Newsletter
# NanoSky
From KING SKYFRONT to the world - NanoMedical Innovation

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# Innovative Minimally Invasive Treatment led by "Nanomachines × Medical Equipment"

## Contents

# Pursue the Goal of Realization of Revolutionary Diagnostic Imaging and Treatment using Nanomachines

**Center of Open Innovation Network for Smart Health (COINS) Theme 5 is carrying out the research on how to use nanomachines which circle around the body for diagnostic imaging and treatment targeting affected areas.Including sonicodynamic therapy (Sonodynamic Therapy: SDT), which began to move toward practical use already, three people who lead the research group on the current situation talk about R&D, clinical application, challenges and future prospects etc.**


## Yoshihiro MURAGAKI

**Professor,
Faculty of Advanced Techno-Surgery / Department of Neurosurgery, Tokyo Women's Medical University · Institute of Advanced Biomedical Engineering and Science**


He was born in Osaka in 1962. He graduated from Kobe University School of Medicine in 1986, and after working as intern and then an assistant, he went to Pennsylvania University Pathology School in USA (Professor Trojawnoski, Professor Lee) from 1992-1995. He became a director of Neurosciences Center of Tokyo Women's Medical University when he returned. In 2006, he moved to Faculty of Advanced Techno-Surgery / Department of Neurosurgery, Tokyo Women's Medical University · Institute of Advanced Biomedical Engineering and Science. He is in current position from 2011.Doctor of Medicine / Certifying physician of the Neurosurgical Society / Cancer treatment certified doctor.


## Nobuhiro NISHIYAMA

**Professor,
Laboratory for Chemistry and Life Science, Institute of Innovation Research, Tokyo Institute of Technology / Principal Research Scientist, Kawasaki Institute of Industrial Promotion Innovation Center of NanoMedicine**


He was born in Wakayama in 1974. He completed the doctoral program of Graduate School of Engineering, The University of Tokyo in 2001. He became a postdoctoral fellow at Faculty of Pharmaceutical Sciences, Prof. Kopecek Lab, The University of Utah, USA and an assistant professor of di vision of Tissue Engineering of The University of Tokyo from 2001 to 2003. In 2009, he became an associate professor of Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo and at the current position from January in 2013. His area of specialty is the development of drug delivery system (DDS) utilizing polymer assemblies. In 2007 he received Award for Young Investigator in Polymer Science, the Society of Polymer Science, Japan, the 1st The Japan Society of Drug Delivery System Young Investigator Award (Basic) in 2009, and in 2012, the Young Investigator Award of the Japanese Cancer Association.


## Ichio AOKI

**Group Leader, Group of Quantum-state Controlled MRI, National Institutes for Quantum and Radiological Science and Technology (QST) / Team Leader, Functional and Molecular Imaging Team, Department of Molecular Imaging and Theranostics, National Institute of Radiological Sciences (NIRS), QST**


He was born in Kita Kyushu City, Fukuoka Pref. In 1999, after obtaining Ph.D. in the research of functional MRI contrast agent, he did his research on biomedical application of ultra-high magnetic field MRI and functional contrast agent at the laboratory of functional molecular imaging, NIH / NINDS (Koretsky AP Chief). In 2007, he works at National Institute of Radiological Sciences (NIRS) as a team leader and advances R&D of functional and nano contrast agents using high field MRI and the application of pathological conditions. In 2016, the NIRS has been renewed as the National Institutes for Quantum and Radiological Science and Technology (QST). He received 2017 R&D Achievement Award of QST.

## Combining nanomachines and focused ultrasound, investigator-initiated research on pancreatic cancer are being planned.

### ■ First, please introduce yourself.

**Nishiyama:** I am engaged in research on nanomachine technology, a medical technology using polymers in the Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology. In COINS Theme 5, developments of minimally invasive treatment systems and imaging systems that integrate nanomachines and medical devices are ongoing (Fig. 1). Specifically, combining nanomachines with treatments using physical energy such as photodynamic therapy (PDT), boron neutron capture therapy (BNCT, p.10), and sonodynamic therapy (SDT) using high intensity focused ultrasound (HIFU) equipment is being attempted, to dramatically enhance safety and efficacy (Fig.2). While other Themes are focused on medication, we are seeking a novel day-treatment that is less invasive and poses fewer burdens on patients in this Theme. Another one is the development of imaging methods that allow the visualization of a cancer's status without a biopsy. This study identifies how nanomachines act in vivo and is relevant to all COINS nanomachine researches. This research is also needed to realize precision medicine.

**Muragaki:** I am engaged in the treatment of malignant brain tumors in the Department of Neurosurgery, Tokyo Women's Medical University, while developing a precisely-guided treatment having the functions of a surgeon's eyes, hands, and brain in Institute of Advanced Biomedical Engineering and Science. In COINS Theme 5, I conduct research on the combination of two targeted therapies, namely, medication and HIFU.

**Aoki:** I work with research and development focusing on diagnostic technology using magnetic resonance imaging (MRI) in the National Institutes for Quantum and Radiological Science and Technology (QST) which was established two years ago. In COINS, I'd like to visualize how nanomachines are distributed and act in vivo and optimize the nanomachine function to contribute to the realization of secure treatment utilizing imaging.

### ■ To what extent has the development of therapies that combine SDT with nanomachines progressed?

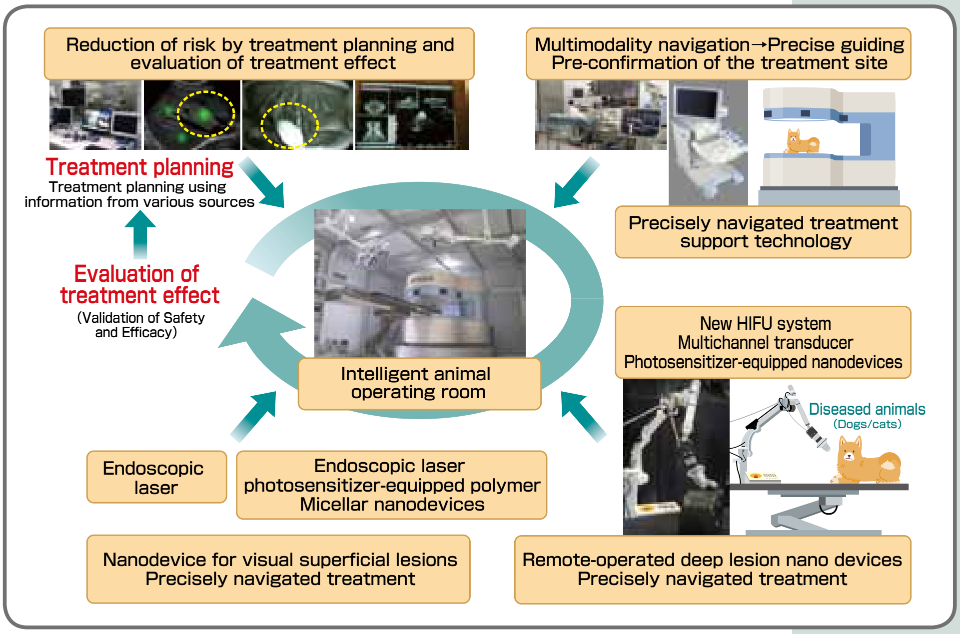
**Muragaki:** In this treatment, nanomachines equipped with the anthracycline anticancer drug epirubicin are accumulated in the tumor, to which focused ultrasound is then applied. After confirming its safety through treating four diseased animals five times last year, a clinical trial was performed in 12 patients with progressive unresectable pancreatic cancer. We are now planning an investigator-initiated Phase I study and are going to set the boundary intensity between effect and adverse reaction for focused ultrasound from now on, sharing information with companies. We are also investigating the mechanism of the SDT effect using nanomachines.

### ■ Linking research on actions and biokinetics of nanomachines to "diagnose and treat at the same time" or "diagnosis more linked to treatment" is also a great theme in Theme 5, isn't it?

**Nishiyama:** I sometimes hear from clinicians that the current diagnostic performance of MRI is sufficient and that no contrast agent of higher performance is needed, but I think such opinions will be changed if its linkage to treatment is considered. If you can predict the effect of the treatment that will be performed in the diagnostic imaging stage, you can provide a big advantage to the patient. This allows the selection of the optimal treatment for each patient. Visualizing the biokinetics of nanomachines may be very useful for both diagnosis and treatment.

**Aoki:** Diagnosis and treatment are essentially different in their concepts: diagnosis requires absolute safety, while the risks of treatments in patients, such as side effects and complications, are assumed. The clinician actually wishes to avoid using a contrast agent in diag-

**Figure 1.** Summary of devices fusing pharmaceutical and equipment actualizing ultra-minimally invasive therapy



nosis because it increases risk. There will be two trends in future diagnostic imaging: an increase in the safety of contrast media and the addition of new values useful in treatment.

