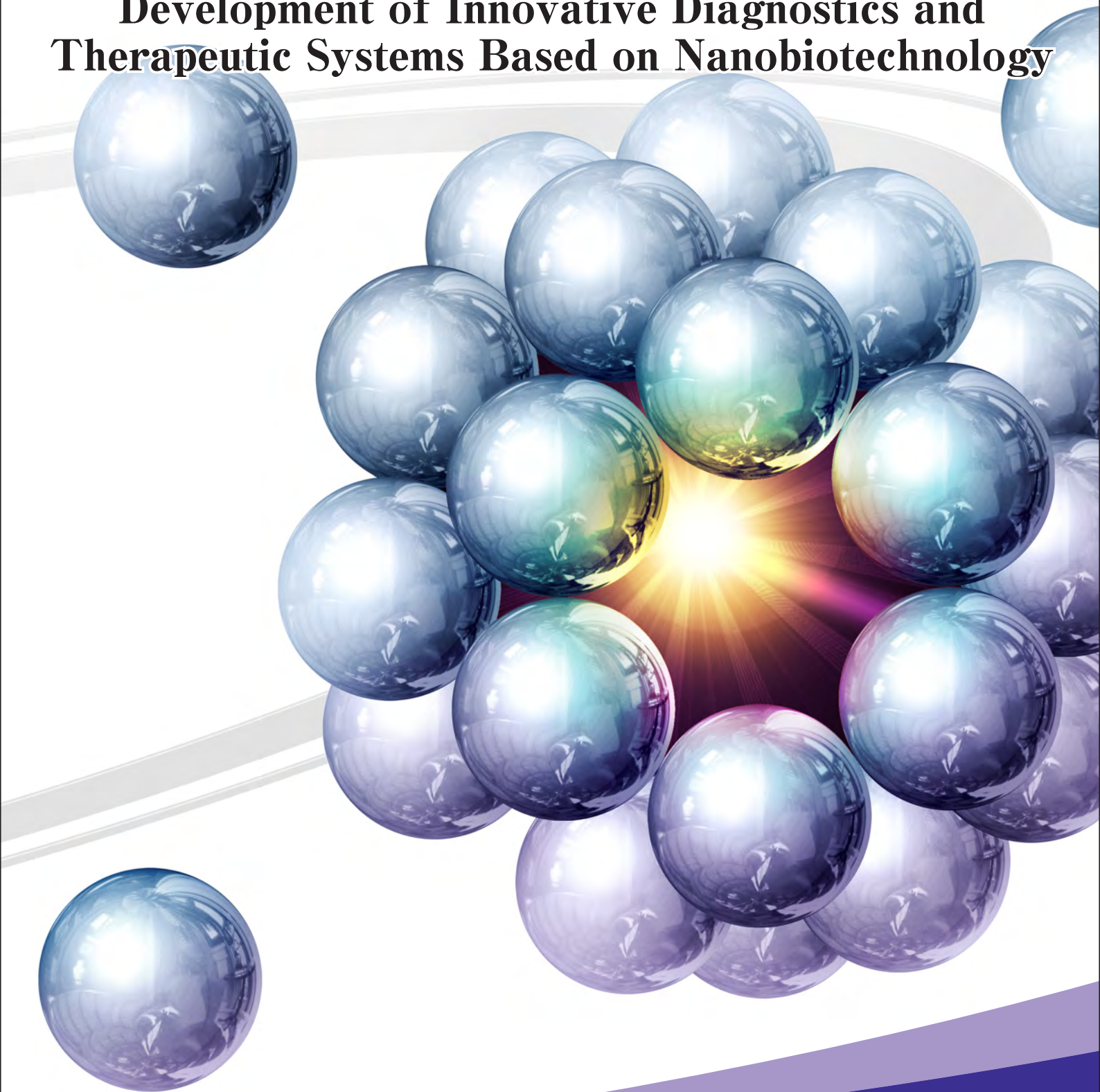
Funding Program for World-Leading Innovative R & D on Science and Technology (FIRST)

# NanoBio

## Development of Innovative Diagnostics and Therapeutic Systems Based on Nanobiotechnology



# Realization of Seamless and Minimally Invasive Diagnostic and Therapeutic System for Intractable Diseases

## Mission

**IN this project, we aim to build a precision diagnosis and treatment system that is implemented in a low invasive and seamless manner for everything from the very early diagnosis up to radical treatment of intractable diseases such as cancer by creating a nanobiodevice which integrates the various functions of medical devices and drugs, etc. on a nano scale.**

