Newsletter

NanoSky

From KING SKYFRONT to the world - NanoMedical Innovation

December 2016 | Vol.2

Nanomachines Changing Cancer Treatment

Contents

Top Message

Nanomachines which support "In-Body Hospital" is being developed to support a Smart Life Care Society

It has been 3 years since The Ministry of Education, Culture, Sports, Science and Technology's 'Radical Innovation and Entrepreneurship Program (COI STREAM)' adopted COINS (Center of Open Innovation Network for Smart Health) started research based in Kawasaki Institute of Industrial Promotion Innovation Center of NanoMedicine (iCONM). Here are about the COINS concept, mission and current progress from COINS's research leader Kazunori Kataoka(concurrently iCONM, Director General).

Kazunori KATAOKA

COINS Research Leader/Director General,
Innovation Center of NanoMedicine,
Kawasaki Institute of Industrial Promotion
Professor, The University of Tokyo

The ideal is that our health is maintained without us knowing and cure illness

In COINS, using a technique called backcasting, we first formed a concept upon picturing an ideal society and what steps are needed to get there, and what we should do and how we can use the science and technology that we have at hand.

We are adopting the concept of "In-Body Hospital" to implement a 'smart life care society' and aim to develop nanomachines (Figure 1).

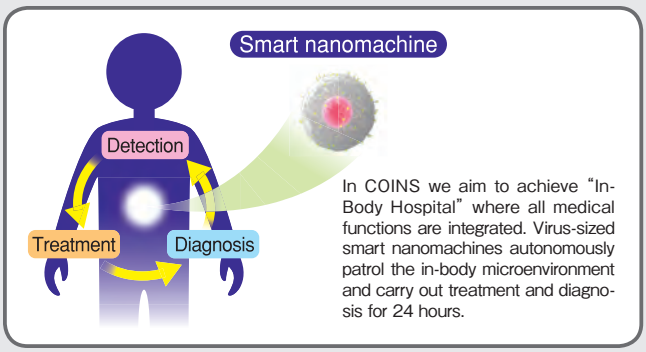
Currently, in order to cure diseases, 'people' such as medical personnel, care workers, families who nurse, 'goods' such as medicines and medical equipment, 'places' such as hospital, 'money' to foster medical expenses and medical personnel, and resources like waiting time and 'time' until healing are becoming commonly used in large quantities. Detriments to society like retiring from work after becoming ill have also been occurring.

People go to hospital because they notice sickness. Our health is also checked so we don't become sick or we are diagnosed and treated to heal our sickness so it is desirable that individuals consciously and actively participate in medical treatment.

The COINS aim of a 'smart life care society' preferably does not require these resources or individual awareness, that is to say, without knowing it, we are aiming for a society where health is cleverly maintained anytime, anywhere for everyone and where illness is cured. Ultimately, the concept is that 'there is a hospital in the body of individuals and they cure themselves' = "In-Body Hospital". For example, this does not mean 'to not get cancer' but rather a state where 'we are not afraid of getting cancer'.

People demand high quality medical care. This is only natural as human beings. At the same time, costly drugs put pressure on medical costs and society is becoming sensitive to the cost burden of treatment and the maintenance of health.

Figure 1. Aiming to implement "In-Body Hospital"



In the case of cars, for example, some of the technology used for the development of the fastest cars, such as Formula 1® or some sports cars, is commonly incorporated into popular cars while bearing the cost in mind.

The development of the latest preventive and therapeutic methods are also a huge cost in medical care and it is natural for this to become significant, so it is also important to make it more acceptable by cost reduction and industrialization. It is necessary to reconcile these 2 conflicting directions. I would like to support this with technology and concepts which have been researched and developed in COINS.

Development of nanomachines to reliably reach affected areas and demonstrate the function

The COINS concept of "In-Body Hospital" cannot be achieved overnight. To this end, COINS initially targeted diseases which have become major social and economic problems and is dealing with 6 themes.

Of these, themes 1-5 aim to develop 'nanomachines' to solve the problems. When looking at from the perspective of engineering, these nanomachines deliver, sensing, processing and operate these functions.

The reason for the 2016 Nobel Prize in Chemistry was for 'fundamental research to imitate the mechanical mechanisms of molecules'. Research and development of molecular machines capable of repeating the same operation by application of physical/chemical stimuli such as light or a change in pH to a small molecule has been evaluated globally.

Immunity in the body is a similar molecular machine, each molecular machine works together creating a wonderful system which can be used repeatedly.

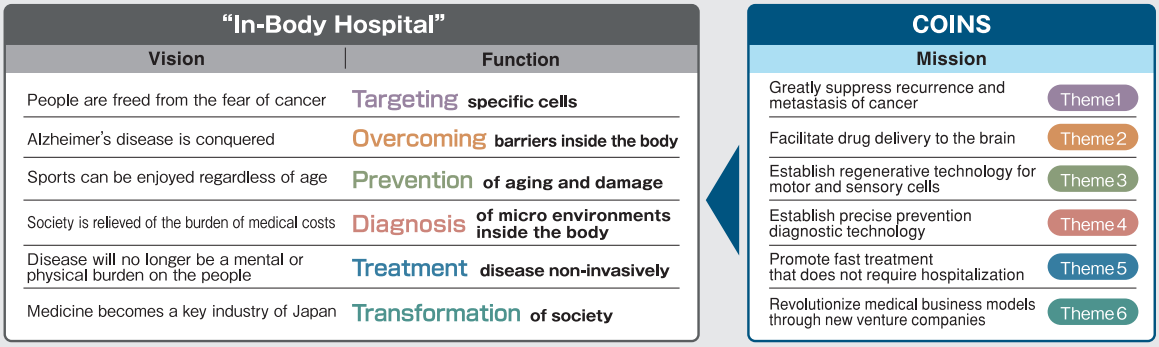
Even the nanomachines we have developed are aggregates of the same molecules, they are intended for delivery, detection, diagnosis and treatment and may be referred to as more advanced molecular machines. These advanced molecular machines become a resource for "In-Body Hospital". In the same way, a home-delivered pizza not only brings the pizza but also changes the toppings according to customer's requirements and cleans the plate (remembering the customer's preferences and always providing the same service).

Among the 6 themes, theme 1 affects about half the Japanese population, and for cancer, which is the cause of 1 in 2 deaths, accumulated research until now has aimed to create nanomachines that go beyond the anticancer drug-encapsulating polymeric micelles which are in clinical trials.

Anticancer agents have the characteristic that the effective dose range and the dose range in which side effects appear are narrow so, by using nanomachines and being certain to deliver an appropriate amount to the affected part, the effect can be increased and the side effects reduced. We already know that delivery can be achieved to some extent so we are now conducting research to further improve the delivery accuracy and encapsulate another therapeutics such as nucleic acids.

To create a highly versatile treatment system which can be used by anyone, anywhere, anytime, we believe the need for nanomachines to deliver medicines, which match the individual cancer patient to the affected area is increasing more than ever. If nanomachine technology advances, there is the possibility that drugs which have not been used thus far because of side effects will be used and not just for cancer. Initially delivering medicines then demonstrating function. We would like to approach step by step to 'implementing a smart life care society'.