### ■ Will there be any difference depending on the modality (medical imaging device)?

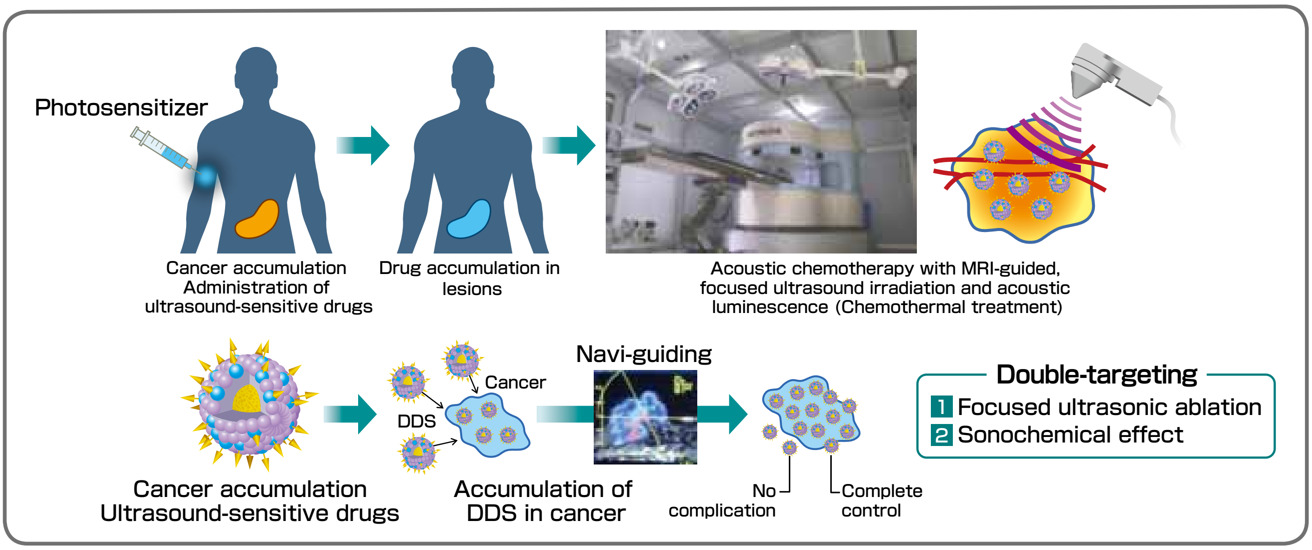
**Aoki:** Currently used modalities each have advantages and disadvantages, and all of them are necessary in clinical settings. In Japan, for example, CT has broadly been introduced compared to other countries, however it has the disadvantage of high medical radiation exposure. Radiation exposure should always be considered in terms of balance between the benefits of medical care and the risks. However, given the recent nervous situation to radiation exposure after the powerplant accident in Fukushima, it is necessary to suppress frequent CT use. I think methods without radiation exposure, such as MRI and ultrasound, and modalities that can be used easily, safely, and inexpensively will be more popular.
**Nishiyama:** Companies have a wait-and-see attitude toward the use of nanomachines to enable advanced imaging that would be difficult to achieve with the existing contrast media. We believe that our success in concurrent diagnosis and treatment will be a breakthrough.
**Aoki:** That would be nice if we could make it possible to switch diagnosis and treatment by changing what is carried on nanomachines.
**Nishiyama:** Without the added value of visualizing treatment, in addition to diagnosis, the practical application of the combination of nanomachines and imaging tests may be difficult.
**Aoki:** I agree. I think that the need for a contrast agent used only for diagnosis is high if it is safe, and I believe companies will be interested in it if it is a diagnostic method that can be used in popular modalities such as MRI. Recently, several contrast agents have had their patents expired, and it seems that there is a demand for new products. However, if the range of target diseases is narrowed too much, the number of target patients will be too small for the companies to take action.
**Muragaki:** The key is whether or not we can, as academics, prove indications and depict a business model to persuade the companies.
**Aoki:** To this end, it is important to share R&D processes with companies.

## Beyond R&D, there are barriers to clinical popularization even after the diagnosis and treatment are approved.

### ■ Are there any difficulties in development, approval, or clinical use of the treatment method with integrated nanomachines and medical devices?

**Nishiyama:** The Pharmaceuticals and Medical Devices Agency (PMDA), an independent administrative institution in charge of directions and reviews, seems to be cooperative in the development of epoch-making treatments originating in Japan in states from development to approval.
**Muragaki:** Sometimes, new treatments cannot be managed in accordance with conventional regulations, and we ask to respond to such cases flexibly. After approval, on the other hand, one may fall into unexpected pitfalls of the Drug Price system and Health Insurance. We were able to expand the indications of PDT to ma-

**Figure 2.** The 4th and latest treatment following operation, radiotherapy, and chemotherapy — chemothermal therapy through double-targeting



lignant brain tumors in 2014 by conducting investigator-initiated clinical studies. However, the photosensitizer used in PDT for the price proportional to the amount for nearly 2 years after the approval was then covered by the DPC (diagnosis, procedure, combination) system as one of the so-called "lump" drugs used in hospitalization for malignant brain tumors, and the drug cost was not applied. Although the treatment is beneficial for patients, it is difficult to provide in the current Health Insurance system. We are requesting the MHLW to improve this issue. I realize that it is difficult to change the determined framework once a treatment has been launched. This may also be the case in diagnosis and treatment using nanomachines. In addition, if nanomachine DDS targeted to the affected site is actualized, it reduces the dose and amount of drug use in companies and hospitals, that is to say, it reduces a company's profits, and therefore, the incentive for companies to go toward DDS becomes smaller. Successful matching of patients' benefits to corporate profits is important.

**Nishiyama:** Developments and clinical studies can be conducted in consultation with the PMDA, but systems providing no incentive to companies and hospitals are problematic. We have to consider business models in the early stage. Dr. Muragaki's experiences in the approval of PDT and its clinical use will be utilized in COINS in the future.

**Muragaki:** Pharmaceutical companies and medical device companies have their own management policies and different profit-making structures, so they are not ready to enter the development of such new treatments. Medical device companies sell devices to medical institutions to make profits and they want to raise the price (of the medical devices), while pharmaceutical companies want them to sell medical devices at lower prices to increase use of the drugs. Such a situation was present for PDT, and eventually, the problem was resolved by integrating the PDT division of the medical device companies into the pharmaceutical company. For SDT, we foresee future business models and have been asking several companies to discuss among themselves from the beginning, because academia is not good at things like this.

**Nishiyama:** Health care is a service and medical institutions and companies should be paid for patients' benefits. Such systems should be adopted.

**Aoki:** Despite the growing number of diagnosis and treatment methods that use medicinal products and medical devices as a unit, there has been no organization to evaluate them together, posing obstacles to R&D and their practical application. I hope that the Japan Agency for Medical Research and Development (AMED) established in 2015 will make a cross-cutting effort to promote the R&D for the methods.

## ■ New treatments combining pharmaceutical products and medical devices pose various issues, including the development of R&D strategy, funding, mode of information sharing with companies, patent strategy, and management from application for approval to post-marketing, and there is know-how to overcome these challenges.

**Muragaki:** Yes. The project we are involved in has been advanced by lucky, coincidental encounters. However, for our next-generation researchers, we have to consider the Japanese system from R&D to practical application.

**Nishiyama:** Separately from the optimization of nanomachines, it is important to retain the findings for the future purposes. Everyone may do the same things and make mistakes at the same points. There are many things that you don't understand through successful stories only. Sharing information on failures will raise the level of nanomachine research.

**Aoki:** COINS functions as a place to share such information, doesn't it?

**Muragaki:** Today, our gathering is exactly the place like that too (laughter).

**Aoki:** COINS gathers researchers who are conscious of social implementation. I hope that we will also cooperate with people out of our specialties, coordinators, and companies to proceed to the same goal.

## ■ Lastly, what are your future aspirations?

**Nishiyama:** Dr. Muragaki will advance the investigator-initiated research on SDT, and the research on BNCT will further be deepened. However, it is still a long way to achieve the "In-body hospital". When COINS enters Phase III of the research aiming at practical application of the research in the 2019 fiscal year, I would like to develop simple, high-performance, and safe smart nanomachines capable of social implementation using not only combinations of existing materials but also new materials.

**Muragaki:** COINS intends to investigate the mechanism of SDT in detail and establish an investigator-initiated clinical trial protocol in a method that enables its benefits to be actualized, leading to approval by regulatory authorities and adoption as the standard treatment.

**Aoki:** We would like to seek precision medicine by imaging with nanomachines to predict treatment effects and perform treatment based on the predictions.

## ■ Thank you very much.

(Interviewer: Science Writer Ayumi KOJIMA)

# Interview with Researcher

**Kohei SOGA**

Professor, Department of Materials Science and Technology, Tokyo University of Science,
Imaging Frontier Center, Tokyo University of Science
Research Institute for Biomedical Sciences, Tokyo University of Science

## Aim at Damageless Imaging and Therapy using Near-Infrared "Biological Window"

**Professor Kohei Soga of the Department of Materials Science and Technology, Faculty of Industrial Science and Technology, Tokyo University of Science / Imaging Frontier Center, Research Institute for Science and Technology, joined COINS Theme 5 as new member in 2016 and he is a pioneer of bioimaging using near-infrared light. We asked him about the background and recent results of the research on near-infrared bioimaging, which is expected to be applied clinically, as well as on the integration of bioimaging and therapy.**

### Challenge in the area where no one has gone, leading to success in the live imaging of nematodes

Prof. Soga has been conducting his research on nanoparticle light emitters (ceramic nanoparticles containing rare earth elements such as ytterbium and erbium, 10 to 200 nm in diameter) since 2004, and has used them to actualize bioimaging with near-infrared light. The rare-earth-doped ceramic nanoparticles emit fluorescence when subjected to near-infrared light with photon energy lower than that of visible light, and also emit visible light through up-conversion (conversion from long-wavelength light to short-wavelength light).