Japan has entered a super-aged and mature society and various problems have become evident in the medical system, such as increased medical costs, a shortage of doctors, imbalance in the import and export of medical industries, the citizens' demands for higher quality medical care, and there is a strong demand for radical innovation. Therefore, we would like to contribute to the realization of a health-sustainable society by providing highly versatile solutions with revolutionary diagnostic and therapeutic systems based on nanotechnology and materials technology in which Japan leads the world. To do so, in addion to promoting scientific and technological innovation, innovative measures, namely social and economic innovation, are essential for the promotion of social deployment of research results that have clear goals in healthcare and medical system, and we will strive toward its realization. Furthermore, it is our sincerest wish that the development of human resources in the integrate field of medicine, pharmacology and engineering through the promotion of this project will serve as the driving force to bring about further innovation, and carry the world through creating new academic fields and industries centered on medical science.


Core Researcher / Sub-Project Ⅱ Leader

**Kazunori KATAOKA**

Departments of Materials Engineering,
Graduate Schools of Engineering,
Division of Clinical Biotechnology,
Center for Disease Biology and Integrative Medicine,
Graduate School of Medicine,
The University of Tokyo, Professor


"**F**unding Program for World-Leading **I**nnovative **R**&D on **S**cience and **T**echnology" (FIRST)

It was launched by the Japanese government with the FY2009 supplemental budget. The aim of the FIRST program is to advance leading-edge research and development that will strengthen Japan's international competitiveness while contributing to society and people's welfare through the application of its results. Program planning and core-researcher/research-project selection was carried out by the council for science and technology policy in the cabinet office. There were 565 applications from which 30 core researchers had been selected.

# Members

## Kazunori KATAOKA

●Core Researcher
●Sub-Project Ⅱ Leader

Departments of Materials Engineering,
Graduate Schools of Engineering,
Division of Clinical Biotechnology,
Center for Disease Biology and Integrative Medicine,
Graduate School of Medicine,
The University of Tokyo, Professor

### Development of Supramolecular Nanocarriers for Drug and Gene Delivery

Nanobiotechnology- and nanobioengineering-based medicine that is aimed to control the cellular function and fate in a desirable manner, should be the key to success in the treatment of intractable diseases and tissue engineering. Thus, there is recently a strong impetus to the development of funcitonal nanodevices that promote cell differentiation at the desired site or deliver therapeutic agents such as drugs and genes to the targeted cells. We develop supramolecular "smart" nanocarriers including polymeric micelles, polymeric vesicles and multi-layered nanoparticles, through the self-assembly of artificial and natural materials, and carry out the nanocarrier-mediated therapy by facilitating the translation of basic achievements into clinical applications. Our goal is to produce revolutionary medical nanodevices, thereby contributing to realization of the futuristic medical system.

## Takanori ICHIKI

●Co-Core Researcher
●Sub-Project Ⅰ Leader

Department of Bioengineering &
Institute of Engineering Innovation,
Graduate School of Engineering,
The University of Tokyo, Associate Professor

### Development of Nano Diagnostic Device for Early Cancer Detection

Recently microRNAs were revealed to exist stably in body fluids like blood in a protected form within exosomes secreted from cells, and they are expected as promising biomarker candidates for the early cancer detection. In this study, we aim to establish microRNA screening as a rapid and less invasive cancer tests. We are going to develop the nanodiagnostic device which enables the on-chip sequential processing of purification, amplification and analysis of microRNA from a tiny amount of body fluid and establish the core technology for the future "nanodiagnostic device".

## Tsuneo SAGA

●Co-Core Researcher

Diagnostic Imaging Program,
Molecular Imaging Center,
National Institute of Radiological Sciences,
Director

### Research on Nano-DDS Imaging

We are aiming for the establishment of "visible nanodevice" that contains multiple imaging agents such as PET/SPECT and MRI. With the imaging device having high sensitivity, quantitative ability, and spatial resolution, we can detect cancer at its very early stage. In addition, the imaging of the DDS process enables prediction and early evaluation of treatment effect. We label micelle-type nanodevice with positron emitter (Cu-64, etc.), ganma-ray emitter (In-111, etc.) and MRI contrast agents (Gd, Mn, etc.), and evaluate/optimize the biodistibution for the realization of high-quality multi-modal imaging of cancer.