Figure 2. COINS Vision and Mission



To Design the Next Anticancer Drug-Encapsulating Polymeric Micelle

The mission of COINS theme 1 is to evolve anticancer drug-encapsulating polymeric micelles which are the basis of the concept of "In-Body Hospital" and to create the next generation of DDS[*1] (drug delivery systems). The theme 1 leader, Associate Professor Kanjiro Miyata of the Department of Materials Engineering at The University of Tokyo and the Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, Tetsuya Hamaguchi, Medical Director of the Department of Gastroenterology in the National Cancer Center Central Hospital who is involved in the clinical development of anticancer drug-encapsulating polymeric micelles in Japan and Kenichiro Naito, Director of Research Division in NanoCarrier Co., Ltd. talked about the current research and future progress.

Tetsuya HAMAGUCHI

**Medical Director,
Department of Gastroenterology,
National Cancer Center Central Hospital**

A resident in the National Cancer Research Center Department of Internal Medicine and studied under Dr. Yasuhiro Matsumura of the Exploratory Oncology Research & Clinical Trial Center at the National Cancer Research Center East Hospital. Involved in clinical studies of anticancer drug-encapsulating polymeric micelles. Also involved in the management of the multi-institution, collaborative clinical studies group in the colon cancer group executive office of the Japan Clinical Oncology Group and has also assisted research representatives/the research executive office in several phase III studies.

Kanjiro MIYATA

**Associate Professor,
Department of Materials Engineering
Graduate School of Engineering,
The University of Tokyo**

Gained PhD (engineering) under the guidance of Professor Kazunori Kataoka in 2006 in the Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo. Subsequently became a Project Assistant Professor in the Department of Bioengineering, Graduate School of Engineering, in 2009 moved to the Center for Disease Biology and Integrative Medicine as an Assistant Professor and in 2013 promoted to Associate Professor. Transferred to the Department of Materials Engineering, Graduate School of Engineering in 2016 and presided over the research laboratory. The main research topic is the 'development of nucleic acid-encapsulating nanomachines based on polymeric materials'.

Kenichiro NAITO

**Director of Research Division,
Head of Discovery Research,
NanoCarrier Co., Ltd.**

Research Division Manager in the Research Division of Nanocarrier Co., Ltd., and responsible for the investigation laboratory and nonclinical evaluations (for about 3 years). In previous job (in a major Japanese pharmaceutical company), led the overall research strategy planning after involved in cancer drug research and strategy planning. Currently devoting efforts to transitioning to the early clinical stage of antibody-bound polymeric micelle No.1 which will be the next-generation technology and advancing application of the same technology to intractable cancer jointly with Matsumura's group in the National Cancer Research Center and iCONM. Also supporting the early approval of drugs during clinical trials from the nonclinical standpoint.

Increased accumulation of drug at a cancer site using anticancer drug-encapsulating polymeric micelles bound to anti-TF antibody

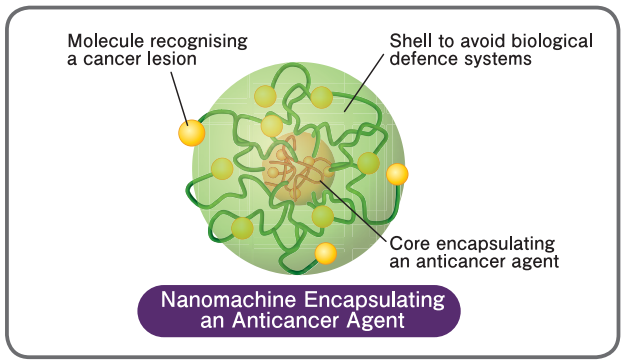
■ Please introduce your current work.

Miyata: In theme 1, I am creating nanomachines which target cancer. When I was in the Kataoka Laboratory, the development of polymeric micelles encapsulating anticancer drugs (Figure 1) had been advanced considerably. So, I've taken on researching new polymeric micelles which contain nucleic acid drugs.

Hamaguchi: I'm a medical oncologist in the Department of Gastrointestinal Medicine at the National Cancer Center Central Hospital. I met Dr. Yasuhiro Matsumura (Exploratory Oncology Research & Clinical Trial Center in the National Cancer Research Center) when I became a hospital resident in 1997 and from the outset I was involved in clinical studies of doxorubicin (Adriamycin)-encapsulating polymeric micelles until 2002. I also took my pre-clinical studies with Dr. Matsumura. Subsequently, as a clinician I specialised mainly in the drug treatment of colon cancer and I also conduct clinical studies.

Naito: I was engaged in anticancer drug research in a big Japanese pharmaceutical company for more than 30 years, for about the past two and a half years I've been in charge of the research of the first and the next generation of anticancer drug-encapsulating polymeric micelles and subsequently polymeric micelles in NanoCarrier Co., Ltd.

Figure 1.
A Polymeric Micelle Encapsulating an Anticancer Agent



■ What about the position of theme 1 in this COI program?

Miyata: The goal is to create newer and better nanomachines than the first-generation of polymeric micelle formulations which are already in clinical trials. "In-Body Hospital" cannot be achieved by even slightly changing the encapsulated drugs or modifying the polymeric micelle. 'What is not working' with the current polymeric micelles, as well as anticancer agents and molecular target drugs, is likely to be the key to creating new nanomachines. For example, we are considering targeting brain tumors and pancreas tumors which are hard to reach by anticancer agents.

Naito: Depending on the most difficult part, to create a new nanomachine, on Prof. Miyata, NanoCarrier is focusing on the clinical development of the first generation nanomedicine and the nanomedicine attached to an anti-tissue factor antibody (anti-TF antibody)[*2] which acts as a sensor for cancer tissue as the second generation. I'd like to get this targeted polymeric micelle into a clinical trial next year or the year after.

In actual fact, slightly changing the chemical structure and administration method increases the efficacy and may decrease side effects. When aiming at technically difficult things, I think using a drug well-known its effects and mechanism is a short cut to make a good nanomedicine.

Miyata: Mass production is difficult when academia creates fancy materials from a narrow vision as they may well be materials which cannot be put into practical use. We will steadily continue our research to avoid this.

It is also possible to encapsulate existing anticancer drugs into polymeric micelles

■ What kind of effect can be expected from a combination of an anticancer drug-encapsulating polymeric micelle and an anti-TF antibody?

Naito: Accumulation of first-generation polymeric micelle formulations in cancer tissue is higher than for the anticancer agent encapsulated in micelle itself due to the EPR effect (Figure 2). However, micelles attached to anti-TF antibodies more easily accumulate in cancer because of the action of the antibody. Therefore, combining these two (micelle and antibody) will further increase the rate of accumulation in cancers.

Miyata: Anti-TF antibodies can recognize not only the cancer cell surface but also the cancer-related stromal tissues. For that reason, they can target a wide scope of cancers which do not express specific markers on their surface. This fits the concept of "In-Body Hospital" which targets a variety of specific tissues.

Naito: The number of anticancer drug molecules at-

tached to one antibody is usually limited to 3 or 4, when an anti-cancer agent is directly bound to an antibody but the amount of drug which can be carried by one antibody will be 100 times that or more when micelle technology is applied. This expands the choice of drug, its action and its dose.

Hamaguchi: Unlike animal experiments, when drugs are actually used clinically the individual differences in cancer cells are marked even in the same cancer and the same person depending on the disease condition. If you can make new drug candidates that are highly effective and gather safely, we will evaluate finely how to use clinically. I'm looking forward to it.

Although the number of drugs for colorectal cancer, which I specialize in, has increased and standard treatment changed around 3 years ago, there haven't been so many new drugs since then. A breakthrough is also necessary in the treatment of stomach cancer. Scirrhous gastric cancer, which advances rather rapidly

and has a poor prognosis, metastasizes to the peritoneum and is prone to fibrosis, thereby showing the characteristic that drugs can barely reach it, similar to pancreatic cancer. Thus, if pancreatic cancer can be treated with drug-encapsulating polymeric micelles, then I expect that they can also be used for scirrhous gastric cancer.