He majored in metallurgy in the Faculty and Graduate School of The University of Tokyo, where he researched the structure and physical properties of rare-earth-element-containing glass, particularly glass laser materials. Thereafter, he energetically started to research on nanoparticles containing rare earth elements in parallel with optical fiber materials and the physical properties of boron icosahedral cluster solid (boron).

The reason he began researching and developing bioimaging using near infrared light was an approach from bio-researchers in Tokyo University of Science who were interested in the research of rare-earth-containing ceramic nanoparticles. Fluorescence imaging with fluorescent dyes can use abundant colors and provide sensitive and dynamic imaging, while excitation light degrades the dye and attenuates the fluorescence in a short time, resulting in a short observation time. They asked Prof. Soga if there were any measures taken for this short observation time.

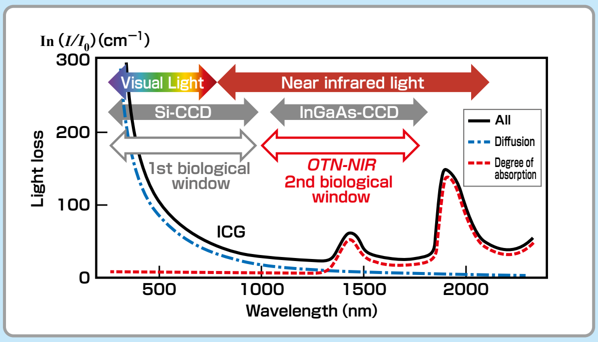
While he was examining the actualization of bioimaging by improving this rare-earth-element-containing ceramics nanoparticle for about a year, Prof. Soga thought that "bioimaging uses visual light in excitation and imaging, but must visual light be used? How about near-infrared light?" In optical communication, which he had studied for a long period, infrared light is used, taking advantage of its low light loss. Prof. Soga is familiar with the properties of near-infrared light and was interested in using near-infrared light for fluorescent bioimaging.

He studied near-infrared light and learned that it is called a "biological window" because its wavelength is as long as 700 to 1500 nm, allowing greater observation depth with little light loss. Particularly, wavelengths from 1000 to 2000 nm have high penetration ability with respect to the body (Fig. 1).

Conventional bioimaging uses fluorescent dyes that emit light in the visible range excited by short-wavelength UV light (wavelength 380 to 450 nm) and blue light (wavelength 450 to 495 nm). This method has the disadvantages not only of rapid discoloration of the dyes, but also an observation depth as shallow as a few millimeters, which is difficult to distinguish from autofluorescence, as described above. On the other hand, using near-infrared light may prolong fluorescent light duration and increase observation depth from a few millimeters to several centimeters. However, "No study of fluorescent bioimaging with excitation and observation by near-infrared light with a wavelength longer than 1000 nm was available. This may be because there were no favorable fluorescent probes or there was no camera for biological materials to detect the near-infrared light. I decided to take the challenge while wondering whether research on a theme studied by nobody would be successful," said Prof. Soga.

The camera commonly used in fluorescent bioimaging is a Si-CCD camera, which images by transforming light to electrical signals with a silicone device as charge-coupled device (CCD). This camera allows observation from the visible light range to near-infrared light around 900 nm. However, it cannot be used in any wavelength range over 1000 nm,

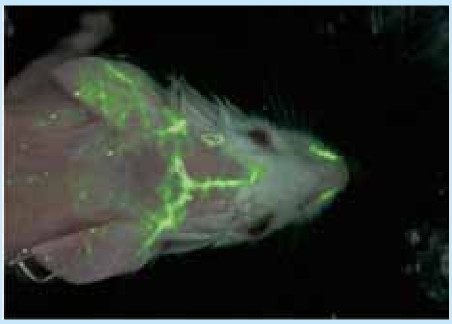
**Figure 1.** Light loss spectrum of human skin




R. Rox Anderson, John A. Parrish
Journal of Investigative Dermatology, Vol. 77, Issue 1, p13–19 redesigned

Light of shorter wavelength applied to human skin results in stronger light scattering, and longer wavelengths result in greater absorption. Wavelengths 500 to 1000 nm from the visible range to near-infrared range has been known as the "biological window," allowing great observation depth under the skin surface since 1980s. Prof. Soga and his colleagues developed InGaAs CCD cameras and demonstrated that wavelengths longer than 1000 nm (over a thousand nanometers: OTN) has far higher penetrating ability. They named this near-infrared range OTN-NIR and call it "the second biological window."

**Figure 2.** Fluorescent bioimaging images



Ytterbium-containing ceramic nanoparticles are injected in mice and fluorescent-imaged with Fluorescent Imaging Device SAI-1000, developed by Prof. Soga and his colleagues. The blood vessels are clearly imaged.

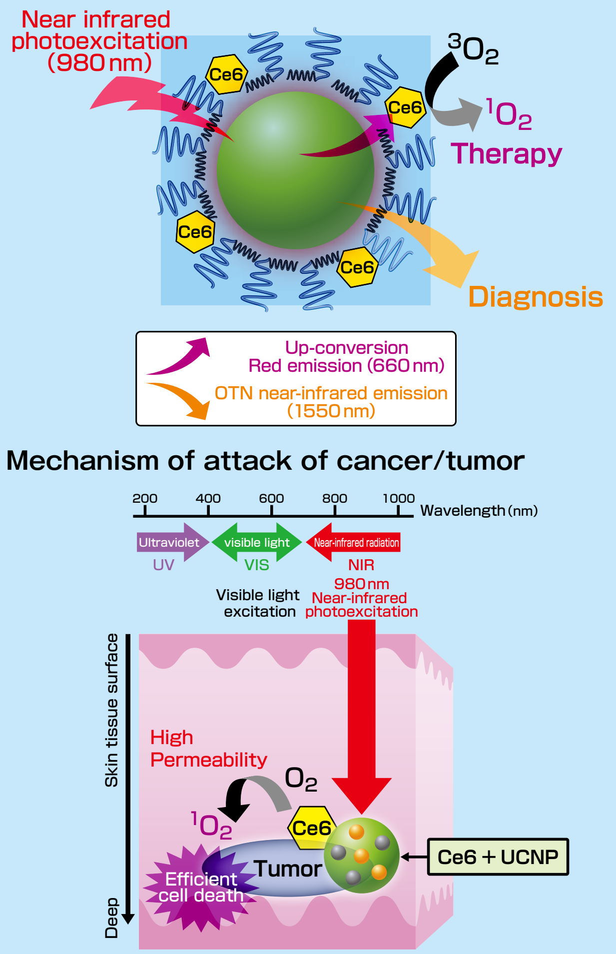
which is suitable for imaging of the deep in vivo area. Thus, Prof. Soga and his colleagues developed a system that enables in vivo observation in this wavelength range using an InGaAs (indium-gallium-arsenide) CCD camera, which is used to detect near-infrared light in the optical communication area. "It was lucky that the optical communication bubbles had collapsed, and cameras and other devices were available at lower costs."

Then, they created a prototype fluorescent microscope system that excites rare-earth-doped ceramic nanoparticles with 980 nm near-infrared light to have them emit near-infrared light fluorescence with a wavelength of 1550 nm, and successfully imaged live nematodes in 2008. This was the first live imaging in this wavelength range in the world. Prof. Soga looked back to that time and said "Probes other than fluorescent dyes, such as rare-earth-doped ceramic nanoparticles, were unfamiliar to biologists and we wanted to show how to use them.

## Developing and marketing a device for small animal observation

Next, he worked on developing this imaging system to observe small animals such as mice. Saving money by turning the laboratory light off without buying a dark box, a prototype of fluorescence animal imaging system with a laser excitation was developed. He felt great pleasure in 2010 when the gastrointestinal tract of was clearly imaged in a mouse fed with the rare-earth-doped ceramic nanoparticles. The device was refined in cooperation with Shimadzu Corporation in expectation of its practical application, and it was marketed in 2014. "The first prototype created in

**Figure 3.** Structures of Ce6+UCNP




Rare-earth-doped ceramic nanoparticles have the disadvantage of easy aggregation at biological salt concentration, and the particles modified with polyethylene glycol (PEG, blue) are stably dispersed. This actualizes the EPR effect to accumulate the particles in the cancer. Ce6 is a photosensitive substance and releases active oxygen to destroy cancer cells when Ce6 is exposed to near-infrared light. Concurrent use with an imaging system allows simultaneous cancer therapy with PDT (adapted from Reference 1).

cooperation with Shimadzu was in refrigerator size, but I requested of them to make the device lighter and smaller so that it could be brought into the small animal laboratory, and they created a device the size of a printer and weighing 17 kg. We were advised by the professor of designology from Department of Design at Nagoya Zokei University etc. about the computer software screen, creating a user-friendly design." Figure 2 shows an image of mouse blood vessels obtained by injecting rare-earth-doped ceramic nanoparticles using this image system. Rare-earth-doped ceramic nanoparticles used in this system have already been launched as well.