## Hiroshi ISEKI

●Co-Core Researcher

Faculty of Advanced Techno-Surgery,
Institute of Advanced Biomedical Engineering & Science,
Tokyo Women's Medical University, Professor

### Engineering Based Medicine Advanced Eye, Hands & Brain for Suregeon

Our laboratory is developing and proposing various surgical assisting systems. Intraoperative MR scanner and surgical navigation provide advanced vision for surgeons.Novel surgical informatics, such strategic desk and workflow analysis, works as advanced brain. Concerning the therapeutic devices as advanced hands for surgeons, we develop a new surgical instruments as well as its evaluation method to show scientific efficacy for governmental approval. We are especially focusing on combination product composed of domestically-developed therapeutic device and special drug enhancing the therapeutic effect. It will achieve cutting-edge local therapy of malignant tumor. As we have the experience of Japan's first investigator initiated trial of therapeutic device in photo-dynamic therapy for brain tumor, we can realize precise sonodynamic therapy for solid organ tumor using high-intensity focused ultrasound and special drug in this research grant.

## Hiromichi KIMURA

●Co-Core Researcher

Pharmaco-Business Innovation,
Graduate School of Pharmaceutical Science,
The University of Tokyo, Professor

### Development of Evaluation Method for Eco Medicine Based Upon Cutting-edge Nanobiotechnology

There is an accelerating global trend of R&D utilizing cutting-edge nanotechnology of both drugs and medical devices. Our research takes a holistic perspective to objectively evaluate the effect of the commercialization of such innovation on the medical and social system, including national medical expenditure. As the foundation we analyze the cost efficiency of these products utilizing nanotechnology, in terms of health economics. Then their systemic impact will be explored including the direct reduction of medical costs; the number of consultation and hospitalization period; efficiency of health care productivity. The scope of the research will also explicitly assess the effect on productivity; environmental impact; job creation; to provide the broader societal context / dynamics.

## Tsuyoshi TAKATO

●Co-Core Researcher

Department of Oral and Maxillofacial Surgery,
Graduate School of Medicine,
University of Tokyo, Professor

### Regenerative Medicine in Oral and Maxillofacial Regions

In order to broaden the indication range of regenerative medicine to trauma, tumor, congenital anomaly, for example, cleft lip and palate or microtia which is a congenital anomaly of the ear, we are now focusing on tissue engineering in research works, especially in bone and cartilage. We have established Division of Tissue Engineering in Tokyo University Hospital and our department has two endowment departments in Tissue Engineering Division. These staffs are focusing on translational research works in Oral and Maxillofacial regions.