Naito: As a venture company and in terms of development cost and time, I'd like narrow down cancer targets in consultation with Dr. Hamaguchi and other clinicians and manufacturers of diagnostic agents.

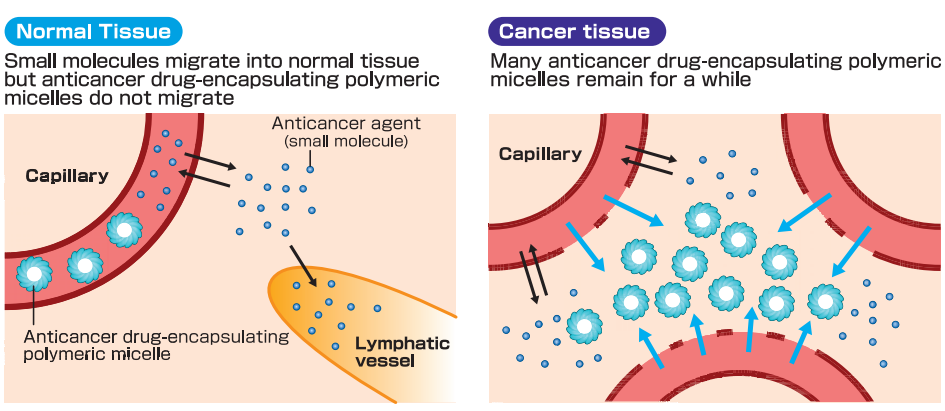
Hamaguchi: Immune checkpoint inhibitors were initially approved for melanomas then for lung cancers considering the characteristics of such cancer and this means using them while carefully monitoring their mechanism such as pharmacokinetics in cancers for which there are no treatments.

■ It is considered that anticancer agents which could not be used until now because of strong side effects can now be used by encapsulation in polymeric micelles.

Hamaguchi: Although individualized treatment using biomarkers to predict the therapeutic effects and side effects of drugs is now progressing, there are many cancers which cannot be classified and, in this instance, they are treated using evidence-based anticancer agents as in the past. The therapeutic effects and side effects may change depending on the length of the administration period even with for the same anticancer agent but the side effects can be lessened by encapsulation in a polymeric micelle and drugs which could not be used can now be. For example, neurological impairment occurs with platinum formulations in about 6 months due to their accumulation. Because polymeric micelle formulations markedly accumulate in cancer tissue there is the chance that they won't accumulate in the nerves.

Miyata: Resistant cancers may not be cured even if a polymeric micelle which contains an existing anticancer drug can reach it. In this case, new drug candidates which are expected to have a synergistic effect when in combination are encapsulated in polymeric micelles and it is thought that it is better to accumulate 2 different drugs in the cancer in the same profile (see p. 8). In this way, existing cancer agents may also show effectiveness.

Figure 2. EPR Effect (Enhanced Permeability and Retention Effect)



Angiogenesis and the permeability of the blood vessel wall are aggravated in cancer tissue compared to normal tissue and it is known that macromolecular substances readily accumulate because the lymphatic system which discharges these macromolecules has yet to develop.

It is important for engineering researchers to share information and cooperate with clinicians and companies

Miyata: Theme 1, in particular, is strongly connected to society and we can recognize the current problems when talking and cooperating with clinicians and companies. It is important for researchers in the field of engineering to understand, share and think together about the dose and administration period. There is a deluge of articles at our research site stating that 'if nanoparticles are made with a diameter of around 100 nm then they will all accumulate in the cancer'. However, cancer tissue is, in fact, diverse so the size effect will vary greatly depending on the type, site and stage. Therefore I think research into the tissue permeability of nanomachines will become valuable in the future (see p.10). It may only be about size but size is really important in the development of nanomachines. We are aware of designs which do not end up as research in published articles. Based on the objective of "In-Body Hospital", we would like to promote research from both perspectives of forecasting while backcasting which advances one step at a time based on our technology. If it is evidenced that the amount of drug which accumulates specifically in the target disease site is increased by using targeting ligands, such as anti-TF antibodies, then I think it will also pay off in research into a breakthrough in blood-brain barrier work in theme 2 as well as for theme 1.

■ What's your impression of coming to the iCONM?

Miyata: When I come here, I talk with people working on other research themes and I am able to talk to specialists in various fields as well. There's equipment here not found in university laboratories. The hurdle when starting joint research is low so I'd like to get started soon because new ideas for collaborative research are now emerging.

Hamaguchi: Today was my first visit. I could get an idea of the initial stages of drug R&D.

Naito: NanoCarrier has our lab here. Dr. Matsumura's Laboratory, which is doing joint research with NanoCarrier, is also carrying out animal experiments here. We are using our lab as a forum for discussion and conducting research together here.

■ iCONM is seen as becoming a 'third place' and a 'co-working space'. Finally, please tell us about your future ambitions.

Miyata: In the nanomachines enveloping nucleic acid drugs currently being developed, the size is controlled to 1-2 nm and we are checking that that size is maintained *in vivo*. I would like to carry out a detailed investigation of how those nanomachines enter cancer tissue and cancer cells and clarify what kind of parameters are necessary and what kind of technology is necessary to strike at intractable cancer.

Hamaguchi: I'd like to keep drawing out the good qualities of drugs and assist in the spread of new drugs around the world while being involved from the early stage of drug development. We are more than happy for a drug to be effective, to have few side effects and for treatment to be maintained.

Naito: As a bridge between the nanomedicines which are developed by Prof. Miyata and the clinicians like Dr. Hamaguchi, NanoCarrier would like to modify the nanomachine to get good results in clinical and to support clinical development if required, and also would like to improve the nanomedicine by considering the request from clinicians.

Miyata: A strength of this project is that you can cooperate right from the start through to the end.

■ Many cancer patients are waiting for highly effective drugs with few side effects. I expect R&D to progress further.

(Interviewer : science writer Ayumi KOJIMA)

Terminology

＊1 DDS
Abbreviation for Drug Delivery System. A general term for technology aimed at increasing the therapeutic effect of physiologically active substances, such as genes and drugs like anticancer agents and contrast agents, and at reducing side effects by 'allowing them to act at the required site and at the required dose when necessary'.

＊2 Anti-tissue factor antibody
Tissue factor(TF) is an exogenous blood coagulation initiation factor, which is often expressed in cancer cells and in the blood vessels in cancer tissue. TF is expressed in many cancers, such as pancreatic cancer and brain cancer, and the higher the expression of TF the higher the malignancy and poorer the prognosis. Therefore, it is expected that the development of anti-TF antibodies and DDS-targeting TF will lead to effective treatment of intractable cancers.

Reserch Highlights 1

Theme 1

Success in Developing a Nanomachine Targeting Cancer Stem Cells[*1]

~ confirming success of a model of exposure to asbestos leading to malignant mesothelioma[*2] ~

Standard treatment for malignant mesothelioma caused by exposure to asbestos has yet to be established and the development of new cancer drugs is awaited. We have succeeded in developing nanomachines which selectively accumulate in malignant pleural mesothelioma tissue and release drug into cancer cells to treat them. Based on this result, I expect that we can contribute to the establishment of an effective treatment for refractory cancers like mesothelioma in the future.