## The goal is to link near-infrared fluorescent light imaging to therapy.

Currently, Prof. Soga and his colleagues are focusing efforts on developing fluorescent probes. They are developing the rare-earth-doped ceramic nanoparticles that they have long carried on their research, quantum dots, and carbon nanotubes as well as probes containing organic fluorescent dyes, and they are also investigating to confirm the stability and safety in the tissues for each device.

Recently, they successfully performed photodynamic therapy (PDT) in mice by modifying ytterbium/erbium-containing ceramic nanoparticles with PEG and binding them to photosensitive substances that generate active oxygen when illuminated (Fig. 3)[*1]. In this method, the EPR effect (Enhanced Permeability and Retention effect) of PEG-modified nanoparticles is expected to accumulate the nanoparticles in cancer, allowing imaging to simultaneously determine the size of the cancer in parallel with cancer therapy with PDT.

Currently, the PDT covered by Health Insurance for indications such as lung cancer, esophageal cancer, and malignant brain tumor uses laser at wavelengths as short as 400 to 600 nm. Therefore, the PDT is used only for exposed lesions on the body' s surface or in the lumen and performed endoscopically or in conjunction with craniotomy. If that can be performed with the use of near-infrared light, noninvasive imaging and PDT from the body' s surface become possible. Professor Soga says, "I would like to lead to clinical research within a few years."

COINS Theme 5 is planning to put nano-thermal imaging into practice. In this method, pH and temperature are measured in the environment where the phosphor is placed with use of near-infrared light having great observation depth, and the measurements are mapped and used in thermal therapy. A basic experiment for thermometry has already been performed successfully using PEG-modified ceramic particles containing ytterbium.[*2]

His elder brother is the conductor Mr. Daisuke Soga, and Professor Soga also has an art lover side and likes colorful works such as the artworks of Joan Milo and the musical pieces of Maurice Ravel, and he loves to collect potteries made by Living National Treasures. "I like considering original solutions for an issue and often come up with ideas while walking because the brain fully works then. I feel happy to be a researcher in such moments."

There is no doubt that Professor Soga will, while he is commuting or taking a walk, generate ideas on utilizing the advantages of near-infrared light that causes no exposure and hazard to human body, and that further progress will be made in the applications of near infrared light to bioimaging and clinical practice.

(Notes: science writer Ayumi KOJIMA)

PROFILE

### Kohei SOGA

He was born in Tokyo in 1967. He grew up in both Osaka and Tokyo. He graduated from Department of Metallurgy, Faculty of Engineering, The University of Tokyo in 1990 and completed Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo in 1995 and obtained PhD. He worked at the Graduate School of Engineering, The University of Tokyo as a research associate, also at Rutgers University, New Jersey State as a postdoctoral fellow, and at Department of Materials Sciences and Technology, Tokyo University of Science as a lecturer and became an associate professor in 2007. He is in current position from 2012.

## Reference


＊1 M. Kamimura, K. Soga, et al., Chem. Lett., 46 (2017) 1076.
＊2 M. Kamimura, K. Soga et al., J. Mater. Chem. B (2017)

Reserch Highlights 1

Theme 5

# Study on the Practical Application of Sonodynamic Treatment with the Concurrent Use of Nanomachines and Ultrasound to Actualize Minimally Invasive Cancer Treatment

**Aiming surgery, drug therapy, radiation therapy and social implementation of a minimally invasive therapy that is both "friendly to the body" and "intense", researches are underway to unveil the mechanism of action of sonodynamic therapy with the concurrent use of nanomachines and ultrasound. Faced with the challenge of filing two applications for approval as a pharmaceutical product and medical device at the same time, the industry and academia are working together to tackle the challenge.**


## Yoshiyuki KONISHI

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## Kazuhisa TAKEMAE

Principal Investigator,Research Strategy Dept.
Global R&D Dept.
Pharmaceutical Division
Kowa Company Limited


In recent years, interest in minimally-invasive treatments has increased. Advances in engineering and physical science have made progress in diagnostic and therapeutic equipment. Among them, we are conducting researches aimed at the practical application of sonodynamic treatment using ultrasound and nanomachines. Treatment using ultrasound has been put into practice, and High-Intensity Focused Ultrasound (HIFU) treatment, among others, treats the affected area with thermal effects. HIFU treatment is used for a variety of diseases and has been approved by the pharmaceutical authorities for indications of pain relief in prostatomegaly, hysteromyoma, and bone metastases. While HIFU therapy alone exerts effects, it requires higher energy to obtain thermal energy and is associated with the risk of radiation to an unintended site because it is refracted and reflected by the effects of air and bones in the body. We are therefore conducting, in an experiment facility of iCONM, research and development of a minimally invasive treatment system with sonodynamic therapy (SDT) that combines a nanomachine and ultrasound, as a treatment to reduce the risks of HIFU therapy and potentiate cytotoxicity (Fig. 1). This R&D will elucidate the combination effects of nanomachines and ultrasound, allowing less invasive treatments than HIFU treatment alone (Fig. 2). Specifically, the combined effects of HIFU irradiation and nanomachines were examined by administering them to immunodeficient mice with mouse-derived colorectal cancer cells (Colon26) or human pancreatic cancer cells (MIA PaCa 2) implanted in them. The results showed that the combination of both treatments had growth suppression effects superior to those by the use of HIFU irradiation or nanomachines alone, at doses lower than those in HIFU irradiation or nanomachine technique alone (Fig. 3). The effect of active oxygen that is also noted in photodynamic treatment has been reported as a mechanism of action of SDT. Thus, in the present research, we are conducting basic studies to identify reactive oxygen species generated by the combined use of HIFU irradiation and nanomachines and their effects.

A major barrier to social implementation is the approval by regulatory authorities of medicinal products, medical devices, and regenerative medicine products. The recent legal revisions in Japan have resulted in priority reviews of innovative pharmaceutical products, medical devices, and regenerative medicine products. Applications for approval of pharmaceutical products are reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA). It is important to develop optimal non-clinical and clinical plans via thorough discussions with the PMDA not only in application process but also from the preclinical stage. The key to the present treatment is how the filing of both "medicinal products" and "medical devices" applications will be, and the mechanism of action of the treatment is essential for discussions in this process. Information on the mechanism of action is very important not only in terms of efficacy, but also from the point of view of how safety should be evaluated.

Previous studies suggest that several types of active oxygen may be involved in the mechanism of this treatment, in addition to nanomachines equipped with anticancer drugs and the thermal treatment effects of ultrasound. We will further study the effects of active oxygen, which have not been well understood until now, using the latest assessment devices in the iCONM from both in vivo and in vitro aspects, and further deepen our knowledge of pharmaceutical strategies required for social implementation.

**Figure 1.** Overview of sonodynamic therapy (SDT)

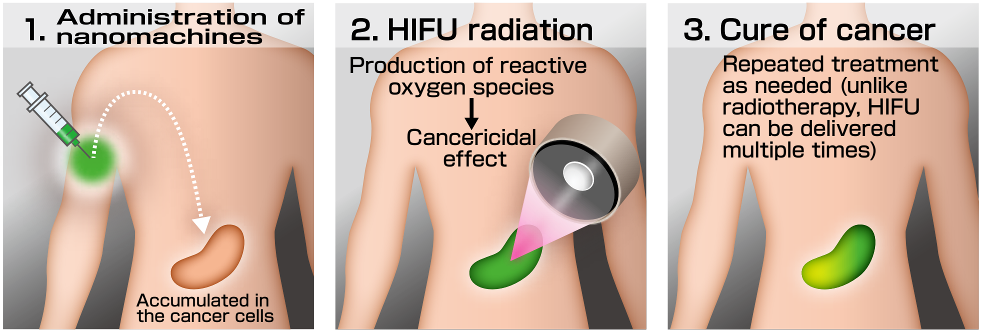



**Figure 2.** DDS drugs and high-intensity focused ultrasound (HIFU)

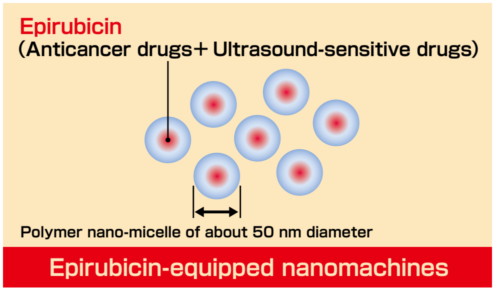
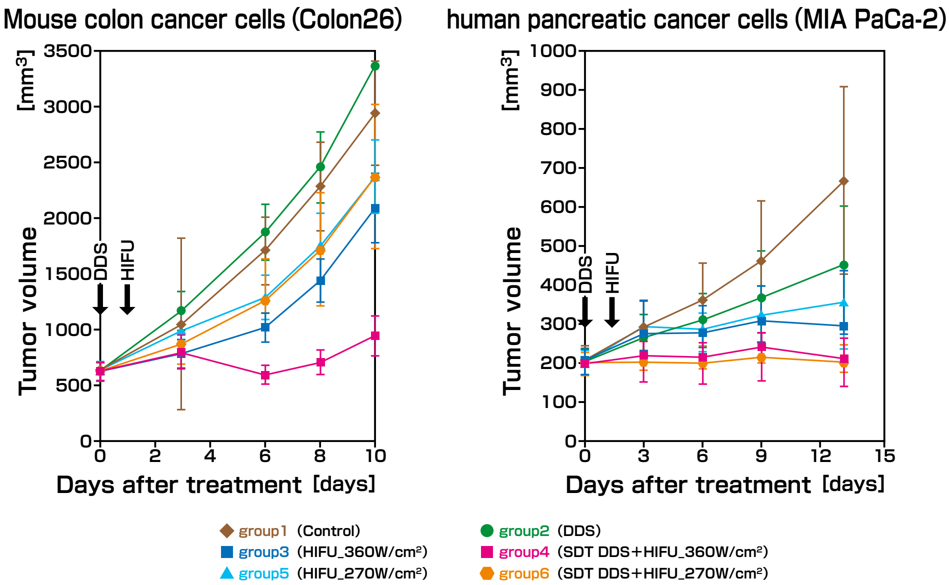