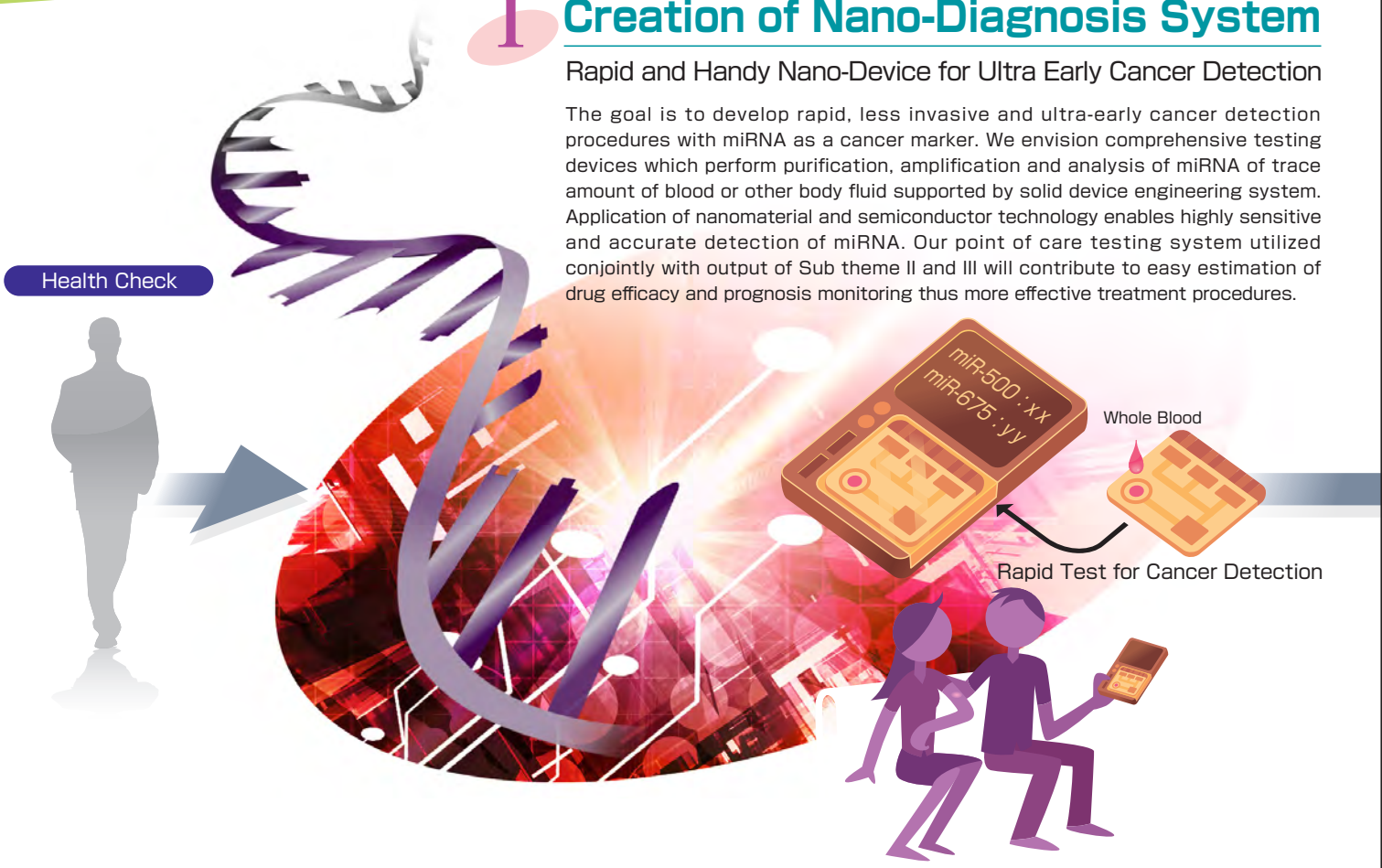
# Creation of Diagnostic and Therapeutic Systems Utilizing Nano Bio Technology

Ultra-early, Accurate Diagnosis and Targeted Therapy for Cancer

## I Creation of Nano-Diagnosis System

### Rapid and Handy Nano-Device for Ultra Early Cancer Detection

The goal is to develop rapid, less invasive and ultra-early cancer detection procedures with miRNA as a cancer marker. We envision comprehensive testing devices which perform purification, amplification and analysis of miRNA of trace amount of blood or other body fluid supported by solid device engineering system. Application of nanomaterial and semiconductor technology enables highly sensitive and accurate detection of miRNA. Our point of care testing system utilized conjointly with output of Sub theme II and III will contribute to easy estimation of drug efficacy and prognosis monitoring thus more effective treatment procedures.




## IV Creation of Nano-Reconstruction System

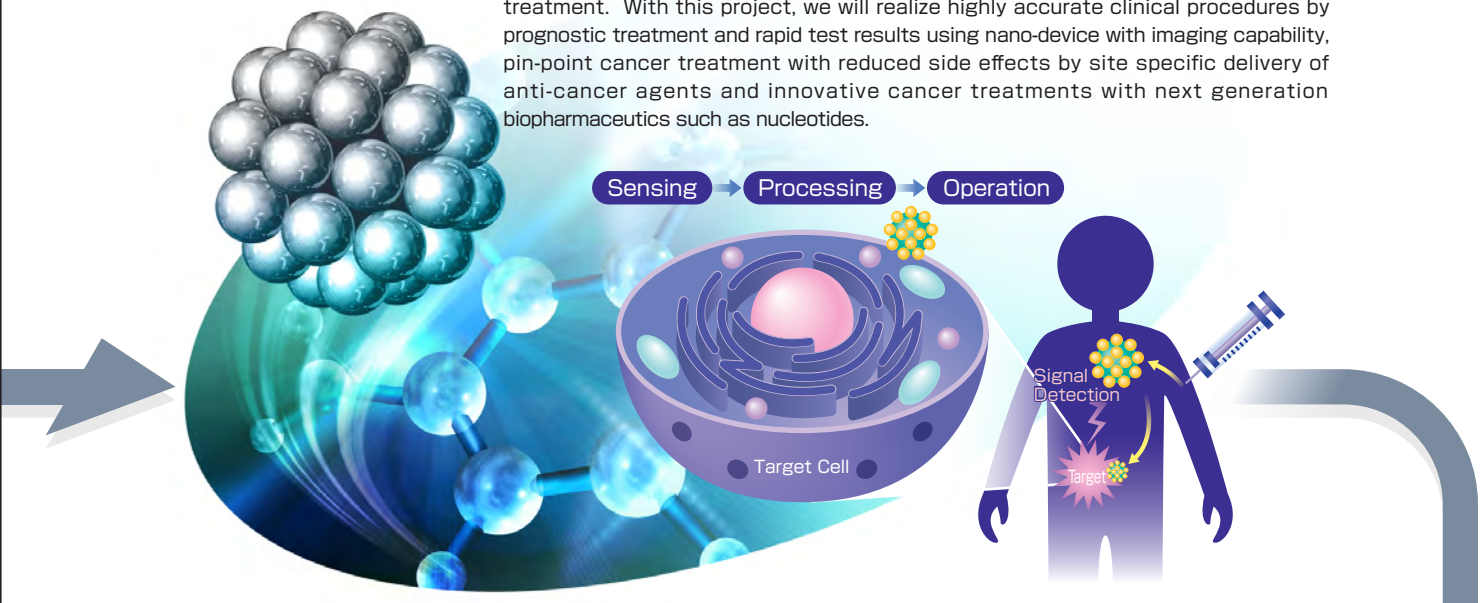
### Reconstruction by Regeneration-Inducing Implant Device