Hiroaki KINOH

Deputy Head/Principal Research Scientist,
Kataoka/Kinoh Laboratory,
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Horacio CABRAL

Associate Professor, Department of Bioengineering,
Graduate School of Engineering,
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It is known that conventional cancer treatments like chemotherapy and radiotherapy are not successful in treating malignant mesothelioma and it is thought that many cancer stem cells are present. Therefore, the development of therapeutics for cancer stem cells in malignant mesothelioma is being carried out vigorously all over the world at the moment.

By confirmation using aldehyde dehydrogenase (ALDH), which is known as a cancer stem cell marker, we have found that there are many cancer stem cells in malignant mesothelioma. Subsequently, as a result of an investigation into substances which are effective against cancer stems cells using this activity as an indicator, it has been found that the cancer stem cell killing effect of staurosporine[*3] is very high.

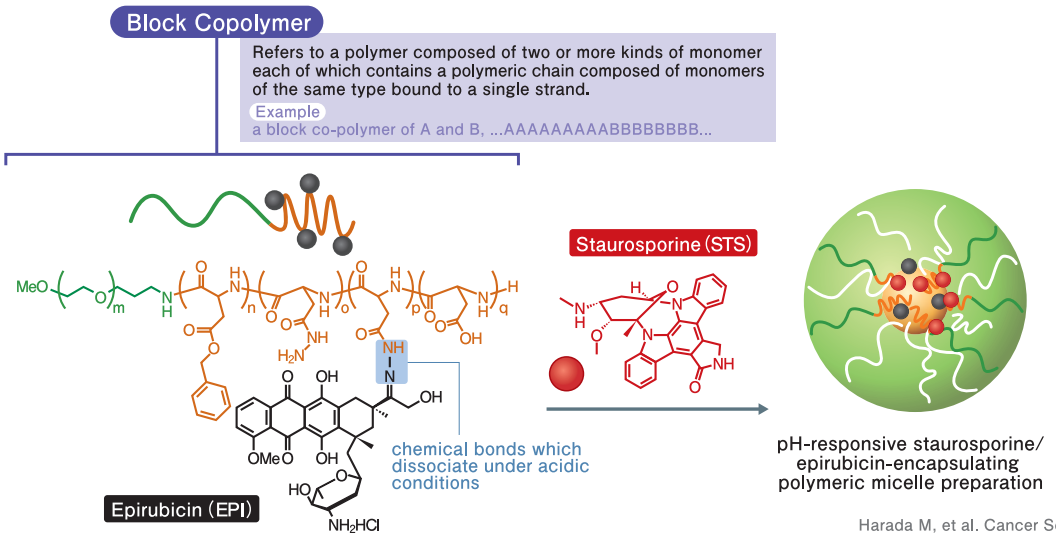
Staurosporine, however, is barely soluble in water and that it is deactivated in blood. When trying to encapsulate staurosporine in a polymeric micelle to overcome this problem, it was found that it can be efficiently enveloped in epirubicin-encapsulating polymeric micelles[*4] which our research group have already made. These staurosporine/epirubicin-encapsulating polymeric micelles respond to the low pH environment in and around cancer cells and the release of staurosporine was correlated with the release of epirubicin (Figure 1).

We have further confirmed in cell experiments that these polymeric micelles are also effective against cancer-stem cells, which are resistant to treatment with anti-cancer drugs. This novel polymeric micelle was intravenously administered to a malignant pleural mesothelioma mouse model[*5] and the survival rate was investigated to confirm the therapeutic effect of staurosporine/epirubicin-encapsulating polymeric micelles on malignant mesothelioma. As a result, all animals in the untreated group died after 1 month and all animals in the epirubicin group died after 2 months. Death of 70 % or more animals was confirmed in about 3 months in the epirubicin-encapsulating polymeric micelle treatment group, while survival of all mice was confirmed even after 3 months in the staurosporine/epirubicin-encapsulating polymeric micelle treatment group (Figure 2). Moreover, recurrence of cancer was not seen in half or more of individuals even 9 months after discontinuation of administration.

These results suggest that a formulated nanomachine containing a combination of existing anticancer drug and staurosporine is suitable in the effective treatment of cancer tissues in which many cancer stem cells are present. In fact, it has been confirmed that staurosporine/epirubicin-encapsulating polymeric micelles show marked efficacy against other cancers (such as lung cancer, stomach cancer and breast cancer).

We would like to contribute to the establishment of an effective treatment for highly malignant cancer giving rise to recurrence and metastasis by expansion of these results in the future.

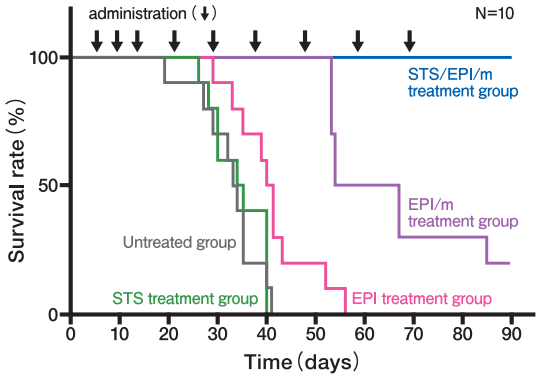
Figure 1. Development of Novel Nanomachines



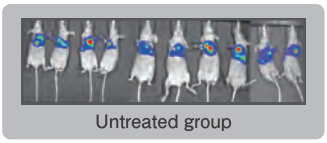
Epirubicin is chemically bound to a block co-polymer. Staurosporine is, however, encapsulated in polymeric micelles without chemical bonding by a mutual interaction with epirubicin. In the mechanism of drug release within cells by pH-responsive polymeric micelles, it is known that (1) micelles enter cells via vesicles made of collapsed membrane known as endosomes, (2) chemical bonds dissociate due to a pH decrease within endosomes, and (3) drug is released from micelles, and the novel polymeric micelle in this study can release epirubicin and staurosporine within cells by the same mechanism.

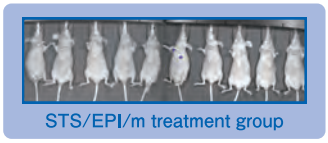
Figure 2. Effects of Novel Nanomachines against a Mouse Model of Malignant Pleural Mesothelioma

a. Change in mouse survival rate in each treatment group



b. Main in vivo Tumour Image





EPI/m : epirubicin-encapsulating polymeric micelle
STS/EPI/m : staurosporine/epirubicin-encapsulating polymeric micelle

a. Treatment group not shown in the figure will be supplemented. The survival rate in the treatment group administered with a combination of EPI and STS at about 2 months was 0% and in the treatment group administered a combination of EPI/m and STS the survival rate fell to below 30% after 3 months, which was similar to the EPI/m treatment group.

b. Blue-red line is the tumour detection site. The presence of a tumour was confirmed in almost all mice except those in the STS/EPI/m treatment group.

Terminology

＊1 Cancer Stem Cell

It has recently been thought that cancer tissue is not a population of single cells but many cancers grow from a few 'cancer stem cells'. Cancer stem cells are known to be resistant to conventional cancer treatments like anticancer agents and radiotherapy. Therefore, tissues containing many cancer stem cells are thought to be highly malignant cancers which are liable to cause recurrence and metastasis.

＊2 Malignant Mesothelioma

A disease in which malignant (cancer) cells are formed in the membrane covering the inner thoracic cavity or peritoneal cavity. It is a highly malignant cancer and most sufferers die within 1 year of contracting it. A major cause is aspiration of asbestos and the greater the exposure to asbestos and the longer the period, the greater the risk of onset. Malignant pleural mesothelioma refers to malignant mesothelioma which develops in the membrane (pleura) which covers the inside of the lungs and thorax.