**Figure 3.** Non-clinical therapeutic effect of SDT (mouse subcutaneous transplantation model)

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# Japan's Leading Innovative Medical Technology Boron-mounted nanomachines for boron neutron capture therapy

**Radiotherapy[*1] is an excellent technology capable of pinpointing cancer with X-ray[*2] or particle beam[*3] and aiming at curing with minimal systemic side effects. However, if many small cancers are scattered, it is not easy to treat each cancer one by one through this method. In this study, we aim to treat such cancers in an ultra-minimally-invasive manner, without surgery, and develop neutron-responsive nanomachines for boron neutron capture therapy, which has been clinically studied mainly in Japan, to create an innovative medical technology originating in Japan.**

## Takahiro NOMOTO

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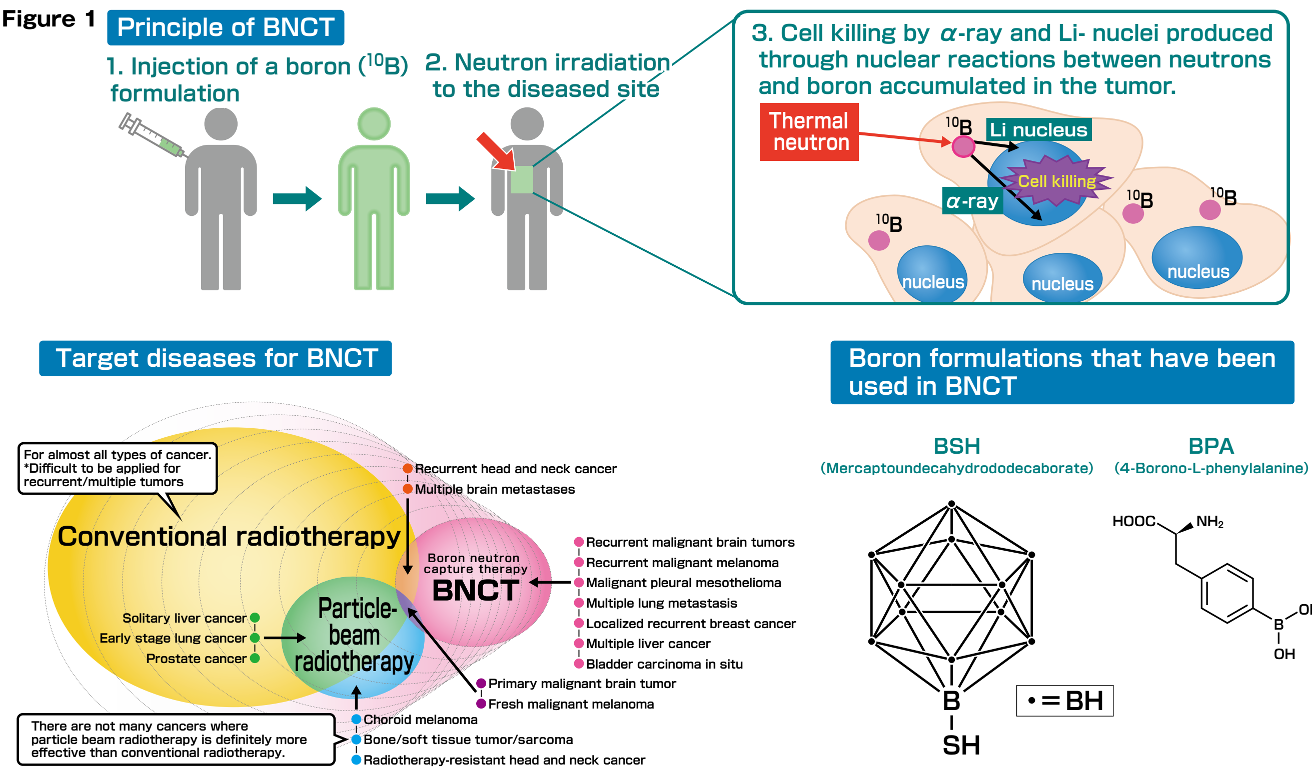
Institute of Innovative Research,
Tokyo Institute of Technology

When boron ($^{10}B$) is irradiated with thermal neutrons[*4], boron and a neutron undergo nuclear reaction to produce a high-energy α particle and a Li atomic nucleus. When this nuclear reaction occurs in the cell, α particles and Li nuclei damage the cellular nuclei to induce cell deaths. This principle has been applied to cancer therapy as boron neutron capture therapy (BNCT) (Fig. 1). BNCT is a technique that selectively kills cancer cells by causing the aforementioned nuclear reactions between boron and neutrons through the accumulation of boron in cancer cells, followed by irradiation of the diseased area with slow neutrons (thermal neutrons and epithermal neutrons). Although boron and slow neutrons have no significant biological effect when they are used alone, strong cytotoxic activity is obtained only if the two are combined. In addition, the range of α particles and Li nuclei in the cells is within 10 μm, which is almost the same as the cell diameter. Therefore, this technology can target a single cell.

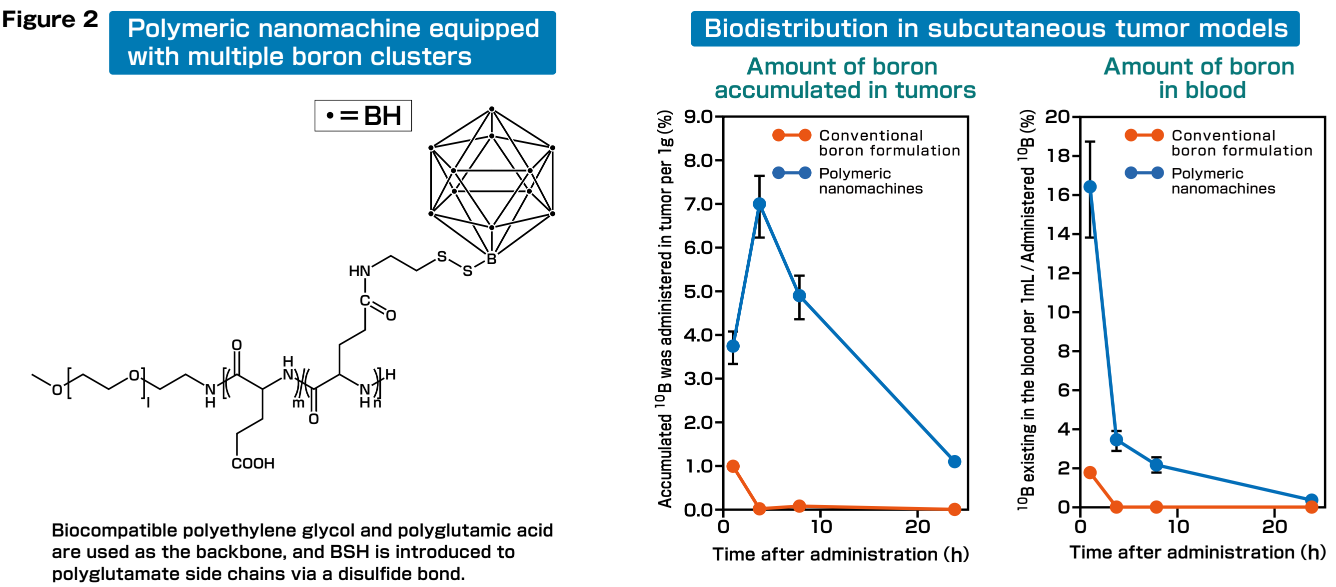
BNCT was first attempted by U.S. researchers between 1951 and 1961, but at that time, the technique for selectively delivering boron to cancer cells was not developed enough, with the low quality of neutron radiation sources. Thus, the therapeutic effects that could have been expected from the above theory was not eventually obtained. Thereafter, Japanese researchers began to play a central role in improving boron formulations and neutron radiation sources in Japan, and BNCT with boron clusters (BSHs) and boronophenylalanine (BPA) has succeeded in achieving excellent therapeutic effects. However, these formulations are still accumulated in a limited number of cancer species, and new technologies to selectively deliver boron to cancer cells are essential to expand the indications of BNCT.