We will develop structural biomaterials that are suited for reconstruction of hard tissue and soft tissue and will establish controlling procedures of nano DDS by examining their interactions (stability, speed and amount of release). In addition, we will optimize signaling factors that promote tissue reconstruction. It will enable us to develop implant devices that accelerate tissue reconstruction by placing nano DDS loaded with signaling factors at desired locations in desired amounts. Implant devices with improved quality and speed of tissue reconstruction will contribute to early rehabilitation and improved quality of life of cancer patients.

## II Creation of Nano-Drug Delivery System (Nano-DDS)

### Pinpoint DDS for Cancer Imaging and Target Therapy

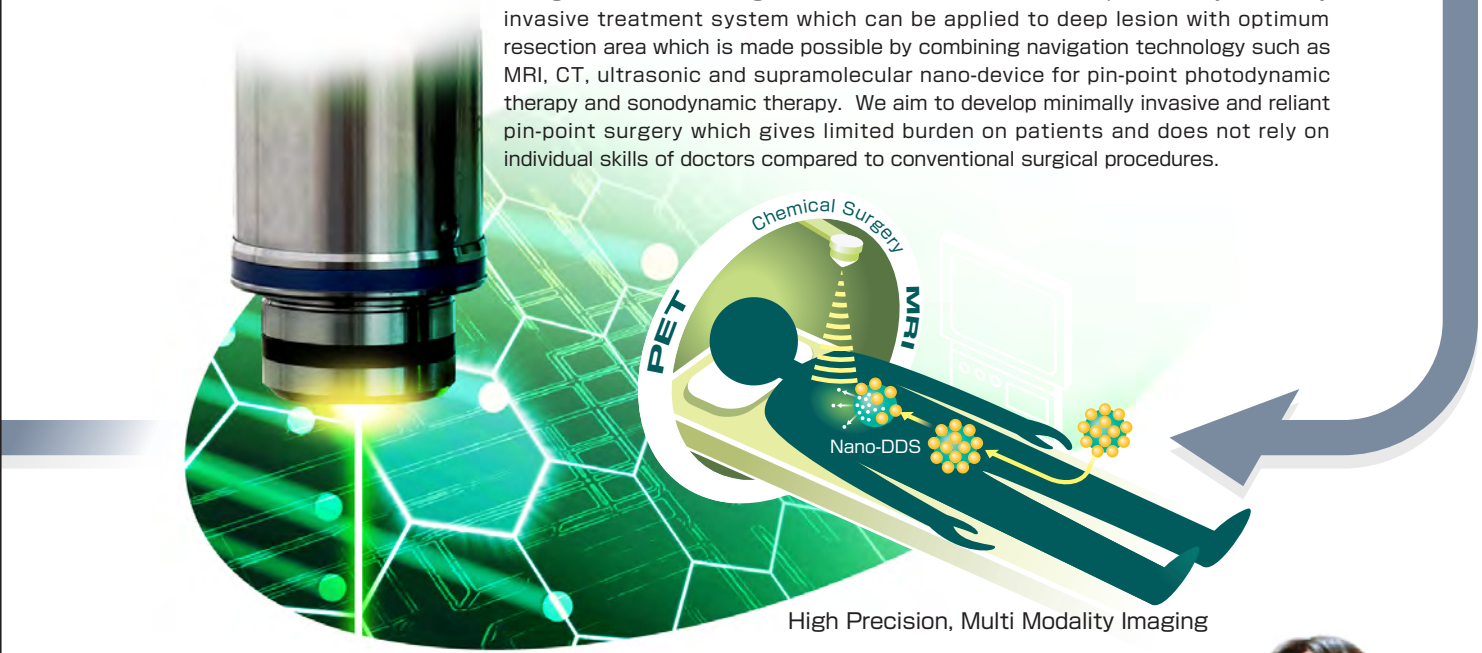
The goal is to develop supra-molecular nano-device equipped with sensing capability to detect the target, processing capability to change characteristic and functions in environment sensitive manner and operating capability to prosecute clinical actions on appropriate timing and location so that we can realize pin-point and precise cancer treatment. With this project, we will realize highly accurate clinical procedures by prognostic treatment and rapid test results using nano-device with imaging capability, pin-point cancer treatment with reduced side effects by site specific delivery of anti-cancer agents and innovative cancer treatments with next generation biopharmaceutics such as nucleotides.




