tokyo Big sight. COINS set up a booth for project introduction exhibition and introduced the research outcome.

- 8.31.2016【Activity】Mr. Paul de Jersey, Governor of Queensland Australia visited iCONM.

- 9.7 – 9.9.2016【Activity】JASIS - an Asia' s largest Analytical instruments and scientific instruments special exhibition was held at Makuhari Messe International Exhibition Hall. Ichiki Lab. from COINS exhibited.

- 9.11.2016【Activity】Science and Technology Department of Embassy of the Socialist Republic of Viet Nam to Japan visited iCONM.

- 9.14.2016【Activity】Mr. Moshe Bar-Siman-Tov, Vice Director General, Israel Ministry of Health Mission, a chief scientist of Israel Ministry of Health and Embassy of Israel visited iCONM.

- 9.15.2016【Activity】 "Medicine-Engineering collaboration Forum in Kawasaki" organized by Kawasaki City was held and iCONM tour was arranged.

- 9.19.2016【News】Interview article of Dr. Liu, Xueying, Research Scientist was published on WEB Newsletter "Kawasaki Innovation Gateway" Vol.3 which is run by Kawasaki city.

- 9.21.2016【News】Thomson Reuters reported that iCONM Senior Research Associate Yasuhiro Matsumura (Division Head, Division of Developmental Therapeutics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Japan) was awarded in the Thomson Reuters Citation Laureates 2016 as a likely candidate to win a 2016 Nobel Prize.

- 9.30.2016【News】Dr. Kazunori Kataoka, Director General (Professor Emeritus, The University of Tokyo) and Dr. Yasuhiro Matsumura, Principal Research Scientist, (Division Head, Division of Developmental Therapeutics, National Cancer Center Exploratory Oncology Research & Clinical Trial Center) were introduced as the Kawasaki based world class scientists who have outstanding research results in Kanagawa Shimbun.

- 9.30 – 10.1.2016【Activity】COINS retreat camp was held at Shonan International village.

- 10.6.2016【Activity】Students from Fukuoka Kasumigaoka High School visited iCONM as a part of extracurricular activities.

- 10.7.2016【Activity】COINS Seminar #19 was held at iCONM.
  Lecturer : Prof. Won Jong Kim (Department of Chemistry Polymer Research Institute, Pohang University of Science and Technology (POSTECH) Center for Self-assembly and Complexity, Institute for Basic Science (IBS)
  Title : "Polymer-based Nitric Oxide Delivery System for Bioapplication"

- 10.8.2016【Activity】Students from Fukuoka Kasumigaoka High School visited Ichiki Lab. The University of Tokyo which is one of the COINS participating institutions as a part of an extracurricular activities.

- 10.12.2016【News】The article of Nanomachines which has been developed by Dr. Kazunori Kataoka, Professor, Graduate School of Engineering, The University of Tokyo was put on Newsweek website.

- 10.13.2016【Activity】Students from International Section, Kawasaki Tachibana High School visited iCONM as a part of extracurricular activities.

- 10.13.2016【Activity】The delegation of Academic Research & Industry - Academia - Government Collaboration, Nagoya University and The University of Minnesota with the connection to Nagoya University visited COINS.

- 10.20.2016【Activity】The delegation of Healthcare Innovation visited COINS from Netherland.

- 10.20.2016【Activity】COINS Seminar #20 was held at iCONM.
  Lecturer: Dr. Michael Sprenger (Senior adviser for IT & innovation, National Institute for IT in Healthcare, Technical University of Eindhoven)
  Title : "The Implementation and Strategy of ICT in Healthcare in the Netherlands"

- 10.25.2016【Activity】COINS Seminar #21 was held at iCONM.
  Lecturer: Dr. Emmanuelle MARIE (Researcher, The National Center for Scientific Research)
  Title : "Polymer coatings for dynamic adjustment of specific and non-specific interactions for cell culture"

- 11.1.2016【Award】Dr. Keiji Itaka, Leader of Theme 3 (Project Associate Professor, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo /Principal Research Scientist, Innovation Center of NanoMedicine(iCONM) was awarded Best Abstract Presentation Award at the 4th International mRNA Health Conference.

- 11.11.2016【News】The paper (refer to News report of 7.19)published in ACS Nano was chosen as one of the Frequent Downloaded Articles and its video was distributed.

- 11.15 – 11.17.2016【Award】Mitsuru Naito, Visiting Researcher, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo received Kawahara prize at the 2nd Annual Meeting of Nucleic Acids Therapeutics Society of Japan held on November 15 – 17, 2016. Awarded title: 「Design and characterization of multilayered hybrid nanocarriers with controllable peptide ligand density」(Co-authors: Hiroyasu Takemoto, Kim Hyun-Jin、Mao Hori, Shigehito Osawa, Nobuhiro Nishiyama, Kanjiro Miyata, Kazunori Kataoka).

- 11.16.2016【Activity】Danish International Market Development Committee visited COINS.

- 12.1.2016【Activity】Institut Teknologi Bandung, ITB, Research Center for Nanosciences and Nanotechnology (NRCN) visited iCONM.