＊3 Staurosporine

It is known that Dr. Satoshi Omura (Nobel Prize in Physiology or Medicine in 2015) discovered an antibiotic which strongly induces apoptosis (cell death). It has potent side effects as it also affects normal cells so has not been put into actual use in cancer treatment but it can be considered to be a potent anticancer agent if it can be delivered to cancer cells only.

＊4 Epirubicin-encapsulating Polymeric Micelle

Epirubicin is a kind of anticancer agent and exhibits an antitumour effect by binding to DNA in cancer cells and inhibiting gene synthesis. Epirubicin micelles refer to polymeric micelles in which epirubicin is encapsulated by numerous block copolymers (see Figure 1). This micelle is currently in a phase I study and is moving towards practical application.

＊5 Mouse Model of Malignant Pleural Mesothelioma

Mice inoculated into the thoracic cavity with malignant mesothelioma cells and which artificially suffer from malignant pleural mesothelioma.

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Discovery of a New Tumor Blood Vessel Permeation Pathway to Increase the Efficacy of DDS in Cancer!

**We have discovered an extremely dynamic phenomenon in which spatiotemporally irregular collapse occurs in the tumor blood vessels and eruption of polymeric micelles into extravascular cancer tissue.
If we can elucidate the mechanism of phenomena and make use of it, it is expected to lead to the development of a new drug delivery method especially one for intractable cancer[1].**

Yu MATSUMOTO
Assistant Professor, Department of Otolaryngology, Auditory and speech surgery
The University of Tokyo Hospital

Tumor blood vessels are known to be fragile and highly permeable. A general concept about the EPR effect in the pastso far[2] (see p. 6, Figure 2) is that there are intracellular spaces and highly permeable pores referred as fenestrations in the tumor blood vessel and it is said that macromolecular substances gradually leak out of blood vessels via these. Many DDS preparations (see p. 7) demonstrate antitumor effects using this EPR effect. However, the fact is that DDS preparations cannot achieve the ideal therapeutic effect against intractable cancers such as pancreatic cancer and scirrhous gastric cancer.

One reason is thick interstitial formation which is characteristic of intractable cancer. It is understood that DDS with a large particle diameter cannot penetrate the interstitium so they remain around the blood vessel. Kataoka's research team has shown that the interstitium can be penetrated by reducing the particle size[3].

In this study, we observed the distribution of polymeric micelles within the tumor in detail over the long term and at short imaging intervals. As a result, we have discovered an extremely dynamic phenomenon in which spatiotemporally irregular collapse occurs in the tumor blood vessels and eruption of polymeric micelles into extravascular cancer tissue. (Figure 1).

Although eruption is a phenomenon which is converged within approximately 60 minutes and was once was impossible to capture with the histological method with conventional fixed thinning, due to our recent efforts, by mouse anaesthesia management and imaging technology have improve[4] and by development of polymeric micelles which have high retention in blood, we realized the acquisition of spatiotemporal information of the distribution pattern of DDS in the tumor.

The results of image analysis and computer simulation following administration of 2 types of polymeric micelle with different diameters showed that the incidence of eruption correlates with the distance between the blood vessel and the tumor, the speed of eruption uses the pressure difference inside and outside the tumor as a driving force and that diffusion after eruption is controlled by interstitial density.

This study newly advocates 'eruption' from 'dynamic vents' which open and close for a short time rather that 'static pores' (Figure 2). If we can elucidate the mechanism of eruption and induce or suppress it in future research, it may become possible for the DDS preparation to efficiently reach cancer tissue. It is expected that this will lead to new treatment methods for intractable cancer.

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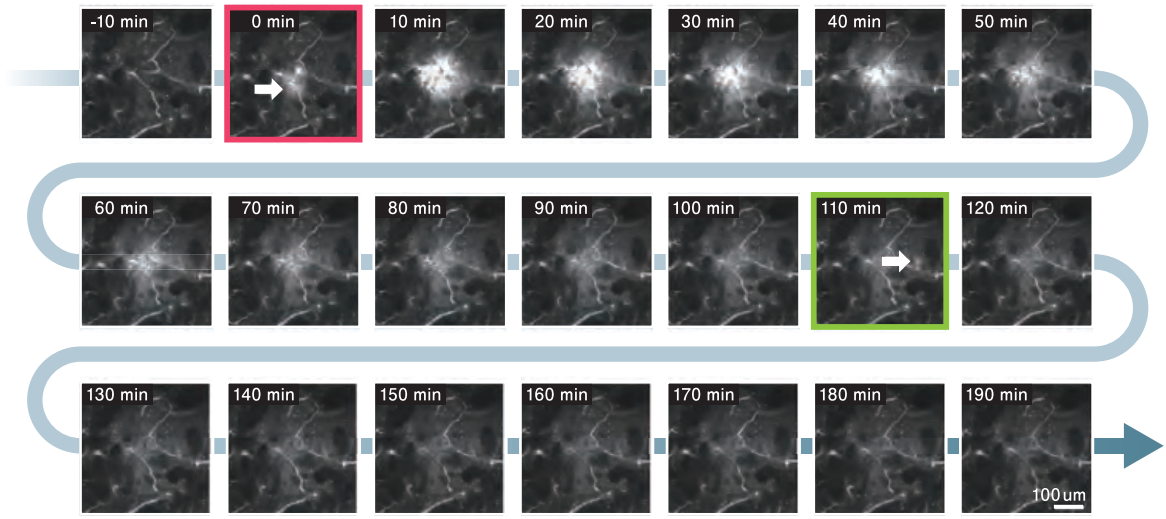
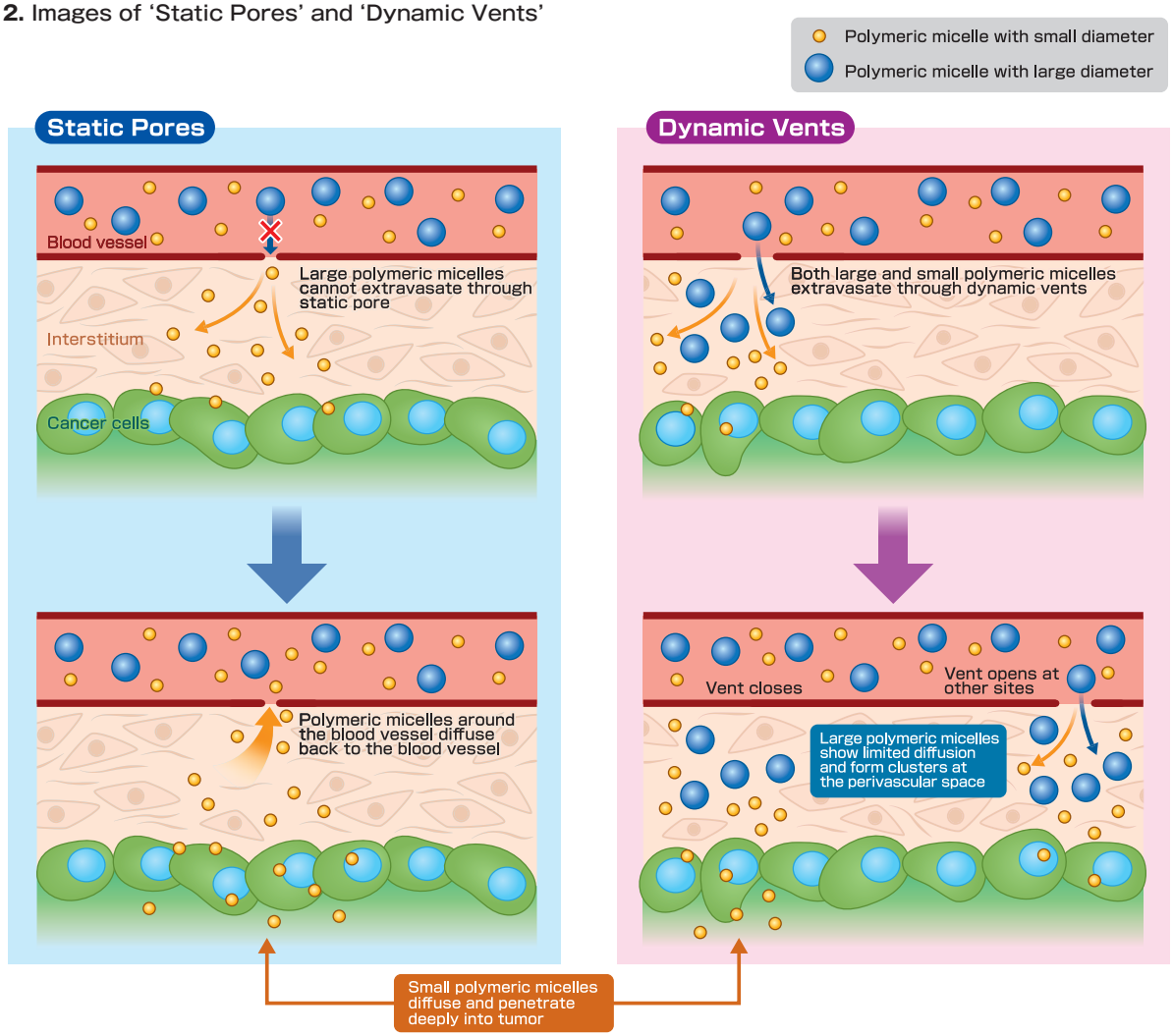
Figure 1. Exploring the cases of eruptionseruption state