## III Creation of Minimally Invasive Nano-Treatment System

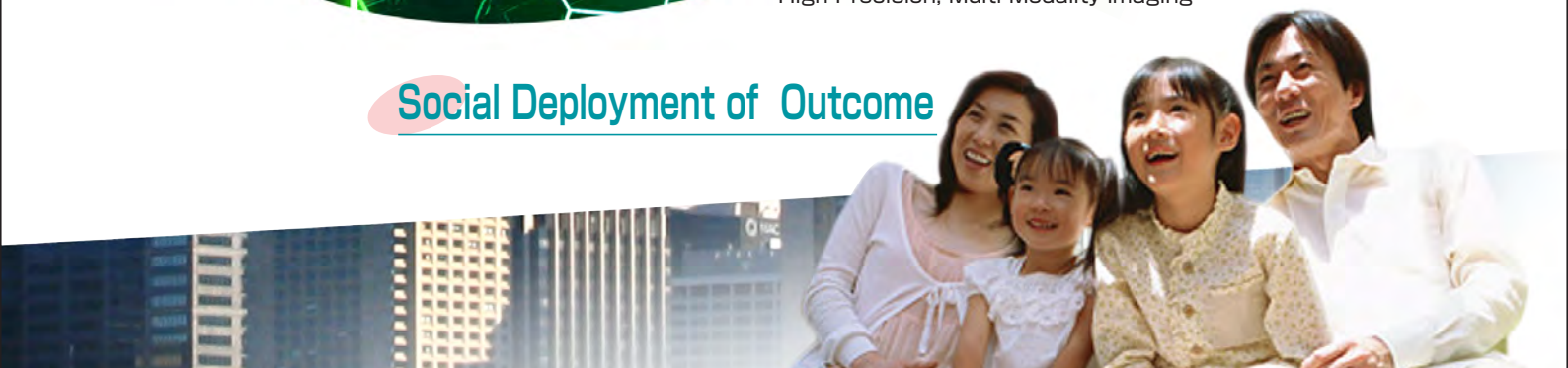
### Minimally Invasive Surgery by Nano Bio Technology

The goal is to realize high QOL and fast rehabilitation of patients by minimally invasive treatment system which can be applied to deep lesion with optimum resection area which is made possible by combining navigation technology such as MRI, CT, ultrasonic and supramolecular nano-device for pin-point photodynamic therapy and sonodynamic therapy. We aim to develop minimally invasive and reliant pin-point surgery which gives limited burden on patients and does not rely on individual skills of doctors compared to conventional surgical procedures.




High Precision, Multi Modality Imaging

## Social Deployment of Outcome



# Members

## Takashi FUNATSU

●Co-Core Researcher

Laboratory of Bio-Analytical Chemistry,
Graduate School of Pharmaceutical Sciences,
The University of Tokyo, Professor

### Development of Sensitive Detection of miRNA by Optical Microscopy

Micro RNAs which were secreted to blood from cancer cells are expected to be prominent candidates for biomarkers of the cancer. We are developing fluorescence microscopy for detecting and quantifying the micro RNAs which were extracted from blood or body fluid. The microdevice which can detect and quantify tiny amount of micro RNAs will enable us to diagnose cancers in early stage at medical institutions or at home.