We are developing nanomachines to deliver boron, in an effort to explore further possibilities of BNCT. Figure 2 shows a polymeric nanomachine, equipped with multiple boron clusters that we have recently developed. Compared with polymeric micellar nanomachines, these polymeric nanomachines are very small in size, accumulate efficiently in tumors, and disappear in a short time from the blood. In BNCT, boron remaining in the blood and normal tissues causes adverse reactions in normal tissues when neutrons are irradiated, and its early excretion from the body is therefore essential. In addition, as described above, the ranges of α particles and Li nuclei are within 10 μm, and boron should be delivered as uniformly as possible to all cells in the tumor. Because of their small size, the present polymeric nanomachines can penetrate deep into the tumor and are expected to kill all the cancer cells. In fact, the polymeric nanomachines we developed have shown tumor accumulation superior to the conventional boron agent (BSH) in subcutaneous tumor models, and neutron irradiation has produced a remarkable anti-tumor effect.

We aim to create innovative medical technologies that originate in Japan and can be exported worldwide through the integration of BNCT technology, developed over a long period in Japan, with the nanomachine technology we have developed.




Cited from Minoru Suzuki. Expanded indications of BNCT. Radioisotopes 64, 59-66 (2015).




Biocompatible polyethylene glycol and polyglutamic acid are used as the backbone, and BSH is introduced to polyglutamate side chains via a disulfide bond.

Nanomachines are capable of delivering more boron than BSH, to keep a high concentration of intratumor boron for a long period.

Both BSH and nanomachines are eliminated rapidly from the blood.

## Terminology

**＊1 Radiation**

Radiation is a collective term indicating particles that flow with high energy (particle rays) and high-energy electromagnetic waves. For example, one of the particle beams, α-ray, is the flow of helium nuclei, composed of two protons and two neutrons, which are referred to as α-particles. On the other hand, X-ray is high-energy electromagnetic waves (light).

**＊2 X-ray**

It is radiation with high transmittance capable of obtaining an anti-tumorous effect by pointing radiation at the cancer.

**＊3 Particle beam**

In addition to α-ray (α particle beam), there are proton beams (hydrogen nuclei [protons]) beam) and carbon ion beams (carbon nuclei beam). Particle beams of nuclei heavier than protons such as carbon nuclei are referred to as heavy particle beams. Radiotherapies utilizing proton beams and heavy particle beams are gathering attention.

**＊4 Thermal neutron**

A neutron is an uncharged particle that makes up a nucleus. A neutron, with its kinetic energy similar to that of thermal motion at ordinary temperature (about 0.025 eV), is referred to as a thermal neutron. In a broader sense, a neutron with energy not more than 0.5 eV is referred to as a thermal neutron as well as a high temperature thermal neutron. An epithermal neutron is a neutron with energy 0.5 to 10 keV.

## Reference


1. Hiroyuki Nakamura. History and Current Status of Boron Compounds/Formulations Radioisotopes 64, 47-58. (2015)
2. Minoru Suzuki Expanded indications for BNCT. Radioisotopes 64, 59-66. (2015)
3. Mi, P., et al. Block copolymer-boron cluster conjugate for effective boron Neutron capture therapy of solid tumors. J. Controlled Release 254, 1- 9 (2017)

# Wataru KUROSAWA

Manager, AJIPHASE Group,
Business Strategy & Planning Dept.,
AminoScience Division,
AJINOMOTO CO., INC.

He is engaged in R&D on medical materials to realize minimally invasive treatment by applying Ajinomoto's amino acid technologies.

## Importance of timing

They say "timing is important". We often encounter the related situations not only in our daily lives but also in research lives. I suppose most of the researchers have similar experiences when they got stuck in the research, such as "It happened to lead the solution when I listened to the lecture at the conference," or "I got an idea at the social gathering after the conference." etc.

It looks like social implementation of research results is also similar to these cases. It is a given fact that excellent research results are available, however, in many cases social implementation is realized through companies. So even cutting-edge technologies would not always lead to social implementation, if there is no merit for companies in terms of intellectual property, or the social infrastructure is not improved enough, which might make you disappointed. It is put into practical use only when the needs of the society and the invented technologies are fully matched. Outdated technologies are out of the question, however, too futuristic technologies might be difficult to realize social implementation. It really makes me feel timing is important.

I had been engaged in various R&D projects in the research institute for 15 years since I joined the company. During the time, I could have precious experience, such as creating the cutting-edge technologies with COINS members, success, failure, and encounter with many excellent researchers. This time, I moved to the headquarters and am currently challenging business development based on our company's technologies. For a corporate researcher, it is surely worthwhile to contribute to the health of human beings through business and to grow companies as well. I will strive to provide new value to the world, while paying attention to the importance of timing.

Created by my daughters. "Bad timing, I was on my business trip."

# Yuki HORISE

Project Assistant Professor,
Faculty of Advanced Techno-Surgery (FATS),
Institute of Advanced Biomedical Engineering and Science,
Tokyo Women's Medical University

She joined FATS in May 2015 as a postdoctoral researcher and works as a project assistant professor from April 2016. As having a motto of medical and engineering integration, she has been engaged in medical device development and human resource development, etc. beyond the framework of engineering.

## Medical-engineering integration and human connection

Faculty of Advanced Techno-Surgery (FATS) is consisted of medical and engineering staff, sharing the same time and space by arranging desks in one room, and various projects are progressing here with "medical and engineering integration" a motto. Institute of Advanced Biomedical Engineering and Science with FATS locates a walking distance to the university hospital and thus closer to clinical practice, involving a lot of medical staff such as doctors and nurses. So, it is the best environment to know about what is actually happening in clinical site.

We are developing a robotic microscope for brain surgery at one of the parts of Smart Cyber Operating theater (SCOT)® project. In the Human Resources Development Project, we organize seminars and clinical site tours for business people, establish a foundation to promote the creation of domestic medical equipment, etc. In addition, promotion of new projects in collaboration with major and small enterprises, etc. from development to education and collaborative research. Since I often meet so many people on a daily basis, I feel that "connection with others" is very important in promoting things in every projects.

I participate in COINS project from FY 2016 and we are developing a sonodynamic therapy (SDT) using DDS. When SDT was implemented to a pet dog suffering from spontaneous cancer, we could not only confirm the safety of SDT but also get result that suggest effectiveness. In October 2017, first-in-human clinical study which started at Tokyo Medical University was successfully completed. We will keep up our work for the development of SDT, believing that it will drastically change human cancer treatment.

SDT Team conducted clinical study at Tokyo Medical University

# e treasure



## Naohiko SHIMADA

Assistant Professor,
School of Life Science and Technology,
Tokyo Institute of Technology


He has found that polymers with ureido groups exhibit temperature responsive behavior in high temperature dissolution (UCST) type in aqueous solution. He is doing molecular design of UCST type polymers and its application to biomaterials.

### When I move my body

We humans, metabolism falls when we become older. As a result, weight increase, and it gets easier to become a lifestyle-related disease such as high blood pressure and hyperlipidemia. Like other people in my age, I also gained my weight drastically compared to my younger days, then, although I did not like exercise, I started going to a nearby sports gym. There are various machines in the gym and you can exercise at your own pace. I succeeded in losing 2 kg in two months with 30 minutes muscle training and 30minutes aerobic exercise! What's even better was that I was able to think while doing an aerobic exercise such as an aero bike. Since I often think while I am sitting, when I think while I am moving, I come up with something different from usual. As well as losing weight, I really feel it was good that I started to go to the gym.

Now usually, we are conducting research on a polymer "thermo-responsive polymer" which undergoes solubility change in response to temperature change. Especially, thermo-responsive polymers that cause compatibilization and change in aqueous solution are widely used as biomaterials such as drug delivery bases and cell culture boards. Most of these were phase separation type which was heated by something called LCST type. However, we have found that UCST-type polymers with ureido groups were extremely unusual macromolecules that causes phase separation by cooling under physiological conditions contrary to LCST type.

I will continue working toward application of this unusual ureido polymer to biomaterials at my daily gym exercise.

Right now, I am thinking while pedaling!



## Sayaka SHIBATA

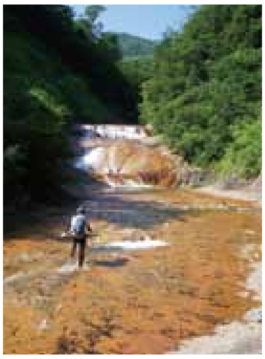
Engineer,
National Institutes for Quantum and Radiological Science and Technology (QST),
Department of Molecular Imaging and Theranostics,
National Institute of Radiological Sciences (NIRS), QST


She is an engineer supporting animal testing by preclinical MRI.She assists to create disease model animal, operate on animals necessary for MRI imaging, administer an anesthetic, make vital management and stain tissue in order for research to proceed smoothly.

### Because I never fail

"Three months for the synthesis of this compound, this is a mouse for this", sometimes unlikely words are said before the experiment. In animal testing using MRI, techniques such as contrast medium administration with a long catheter line, anesthesia management in continuous photography for several hours, methods for fixing to animals during that time are necessary. For various experiments, prepare and practice as much as possible to raise the success rate, meet frequently with researchers, and try not to fail with maximum attention at the real stage. It is my job to help experiments of the synthesized compound with a lot of time and effort and experiments of precious model animals not to fail although it is not like the TV drama "I never fail." I enjoy the process that the paper is completed with the hint of this experiment result and "things that are not yet science" become "science".