Polymeric micelles show good retention in the blood, therefore tumor blood vessels can be identified by fluorescent labelling. Polymeric micelles erupt rapidly from part of the tumor blood vessel in a pancreatic cancer model (0 min) and immediately spread to the surrounding tissues. Eruption is over in 30-60 minutes and polymeric micelles leaving the blood vessel continue to diffuse. Major eruption (0 min, red frame) near the center of the angle of view, and small eruption (110 min, green frame) at another area somewhat to the right.

Figure 2. Images of 'Static Pores' and 'Dynamic Vents'



Listen to COINS' Member

What w

Yuki MOCHIDA

Senior Reseach Scientist, Kataoka/Kinoh Laboratory,
Innovation Center of NanoMedicine,
Kawasaki Institute of Industrial Promotion

In order to find a drug which completely cures all kinds of cancers, I am designing nanomachines for dlug delivery and evaluating their function and effectiveness.

Increasing insight, pursuing an ideal

I was born in Osaka, a city of merchants, and grew up in Tottori, a garden city. An ideal city for me is a convenient place with access to the main stations in Tokyo while being side by side with vibrant shopping streets and abundant nature. Searching for such an ideal city has become my holiday hobby over the past few years and I am going to various areas in Tokyo and enjoying exploring the city. When you actually visit the city and sense its atmosphere, you can understand the real quality and personality of a city which you cannot do from information from the internet. In particular, my instinctive impression of a city often captures its essence and this is what I value most. As intuition is usually based on past comprehensive experience and knowledge, if there is no experience and knowledge in the first place then it's no different from a wild guess. In order to increase the accuracy of intuition and for it to be a really useful reference, we need to acquire experience and knowledge on a regular basis. Even in my research on cancer-targeted nanomachines, I occasionally come up with new designs of nanomachines which I intuitively feel are successful through trial and error. To prevent such ideas from sinking into obscurity, of course, I hope to increase the accuracy of insight by step by step accumulation of knowledge and experience and contribute to the achievement of a smart life care society by creating high-performance nanomachines which form the core of next-generation medical care.

Incidentally, as a result of a fervent pursuit of my ideal city in Tokyo, I started living in Kawasaki city in Kanagawa prefecture.

Members in Kataoka/Kinoh lab from around the world together.

Sabina QUADER

Senior Research Scientist, Kataoka/Kinoh Laboratory,
Innovation Center of NanoMedicine,
Kawasaki Institute of Industrial Promotion

I am developing novel nanotherapeutic drugs effective in many types of cancer. My current research is particularly targeting brain tumours and metastatic breast cancers which are hard to reach tumours.

"Humanity" always leads my scientific enquiries .....

I am from Bangladesh. I was born and raised in Chittagong, the largest port city of Bangladesh. After finishing my MSc degree in Chemistry, I started working as a lecturer at Chittagong University of Engineering and Technology. After two years of teaching, I accepted a PhD scholarship offer from Griffith University, Brisbane, Australia and subsequently completed my PhD there.

I came to Japan in 2010 with a JSPS postdoctoral research fellowship and joined Professor Kazunori Kataoka's laboratory (kklab) at the Material Engineering Department of Tokyo University. In 2015 I became the Senior Research Scientist in Kataoka/Kinoh laboratory at the Innovation Center of NanoMedicine (iCONM). I am conducting research with a focus on developing nanomedicines for diagnosis and treatment of intractable cancers. I feel privileged to be able to get involved in research activities under the direct guidance of Professor Kataoka, a world-leader in the field of drug delivery system.

I live in Japan with my husband who is a writer, researcher and filmmaker and my 9-year-old daughter. Unfortunately my Japanese skill is poor but my daughter who is fluent in Bengali, English and Japanese often helps as an interpreter. During our 6 years stay in Japan, we always sense a feeling of security and sincerity. Japanese people are honest, warm and reserved; overall Japan is a wonderful country. In Japan cutting-edge technology and tradition exist side by side. This particular amalgamation of the modern with the traditional fascinates me in every moment of my Japanese experience.

Together with my adorable daughter who is brimming with curiosity.

e treasure

Masaru UENO

Chief Researcher,
4th Research and Development Team (liquid biopsy)
JSR Life Sciences Corp

Although a liquid biopsy is attracting attention, we are developing research reagents which can be used in other fields and are promoting translational research for diagnostic agents.

Considering our own health will spread new interests

Under the concept of "In-Body Hospital" at COINS, I am trying to create a big dream of prolonging a person's healthy life span. There are many things to learn from that big dream although putting it into practice is still ahead of us.

I recently watched the MBL news of Ichiro's 3000 hits and realised that a great record can be created by maintaining a high level of health over a long period. My feeling that maintaining a high level of health over a long period is important has also become stronger for my work in research and development.

With the practical use of "In-Body Hospital" proposed by COINS which is currently being developed in mind, I thought about what I can do now to maintain health over a long period. I finally then found simple answers and hit on 'exercise' and 'supplements' and started to play tennis, and, while trying to improve physical fitness, I checked every day so see if the effect of supplements had kicked in.