## Mizuo MAEDA

●Co-Core Researcher

RIKEN Advanced Science Institute,
Bioengineering Laboratory,
RIKEN, Chief Scientist

### DNA-functionalized Nanoparticles for Reliable Gene Sensing

We have prepared DNA nanoparticles with a nanometer-sized vinyl polymer core or a colloidal gold core surrounded by a single-stranded DNA corona. The DNA nanoparticles disperse completely in an aqueous medium. Interestingly, when complementary single-stranded DNA, whose base number is identical to that of the DNA on the surface, is added to the dispersion of DNA nanoparticles to form the fully matched double helix on the surface, the DNA nanoparticles become unstable and spontaneously form aggregates in a non-crosslinking manner. Furthermore, we found that the double-stranded DNA-carrying nanoparticles acquire high colloidal stability when a terminal single-base mismatch exists at the interface between the DNA corona and the disperse medium. Exploiting the unique colloidal behavior of the DNA nanoparticles, we are devising a facile single-nucleotide polymorphism genotyping method as well as a miRNA detection system. We are applying the SPR imaging technique on our original, power-free microfluidic devices to the detection of the nanoparticles aggregation with high sensitivity in a reliable manner.

## Yasuhiro MATSUMURA

●Co-Core Researcher

Investigative Treatment Division,
Research Center for Innovative Oncology,
National Cancer Center Hospital East, Chief

### Development of a New Formulation of Anticancer Agents Incorporated Micelle Targeting Refractory Cancer

There are few effective regimens for intractable cancers such as pancreatic, stomach, lung, and other cancers. It is also know that such refractory cancers possess abundant cancer stroma. In this project, we will establish several new monoclonal antibodies against cancer related interstitial molecules and then make new formulation of polymeric micelles tagged with the antibodies especially for refractory, stroma-rich cancers.

## Yuji MIYAHARA

●Co-Core Researcher

The Institute of Biomaterials and Bioengineering,
Tokyo Medical and Dental University, Professor

### Study on DNA Sequencing Devices for miRNA

DNA sequencing analysis is expected to be applied for precise detection of microRNA as a biomarker of disieses such as cancer. In this study, DNA sequencing devices will be developed combining semiconductor technology and electrochemical detection methodology.Nucleic acid probes are immobilized on the surface of electrochemical electrodes and signals of single-base extensions are detected electrochemically for microRNA analysis. This method would be suitable for a simple and miniaturized testing system in clinical diagnostics.

## Nobuhiro NISHIYAMA

●Sub-Project Ⅲ Leader

Center for Disease Biology
and Integrative Medicine,
Graduate School of Medicine,
The University of Tokyo, Associate Professor

### Nanocarrier-mediated Imaging and Therapy of Malignant Tumors

Recently, medical devices such as MRI has made great advances. In this Outline, we design supramolecular nanocarriers for the delivery of imaging agents and sensitizers. The combination of medical devices and nanocarriers allows early detection of small pathological changes and pin-point treatment of the diseased sites without damaging normal tissues, improving the quality of life (QOL) of the patients.