"What is important is planning, checking the current location, not giving up." This is what I cherish with the mountain walking which I started after twenty years old. If research goal is the peak of far away mountain, the experiment is just a step. The peak of a big mountain is far away, I can' t reach no matter how much I walk. Even if I become anxious along the way, I continue walking without giving up. There are so many things that I can' t control in the mountain such as unstable weather and trouble, however, when I am moved by superb view beyond my imagining in a few occasions, that makes me feel that I would like to climb again. The road to research is also steep and I get lost sometimes. However, now I think it is not that bad.



Azumayama, Ohtakizawa, 2 days and one night trip to the mountain.

# ACTIVITY REPORT

## 4th COINS Symposium

# Nanotech → In-body hospitals → Smart Life
## ~ Future Health care with Nanomachine ~

On Friday, December 8, the 4th COINS Symposium was held at Kawasaki City Industrial Promotion Hall on the theme of nanotech → In-body hospitals → Smart Life ~ Future Health care with Nanomachines ~

As this time was the second time which was held in Kawasaki, we aimed for a symposium that would be an opportunity to build environments and networks that could accelerate future social implementation and networks while sharing the concept of "In-body hospitals" and cutting-edge outcomes that would contribute to its realization.

Unlike the previous symposium, most of the participants were companies those were not from our participating companies and general. Particularly, it seemed that interest in "In-body hospitals" and COINS' s efforts were increasing among the society here in Kawasaki.

In oral sessions "Overcome Cancer by Nanotech" and "Healthy life span with "In-body hospitals", there were presentations about the latest research results leading to the development of innovative diagnostic and therapeutic technologies and realization of "In-body hospitals" by DDS using nanotechnology. The voices of admiration and expectation were raised from the venue. In the poster session, 34 researchers and companies gave presentations and active discussions were held between participants and presenters.

In the final panel discussion, on the theme of "Health care in smart life care society", after a keynote lecture / short presentation from panelists, there were active discussions on one of the future health cares "In-body hospitals", how it could be accepted by society and important points and way of thinking also with the participants at the venue.

It became a very meaningful symposium to give momentum to the progress of research and development / social implementation toward the final phase of COI (2019-2021).

Twan Lammers
Full Professor, Department of Nanomedicine and Theranostics, ExMI, RWTH Aachen University Clinic

Liangfang Zhang
Professor, Department of NanoEngineering, University of California San Diego

Panelist
**Takanori ICHIKI**
Professor, Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo
COINS Theme 4 Leader

Panelist
**Toshio ASANO**
Executive Advisor, Asahi Kasei Corporation
COINS Advisor

Panelist
**Taro TSURUKAI**
Director, Johnson & Johnson Innovation
New Ventures Japan

Panelist
**Hiroshi MASUMITSU**
Editorial Board Member, Science Department, Editorial Office
Yomiuri Shimbun

Moderator
**Hiromichi KIMURA**
Kawasaki Institute of Industrial Promotion Innovation Center of NanoMedicine
COINS Project Leader

panel discussion

## Topics July – December, 2017

- 7.3.2017 【News】 An issue regarding of Prof. Kazunori Kataoka, Director General of iCONM (COINS Research Leader) was introduced. The title: Realization of nanomachines "Fantastic Voyage" changes health care.
- 7.6.2017 【News】 Article of Dr. Kazunori Kataoka, COINS Research Leader, Dr. Yasuhiro Matsumura, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center (COINS Theme 1), Dr. Ichio Aoki, Team Leader, National Institutes for Quantum and Radiological Science and Technology, Functional and Molecular Imaging Team, Department of Molecular Imaging and Theranostics, National Institute of Radiological Sciences (COINS Theme 5)' s interview and its research were introduced in Yomiuri Shimbun Evening paper P. 6 "Research Front". The title: Drugs that target cancer
- 7.7.2017 【Award】 Ms. Wakako Sakamoto (D1), Ms. Satomi Azuma (M2), Mr. Takuro Ochiai (M1), Dr. Naohiko Shimada (Assistant Professor) and Dr. Atsushi Murayama (Professor) from Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology received The Best Oral Presentation Award from The 33rd Annual Meeting of the Japan Society. Dr. Takuro Ochiai, Dr. Naohiko Shimada and Dr. Atsushi Murayama received The Best Post Presentation Award as well.
- 7.13.2017 【News】 Article of Dr. Kazunori Kataoka (COINS Research Leader) ' s interview was introduced in Yomiuri Shimbun Evening Paper P.3. The title: Drugs that target cancer – flexibility, cheerfulness and passion
- 7.19.2017 【Activity】 COINS Seminar #26 was held.
  Speaker: Prof. Alexander Wei (Department of Chemistry and Materials Science & Engineering, Purdue University )
  Title: Adventures in Drug Delivery, Diagnostics, and Additive Manufacturing with Engineered Metal Nanoparticles
- 7.20.2017 【News】 Article of Dr. Yasuhiro Matsumura (National Cancer Center)' s interview was introduced in Yomiuri Shimbun evening Paper P.6 The title: Drugs that target cancer – Be nice with data
- 7.23.2017 【News】 Article related to iCONM was introduced in Kanagawa Shimbun P.19. The title: Developing Kanagawa Prefecture Coastal Area
- 7.24.2017 【News】 Article related the research of Dr. Takahiro Ochiya, Chief, Division of Molecular and Cellular Medicine Advanced Medical Biology research, Treatment Development Group, National Cancer Center Research Institute (COINS Theme 4) was appeared in Yomiuri Shimbun Morning Paper P.2. Moreover, it was appeared in Sankei Shimbun, Nikkei Shimbun, 40 other local newspapers and TV News as well. It triggered a large public response. The title: Diagnosis of 13 types of cancer with a drop of blood – New test by National Cancer Center – Start clinical test from next month
- 7.27.2018 【Award】 Dr. Shigehito Osawa (COINS Theme 1) received Young Scientist Encouragement Lecture award from The 27th Symposium on Biopolymers Science, The Society of Polymer Science, Japan (SPSJ).

- 8.3.2017【News】Article of King SkyFront Summer Science event 2017 was introduced in Kanagawa Shimbun P.19. The title: Elementary and Junior High School students' have job experience – doctor, politician and researcher – just like adults.

- 8.17.2017【News】Article of Dr, Ichio Aoki (National Institutes for Quantum and Radiological Science and Technology, National Institute of Radiological Sciences) ' s interview about COINS research was posted on New Medical Life Science website. The title: Preclinical research using 1 Tesla desktop MRI

- 8.23.2017【News】Article of Dr. Kazunori Kataoka, iCONM Director General and COINS Research Leader' s interview was published in Asahi Primary School Student Newspaper. The title: Nanomachines for the bright future – "In body hospitals" with micro capsule

- 8.23.2017【News】Interview of Dr. Kazunori Kataoka, iCONM Director General, Research Leader of COINS was posted in EMIRA website. The title: Will there be "In-body hospitals"!? The great revolution of cancer treatment brought by nanotech

- 8.31– 9.1. 2017【Activity】"The JST Fair – Future Industrial Creation with Scientific Technology" which was organized by JST was held at Tokyo Big Site. COINS exhibited our research contents at our booth and introduced COINS challenges and results.

- 9.1.2017【Award】Dr. Takanori Akagi, Project Assistant Professor, Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 4) received Best Presentation Award from The 9th Annual Meeting of the Japanese Association for RNAi (JARI)/ The 4th Annual Meeting of Japanese Society of Extracellular Vesicles (JSEV).

- 9.2.2017【News】Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) was appeared on TBS TV "EARTH Lab. – Think about next 100 years – COINS and iCONMS' approach and effort was introduced.

- 9.5.2017【News】Interview of Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) was posted on website "mugendai". The title: Soon it will be realized! Stun the world with "In body hospitals" Ultimate nanomachines which patrol around the body, detect, diagnosis and treat the disease

- 9.6.2017【Award】Dr. Kensuke Osada, Project Associate Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 1,2,3) received Asahikasei Award 2017 of The Society of Polymer Science, Japan. Title: Control of higher order structures of plasmid DNA by block copolymers and its application toward gene delivery system

- 9.8.2017【News】Research result of Dr. Sabina Quader, iCONM Senior Research Scientist (COINS Theme 1) was posted in the research highlights segment in the Kawasaki City-operated web newsletter "Kawasaki SkyFront – News Letter" The title: Surface modification of nanomedicines enhances their therapeutic effect on brain tumors

- 9.12.2017【Activity】COINS Seminar #27 was held.
  Speaker: Dr. Kohei Yamamizu, Center for iPS Cell Research and Application, Kyoto University
  Title: Application of iPS cell derived blood brain barrier (BBB) model to drug discovery

- 9.21.2017【News】Research of Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) was posted on GIZMODO Japan, excite News and LINE NEWS MAGAZINE. The title: "In body hospitals" has finally come this far. Towards the era where the disease is found automatically in the body and treated

- 9.24.2017【News】Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) appeared on Nihon TV "Nittere Update!".

- 10.8.2017【Appointment】Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) attended an appointment ceremony of National Academy of engineering: NAE as a foreign member, which was held at Headquarters in National Academy in Washington DC, USA.

- 10.10.2017【News】Article of Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader)' s interview was published in weekly magazine SPA! (Vol. 10/10・17 P.41). The title: Fairy bright "Paradox" Japan' s future Excellent health is available inexpensively in 2032 A healthy lifespan is dramatically extended – A society without becoming senile!