- 12.1.2016【Activity】COINS seminar #22 was held at iCONM.
  Lecturer: Dr. Ernst Wagner (Professor and Chair, Pharmaceutical Biotechnology, Ludwig Maximilians-Universität München, Nanosystems Initiative Munich:NIM)
  Title: Nucleic Acid Nanoparticles for Cancer Therapy

- 12.9.2016【News】The paper "Poly(ethylene glycol) crowding as critical factor to determine pDNA packaging scheme into polyplex micelles for enhanced gene expression" which was published online Biomacromolecules was introduced in ACS Editors' Choice.

3rd Retreat Camp

A retreat camp was held under the theme of "How to implement In-body hospitals" at Shonan Village Center on Friday, September 3 and Saturday, October 1, 2016.

For this time, with the aim of strengthening the team building toward the realization of "In-body hospitals", we set a goal to deeply discuss and share the image and tasks at the time of realization of "In-body hospitals".

On the first day, there were group discussions on "Image of In-body hospitals you draw" and "Task of social implementation with innovative technology" responding to a talk "Tasks of practical realization of innovative technology (regenerative medical products et al. as examples) of Mr. Daisaku Sato, Safety measures manager, Health, Medical care, Ministry of Health, Labor and Welfare

On second day, responding to Dr. Koichi Murashita, Vice Director (in charge of research) and Professor, Hirosaki University / Strategy Advisor, COI Research Promotion Organization (Graduate School of Medicine)' s talk "Aim to realize "Lifetime Innovation" – Challenge of Hirosaki COI, where industry, academia and government gather as returning short-lived prefecture as a banner mark and Mr. Tetsuo Hasegawa, Manager for External Affairs for Global Technology, R&D Engineering Management Headquarter, Nissan Motor Corporation' s talk " Various problems accompanying introduction of automatic driving technology" , there were group discussions on how to overcome the problem, presentation of their summary and finally we had three talks of Mr. Haruhiko Manabe, Assistant of Vision 1 Visonary Leader, COI program, JST, Mr. Kazuhiko Tamai, Department Derector, Headquarters International Strategy Promotion Department, Kawasaki City Coastal Area International Strategy, and Dr. Tatsuro Irimura, COINS Advisory Board, Professor, Graduate School of Medicine, Juntendo University.

In this retreat, participants who actively discussed while crossing the theme and age barriers, interworking knowledge gained from the lecture stand out. The retreat was meaningful to deepen understanding by sharing the way to realize in body hospital and issues to be overcome in the future.

(Left) **Daisaku Sato**
Safety measures manager, Health and Medical care, Ministry of Health, Labor and Welfare

(Center) **Koichi Murashita**
Vice Director (in charge of research) and Professor, Hirosaki University / Strategy Advisor, COI Research Promotion Organization (Graduate School of Medicine)

(Right) **Tetsuo Hasegawa**
Manager for External Affairs for Global Technology R&D Engineering Management Headquarter Nissan Motor Corporation

With heated two days, the tie of COINS became even stronger toward the realization of in body hospital.

7th General Meeting

The 7th Group Meeting was held in the main conference room at the Life Science & A Environment Research Center (LiSE) on Thursday, January 27, 2017.

This meeting is held semi-annually with participation of all participating institutions.

In this time, we held a panel discussion after the presentations of theme leaders and participating organizations on the themes of this fiscal year's results and future plans.

The active discussion on new research theme and venture efforts was exchanged towards "In-body hospitals". Moreover, there was a lecture of Professor Kohei Soga, Tokyo University of Science which will participate in COINS from next year on "Biomedical Imaging on NIR II/II (I OTN-NIR)" and report about intellectual property policy by research promotion organization.

Lecture by Prof. Kohei Soga,
Project Professor,
Tokyo University of Science

30 posters were presented for the poster session and active discussions were held in front of the posters. At the conclusion of the meeting, Dr. Tatsuro Irimura, COINS Advisor and Project Professor of Juntendo University, Mr. Toshio Asano, Standing Counsellor of Asahi Kasei Co., Ltd. and Mr. Hiroshi Misawa, Medical Technology Association of Japan gave review of the meeting. It became a fruitful meeting for the participating institutions to further strengthen the unity toward realization of "In-body hospitals".

Review by COINS Advisers

Tatsuro Irimura
Project Professor,
Juntendo University

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

Hiroshi Misawa
Managing Director,
Medical technology
Association of Japan

Editor's Note

The theme 4 team is responsible for the development of diagnostic technology that is accurate and less burdens on the body, which is indispensable for an "in-body hospital" (see Vol 2, p2, 3) that will realize a "Smart life care society" COINS is aiming for. If this is achieved, there is the possibility of changing society and lifestyle significantly by shifting medical care from sick care to health care. With this issue of NanoSky. I hope readers will be able to get the drift of a sense of the progress of research and development over a wide range from fundamental research to practical application while the team is sharing a specific vision. COINS entered Phase 2 this fiscal year and is pressing on with its social implementation. This social implementation includes not simply practical application but also activities such as information dissemination that increase social acceptability. While being conscious of its importance, we are excited about delivering "NanoSky" to everyone next year as well.

(Editor Takashi SUGIMOTO)

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