## Yuichi TEI / Ung-il CHUNG

●Sub-Project Ⅳ Leader

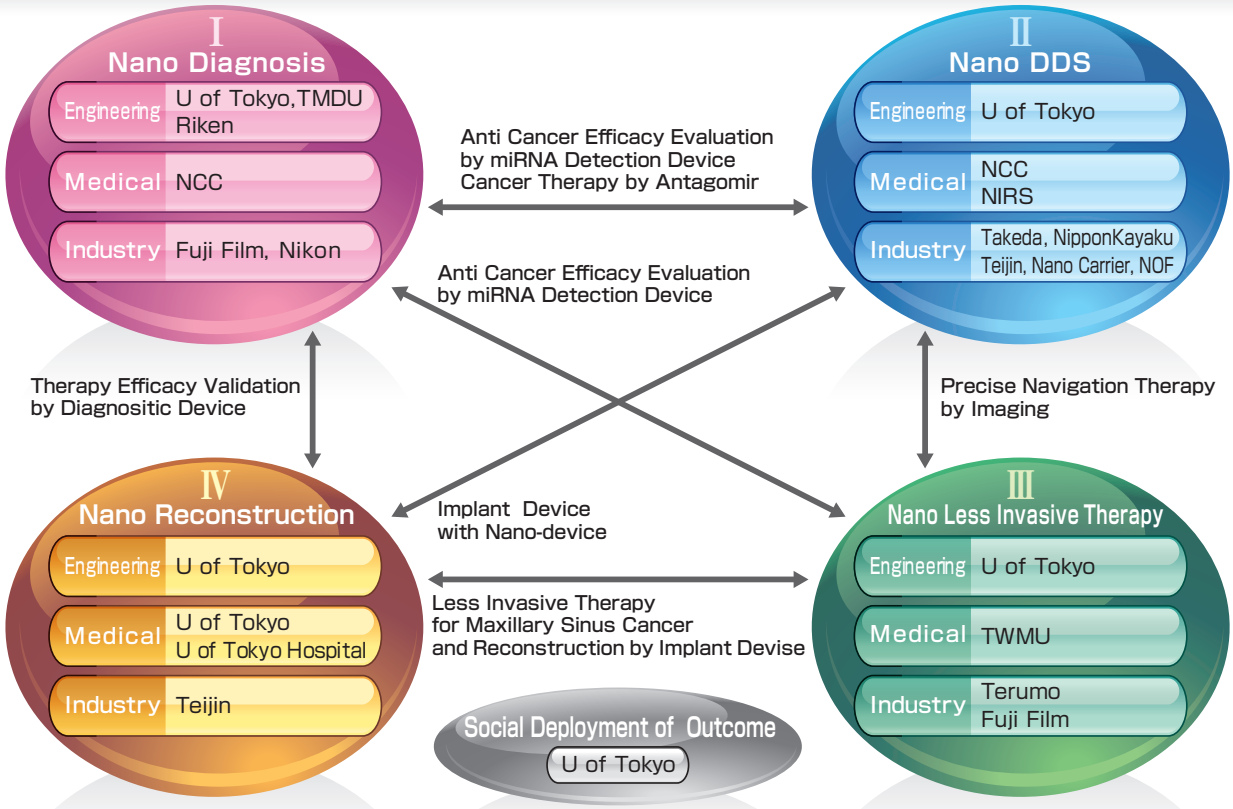
Department of Bioengineering, The University of Tokyo Graduate School of Engineering,
(Additional appointments at Department of Materials Science, Faculty of Engeering at Graduate School of Medicine), Professor

### Development of Innovative Structural Biomaterials for Regenerative Medicine

Regenerative medicine aims to help heal living tissues by integrating scaffolds, cells and signaling factors. From engineering point of view, development of structural biomaterials for scaffolds is an important challenge. Although much emphasis has been put on research on biocompatibility and biodegradability so far, new features including high mechanical performance, precise shape control, high handleability and regeneration-inducing capacity are required. The goal of our research is to create innovative structural biomaterias through 3D manufacturing of biomaterials, precision molecular design and the identification and placement of regeneration-inducing signals.

# Organization

## Project Structure




Operational Support Institution : Japan Science and Technology Agency

## Research Facilities

### Clean Room for Fabrication of Nano Diagnostic Device Prototype and Lithography Equipment

The laser lithography system can delineate high-resolution photoresist patterns below $\mu$m scale based on the CAD (computer aided design)data of microstructures. It is used in prototype fabrication.

### High Resolution CT for Small Animal

It will be utilized to evaluate the effectiveness of nano-device for animal model of disease by non-invasive imaging. Bone analysis and body fat measurement offer necessary quantitative information for researchers.

### Luminescent / Fluorescent in vivo Imaging System

Evaluation of nano-device efficacy on orthotopic implantation model or metastatic model of cancer by quantifying luminescence of cancer cell expressing luciferase gene.
It is also used to monitor, in non-invasive manner, the distribution of nano-device loaded with fluorescent-labeled probes or drugs.

### High field MRI for Micro Imaging

It has magnetic field as strong as 7 tesla, a few time stronger than clinical MRI, for high resolution in-vivo imaging for rodents. The MRI and nano-bio technology combined will provide new methodology for visualization of drug kinetics and therapeutic effect.


### Intelligent Operating Theater

This "Animal Intelligent Operating Theater" is composed of cutting edge technology: open MRI, navigation, ultrasonograph, endoscope and intraoperative information monitoring system for accurate topical therapy and its evaluation. This theater is the greatest environment for development and improvement of various medical therapeutic instruments which guarantee its safety and reliability.


### Confocal Microscope LSM780

It is used to observe intracellular distribution and activity of nano-device at high spatiotemporal resolution.

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