- 10.11.2017【Activity】Dr. Satoshi Uchida, Project Assistant Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 3), Dr. Keiji Itaka, Professor, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (COINS Theme 3) ,Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) and others held a press conference about their paper "Designing immunostimulatory double stranded messenger RNA with maintained translational activity through hybridization with poly A sequences for effective vaccination. Biomaterials 150: 162 (2018)".

- 10.12.2017【News】Article of the press conference which was held on October 11 was posted on JIJI COM and Medical NEWS etc. The title: Development of mRNA vaccine that increased immunopotentiating effect – iCONM and others

- 10.18.2017【Activity】Press Conference was held by iCONM, The University of Tokyo and Tokyo Medical and Dental University on the paper presented by Dr. Yasutaka Anraku, Project Assistant Professor, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (COINS Theme 2 Leader), Dr. Takanori Yokota, Chairman and Professor and Dr. Hiroya Kuwabara, Project Assistant Professor, Department of Neurology and Neurological Science Tokyo Medical and Dental University, and Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) and others "Glycaemic control boosts glucosylated nanocarrier crossing the BBB into the brain. Nature Communications 8: 1001 (2017)".

- 10.20 – 29【News】Article about the press conference was appeared in Nikkei Shimbun P.8, Nikkan Kogyo Shimbun P.21, Kanagawa Shimbun P.21. The title: BBB- crossing nanomachines efficiently reach neurons Kawasaki Institute of Industrial Promotion etc. (Nikkan Kogyo Shimbun) on October 18. It was reported in NHK News on October 29. The title. Development of Micro capsule that deliver drug to the brain.

- 10.29.2017【News】Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) appeared on BS JAPAN "Shock! Future Technology – World will change like this". The challenge of COINS and iCONM were introduced. The title: Japan made nanomachines slip into human body. That SF movie "Fantastic Voyage" finally become a reality.

- 10.30.2017【News】Dr. Akira Matsumoto, Associate Professor, Tokyo Medical and Dental University (COINS Theme 4)' s research was appeared in Nikkei Shimbun P.9. The theme:
  Artificial pancreas, compact and easy to use

- 11.1.2017【Activity】Braizon Therapeutics Inc., iCONM and Tokyo Medical and Dental University made an announcement at the press conference on the establishment of Braizon Therapeutics that venture company responsible for social implementation of research result of COINS Theme 2. The Title: Revolutionary medical innovation using DDS technology to the brain.

- 11.17-18【Activity】4th Retreat Camp was held at Shonan Village Center. (detailed report in P.16)

- 11.18.2017【 Award】Dr. Kazunori Kataoka, COINS Research Leader earned the honor as "2017 Highly Cited Researchers (Top 1% most cited researchers in this area) by Web of Science.

- 11.29.2017【Award】Dr. Kazunori Kataoka, COINS Research Leader received John G. Wagner Memorial Lectureship Award by College of Pharmacy, the University of Michigan. He gave a memorial lecture. The title: Self-Assembled Supramolecular Nanosystems for Smart Diagnosis and Targeting Therapy of Intractable Diseases.

- 12.6.2017【News】Article related to COINS by Mr. Toshio Asano, COINS Advisor (Standing Advisor, Asahi Kasei Corporation) was posted on website of the Pharmaceutical Society of Japan "Katsuyaku no hito".

- 12.7.2017【Activity】COINS New letter Vol.4 was published.

- 12.7.2017【News】Article related the press conference on October 18 was posted on Mainichi Shimbun P.12. The tile: BBB crossing nanomachines Expected to be used for a treatment of Alzheimer' s disease.

- 12.8.2017【Activity】4th COINS Symposium was held at Kawasaki City Industrial Promotion Hall.

- 12.12.2017【Activity】"RIKEN Symposium: RIKEN/iCONM/NIMS Medical Engineering Network" was held at iCONM and next door LiSE.

- 12.12.2017【Appointment】Dr. Kazunori Kataoka, COINS Research Leader earned the honor of Fellow of the National Academy of Inventors (NAI). NAI Fellow status is the highest professional accolade bestowed solely to academic inventors who have demonstrated a prolific spirit for innovation in creating or facilitating outstanding invention that have made a tangible impact on quality of life, economic development and the welfare of society.

- 12.22.2017【Award】Dr. Kazunori Kataoka, iCONM Director General (COINS Research Leader) received "Princess Takamatsu Cancer Research Fund Prize" of 2017 for his pioneering research on "The Development and Clinical Translation of Delivery Systems of Anti-Cancer Reagents based on Polymeric Micelles".

# 4th Retreat Camp —Lean"R&D""Commercialization""Intellectual Property" "Strategy"

On Friday, November 17 – Saturday, November 18, a retreat camp was held on the theme of "Strategy towards realization of In-body hospitals" at Shonan International Village Center in Kanagawa Pref. To promote social implementation of research results to realize "In-body hospital", it is important to foster the strategic viewpoint of the COINS members and creating a chance to review current efforts, thus we organized a workshop on "R&D", "Business, Social Implementation" and "Intellectual Property" this time. First, Dr. Tomohiro Anzai, Theme 6 Leader gave a talk as a theme on "Strategy" and afterwards "R&D Strategy Workshop" was held as facilitated by Dr. Shintaro Sengoku, Tokyo Institute of Technology.

Followed by "Commercialization and Social Implementation strategy workshop" in response to the special lecture "How to commercialize and put innovative research outcome into practical use" by Dr. Chikafumi Yokoyama, CEO, ReproCELL Inc.

Subsequently, Mr. Hirokazu Iwasaki, COINS Research Promotion Leader conducted "Intellectual strategy workshop" and this was followed by group presentations. Excellent groups and individuals were awarded. Three COINS advisors, Prof. Tatsuro Irimura, COINS Advisor (Juntendo University Graduate School), Mr. Toshio Asano (Asahi Kasei Corporation), Mr. Hiroshi Misawa (Medical Technology Association Japan) and an observer, Mr. Hiroshi Kono, Kawasaki Institute of Industrial Promotion, and Prof. Hiromichi Kimura, COINS Project leader and Prof. Kazunori Kataoka, COINS Research leader gave feedback with expectation for the years to come. Some research results have already moved to social implementation; therefore, it is necessary to promote the project even more strategic way. We are planning to organize a retreat camp on entrepreneurship human resources development.


Special lecture by Chikafumi Yokoyama, CEO, ReproCELL Inc.

Feedback by COINS Advisors and observers


Toshio Asano, Executive Advisor, Asahi Kasei Corporation


Tatsuro Irimura, Project Professor, Juntendo University


Hiroshi Misawa, Executive Director, Medical Technology Association Japan


Hiroshi Kono, Chief Coordinator, Life Science, Kawasaki Institute of Industrial Promotion


Through the two days case study workshop, the members have become further united.

# 9th General Meeting —Toward final third phase

The 9th General Meeting was held at the main conference room in the Life Science & Environment Research Center (LiSE) on Thursday, January 25, 2018.

In this meeting, to share the progress of Phase II (2016 – 2018) plans and 2018 plans toward Phase III (2019-2021) as a purpose, after presentations of theme leaders and participating companies, a panel discussion was held on the theme of social implementation of research result and points to build a structure to accelerate it. The members shared the points that cooperation across the themes and strategic use of regulatory measures and intellectual property etc. were very important to maximize the use of results and further promotion of In-body hospitals.

In special session, Mr. Shigeyuki Shiratori, Director of International Strategy promotion, Coastal Area International Strategy Headquarters, Kawasaki City gave a talk on the title of "Establishment of Center at Tonomachi International Strategic Zone King SkyFront" and Mr, Haruhiro Okuda, Vice-Director of the National Institute of Health Sciences (NIHS) introduced NIHS. Participants raised expectation that COINS's efforts will accelerate in the future by accumulating important institutions in social implementation at King Skyfront.

Prof. Tatsuro Irimura, Juntendo University, COINS Advisor, Mr. Hiroshi Misawa, Medical Technology Association of Japan and Mr. Haruhiko Manage, JST, COI vision 1, visionary leader gave feedback such as the point and stance to promote social implementation from research result. It was very fruitful opportunity to share the awareness of making best effort for realization of In-body hospitals by entire COINS.


Shigeyuki Shiratori, Diretor, Kawasaki City


Haruhiro Okuda, Vice-Director, NIHS

## Editor's Note

The mission of COINS Theme 5 is "No hospitalization · Realization of day treatment". We aim to develop a system that can combine detection, diagnosis, and treatment by combining the functions of nanomachines and medical devices, and we are trying our best every day. In point of integrating the functions of treatment and diagnosis, it can be said that it is closer to "In-body hospitals" than other themes, and some results are already in the clinical trial stage, so that it may be the Theme that feels the realization of "In-body hospitals". On the other hand, as the social implementation is progressing, the differences from current healthcare systems and business situations started to be seem as a big problem. You might be able to catch a part of the problem in "Talking about Theme". Theme 5 and eventually COINS's overall efforts will overcome such challenges and expect to be the driving force to build economic and social systems that will support Japan in the near future. We will continue to strive to make this "NanoSky" reports the progress and the heat of people involved in that progress.

(Chief Editor Takashi SUGIMOTO)

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