By exercising, my daytime mood was refreshed but at night I felt very tired so now I've begun to look for something else when I'm tired. It seems that it is a fascinating field and it appears that the feeling of tiredness is probably due to stimulation of the brain by reactive oxygen. For removal of active oxygen from the brain, carnosine, which is dipeptide of β-alanine bound to histidine, can be purchased. I'm very interested in simple peptides which do not have a complicated structure like polyphenols but demonstrate this effect, and I spend the evening reading related articles while having a drink. As this is done until night time, I get tired (fatigued) and I give my family a cold look... . In future, research on how to eliminate fatigue for health using "In-Body Hospital" is necessary.

Three cute kids eating American corn dogs.

We aim to achieve innovative cancer treatment and are carrying out research onto drug-releasing nanomachines.

Tsukasa CHIDA

Researcher, DDS Group,
DDS Research Department, Fuji Research Laboratory,
Pharmaceutical Division, Kowa Company Ltd.

The achievement of "In-Body Hospital" along with my child's growth

What I cherish is 'the time spent with my family'.

During my work while coming and going between Kowa's Fuji Research Institute (Fuji City, Shizuoka Prefecture) and the Innovation Center of NanoMedicine (Kawasaki City, Kanagawa Prefecture), time spent with my wife and my son, who will be 1 this year, is irreplaceable time which heals daily fatigue. On holidays, especially, I am trying to show various scenes to my son whose expression of feelings has become enriched and I sometimes walk on the Tama River bank next to the Innovation Center of NanoMedicine.

When I think about it, the Innovation Center of NanoMedicine, which is the research base of this COINS project, will celebrate one year since its establishment. I felt expectation and trepidation about the birth of my first son and it was such a great year that the days when I was engaged in establishing a collaborative laboratory between COINS and our company seemed like only yesterday.

Among the cutting-edge research facilities, what can be achieved as a business? Although I started from the point of preparing the research environment for this, I am moving forwards little by little while being supported by the staff of iCONM and seniors in the workplace. Like my eldest son who still cannot walk yet, Kowa's challenge for the future is just beginning.

When I think carefully about the future of my family in the vision of COINS 20 years on and when I think that "In-Body Hospital" has to be achieved around the time my child becomes an adult, as a researcher by body tenses at the same time as the feeling of expectation for the future grows.

Shizuoka landmark - with my son at Mt Fuji.

6th General Meeting

The COINS 6th General Meeting was held in the main conference room at the Kawasaki Life Science & Environment Research Centre (LiSE) on Friday, June 3rd 2016.

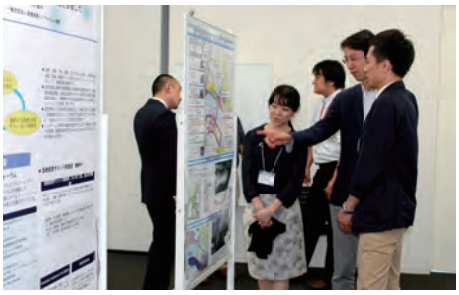
The meeting is held every six months with the involvement of all participating institutions.

Each theme leader and participating institutions announced their intentions in 'what is to be done in the 2nd phase towards the achievement of "In-Body Hospital" (declaration of intent)' based on the results of the initiatives in the 1st phase (FY 2013 to 2015).

Kawasaki City has reported on initiatives to create sustainable innovation based on the results thus far and future plans and prospects and the COINS Research Promotion Organisation and the Kawasaki Institute of Industrial Promotion have reported on the maintenance of compliance.

In addition, we set up poster sessions for research results and a lively exchange of information exchange took place with 29 presentations.

We entered the 2nd phase and held a very meaningful general meeting to further strengthen the tie up between the participating institutions towards achieving "In-Body Hospital".



Poster Session

Discussion

Goings on in the whole venue

Social Event

Topics 2015.10 ~ 2016.6

- 10.30.2015 【Award】The laboratory of Takanori Ichiki, Associate Prof. (COINS theme 4 leader), Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (Takanori Akagi, Nami Hanamura, Takanori Ichiki) received The Institute of Electrical Engineers of Japan's E Department of General Studies Best Presentation Award at The Institute of Electrical Engineers of Japan. Award title: '1 Particle Profiling of an Extracellular Endoplasmic Reticulum in a Micropathway'.
- 12.5.2015 【Report】The joint research group of Takanori Ichiki, Associate Prof., Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (COINS theme 4 leader) et al and Nikon KK have developed the world's first flexible optical sheet sensor which can measure cellular oxygen metabolism without damaging cells.
- 1.1.2016 【Newspaper】COINS and its core base Innovation Center of NanoMedicine (iCONM) was introduced in the hospital newspaper.
- 1.4.2016 【Report】Keiji Itaka, Project Associate Prof., Graduate School of Medicine Center for Disease Biology and Integrative Medicine (COINS theme 3 leader), The University of Tokyo et al held a press conference on their published article (Messenger RNA delivery of a cartilage-anabolic transcription factor as a disease-modifying strategy for osteoarthritis treatment, Scientific Reports). Successfully curbed the progress of osteoarthritis. News article: Nihon Keizai Shimbun, Wall Street Journal Japanese Edition, Toyo Keizai ONLINE
- 1.6.2016 【Newspaper】'Nanomachines' and iCONM introduced to the Asahi Shimbun and Asahi Shimbun DIGITAL. Title 'Not an SF medicine dream'
- 1.14.2016 【Report】Prof. Kazunori Kataoka (COINS Research Leader) of The University of Tokyo Graduate School of Engineering appeared on Asahi TV series Shinichi Hatori Morning Show's 'Original General Research Corner: anticancer drug treatment to a new stage' and explained nanomachines.

- 1.30.2016 【Report】An interview article with Kazunori Kataoka (COINS Research Leader) Prof., Graduate School of Engineering, The University of Tokyo was published in the March 2016 Edition of 'Chichi' . Title: 'This century's achievement was accomplished - tenacity and originality in the research and development of new drug 'nanomachines' which will change the future of humankind -'
- 1.31.2016 【Report】Kazunori Kataoka, Prof., Graduate School of Engineering, The University of Tokyo (COINS Research Leader) appeared on the TBS series 'Running Doctor! Health Diagnosis Changes the Inevitable' and reported on an 'extremely small capsule which destroys only cancer cells'.
- 2.1.2016 【Report】An article on COINS published in the February issue of the monthly magazine 'Information Management' from the Japan Science and Technology Agency. Promotion by industry/academia/government/medicine/finance collaboration was introduced and an outline of COINS's initiatives from the three viewpoints of infrastructure, investment, and human resource development which are important in building an innovation eco-system was given.
- 2.4.2016 【Report】Kazunori Kataoka, Prof., Graduate School of Engineering, The University of Tokyo appeared on the Asahi TV series Shinichi Hatori Morning Show's 'Original General Research Corner: select cancer cells to destroy, radiotherapy front line' and explained nanomachines (continuation of introduction to nanomachines broadcast on 14th January, 2016).
- 2.4.2016 【Activity Report】iCONM and the California NanoSystems Institute (CNSI) cooperated closely and entered into a Memorandum of Understanding (MOU) regarding academic exchange.
- 2.5.2016 【Newspaper】'Nanomachines' and iCONM introduced. 2/4 (Thursday) Yomiuri Shimbun evening publication 'SF actually enters the body and heals disease' , 2/5 (Friday) Nihon Keizai Shimbun morning edition Regional Economic Aspect Kanagawa, 'Innovation Center of NanoMedicine, Kanagawa's Engine, Industry-Academia-Government Collaboration in Advanced Medical Care, Nanotechniques to Treat Cancer'.
- 2.15.2016 【Press Conference】Yu Matsumoto, Assistant Prof., Department of Otolaryngology, Auditory and speech surgery, The University of Tokyo Hospital (COINS participating researcher), Tatsuya Yamasoba, Prof. and Kazunori Kataoka (COINS Research Leader) Prof., Graduate School of Engineering/Graduate School of Medicine, The University of Tokyo et al held a press conference on their published research theme (*Nature Nanotechnology* : 'Vascular bursts enhance permeability of tumour blood vessels and improves nanoparticle delivery'). Discovered a New Tumour Blood Vessel Permeation Pathway to Increase the Efficacy of DDS (drug target treatment) in Cancer!
- 2.18.2016 【Report】The research of Takanori Ichiki, Associate Prof., Department of Bioengineering, Graduate School of Engineering, The University of Tokyo (COINS theme 4 leader) introduced in Kawasaki City's Kawasaki SkyFront i-Newsletter Vol. 6 (February 2016 Edition).
- 2.22.2016 【Activity Report】COINS 5th General Meeting held.
- 2.29 to 30.2016 【Activity Report】Participated in the COI 2021 Conference sponsored by the Ministry of Education, Culture, Sports, Science and Technology and supported by the Japan Science and Technology Agency.
- 3.17.2016 【Report】An article from COINS research leader Kazunori Kataoka published in a corner of the JST 'Journal of Industry-Academia-Government Collaboration' 'Researcher Relay Essay' in January 2016.
- 3.17.2016 【Award】Prof. Nobuhiro Nishiyama (COINS subtheme 5 leader) of the Chemical Resources Laboratory, Tokyo Institute of Technology awarded the 3rd Particle Design Award from The New Pharmaceutical Technology and Engineering Foundation, joint awardee Prof. Kazunori Kataoka (COINS Research Leader) of The University of Tokyo Graduate School of Engineering. Award title 'Development of a polymer micelle-type drug delivery system for targeted therapy of intractable cancer'.
- 3.18.2016 【Activity Report】Published a newsletter 'NanoSky Vol. 1'.
- 3.23.2016 【Newspaper】Project Associte Prof. Kenji Itaka, (COINS theme 3 leader) et al of the Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo published an article in the Nikkei Business Daily on the treatment of developing chondrodysplasia.
- 4.1.2016 【Activity Report】Held COINS Seminar No. 14 in iCONM.
- 4.5.2016 【Activity Report】Held COINS Seminar No. 15 in iCONM.
- 4.14.2016 【Report】Prof. Yoshihiro Muragaki et al of the Institute of Advanced Biomedical Engineering and Science in Tokyo Women's Medical University, a COINS participating institution, developed sonodynamic therapy and published an article in the Nikkei Biotech Online about starting clinical research within a year.
- 4.18.2016 【Report】Kazunori Kataoka, Project Prof., Policy Alternative Research Center, The University of Tokyo, COINS Research Leader (iCONM Centre Director), Hiroaki Kinoh, principal research scientist and Horacio Cabral, Associate Prof., Graduate School of Bioengineering, The University of Tokyo (iCONM visiting research fellow) held a joint press conference with the University of Tokyo, iCONM and COINS on 'Success in developing a nanotech anticancer drug aimed at cancer stem cells' regarding a published article from principal research scientist Hiroaki Kinoh (Kataoka/Kinoh Laboratory Deputy Laboratory Director, visiting research fellow at the University of Tokyo) (Nanotechnology journal published by The American Chemical Society, *ACS*) (*Nano*: Nanomedicines eradicating cancer stem-like cells in vivo by pH-triggered intracellular cooperative action of loaded drugs).
- 5.8.2016 【Report】COINS research leader Kazunori Kataoka (Director of the iCONM and Project Prof. of Policy Alternative Research Center, The University of Tokyo) appeared in the Japanese documentary programme 'Future Eyes'.
- 5.12.2016 【Activity Report】Held COINS Seminar No. 16 in iCONM.
- 5.16.2016 【Report】The University of Tokyo, iCONM, The Tokyo Institute of Technology, the National Institutes for Quantum and Radiological Science and Technology and COINS held a joint press conference on the 'Successful development of a 'nanomachine contrast agent' for detection of tumour malignancy' regarding an article published by Kazunori Kataoka, Project Prof., Policy Alternative Research Center, The University of Tokyo, Director General (COINS Research Leader), and principal investigator Mi Peng, Nobuhiro Nishiyama, Prof., Tokyo Institute of Technology and Aoki Ichio. Team Leader, National Institutes for Quantum and Radiological Science and Technology (*Nature Nanotechnology*: A pH-activatable nanoparticle with signal amplification capabilities for non-invasive imaging of tumour malignancy).
- 5.16.2016 【Activity Report】The 16th Symposium of Gene and Delivery Study Group held at LiSE.
- 5.25.2016 【Activity Report】Held COINS Seminar No. 17 in iCONM.
- 6. 3.2016 【Activity Report】COINS 6th General Meeting held.
- 6.13.2016 【Activity Report】Held COINS Seminar No. 18 in iCONM.
- 6.14.2016 【Report】COINS research leader Kazunori Kataoka (Director General of iCONM and Project Prof. of Policy Alternative Research Center, The University of Tokyo) appeared in 'Medical Frontiers' on NHK World.
- 6.22.2016 【Report】A related article in a joint press conference held on May 16th was featured in MEDTEC Japan Online as a special report.
- 6.22.2016 【Report】Article by Project Prof. Kazunori Kataoka, Policy Alternative Research Center, The University of Tokyo (COINS Research Leader and Director General of iCONM) published an article in the Kawasaki Institute of Industrial Promotion's 'Industry Information Kawasaki June 2016' (published 1st June).

Editor's Note

In this NanoSky Vol. 2, we are focusing on efforts and results to support the creation of nanomachines in COINS theme 1 'significantly inhibiting cancer recurrence and metastasis'. We intend to introduce initiatives in each theme from hereon.

At the beginning of this journal, research leader Kazunori Kataoka talked about the COINS vision of a 'smart life care society', "In-Body Hospital" which achieves it, the relationship between the accomplishment of "In-Body Hospital" and the goals and efforts of the 'theme'. I hope the top message will help everyone understand.

COINS theme 1 aims particularly at establishing ground-breaking cancer treatment by refining the DDS function of polymer micelles which are the foundation of "In-Body Hospital", we have expanded much of the knowledge gained in the process to other themes, and this also plays an important role as the driving force to promote R&D towards "In-Body Hospital" in COINS overall.

From the trialogue and research topic 1 in this journal, the advance in nanomachine development to change cancer treatment with one eye on "In-Body Hospital" and from research topic 2, I hope you are aware of the motivation of researchers in taking advantage of the potential of polymer micelles to obtain new findings.

The next 'listen to COINS' members' is a completely new project and I hope to overcome the misunderstanding (?) of the global negative image such being hard or tough for cutting-edge researchers like this and to have affinity with members of COINS.

The next issue aims at publishing on the theme of a cancer diagnosis system in theme 4 in March next year. Please look forward to it.

Last but not least, I would like to take this opportunity to thank members of the Editorial Committee and everyone for their willing cooperation with this magazine despite the tight schedule. Thank you.

Chief Editor : Takashi SUGIMOTO

Published by KAWASAKI INSTITUTE OF INDUSTRY PROMOTION,
Center of Open Innovation Network for Smart Health (COINS)
Research and Promotion Institute
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Writer: Ayumi KOJIMA
Photograph: Aki TANAKA
Design: Studio L Co., Ltd.