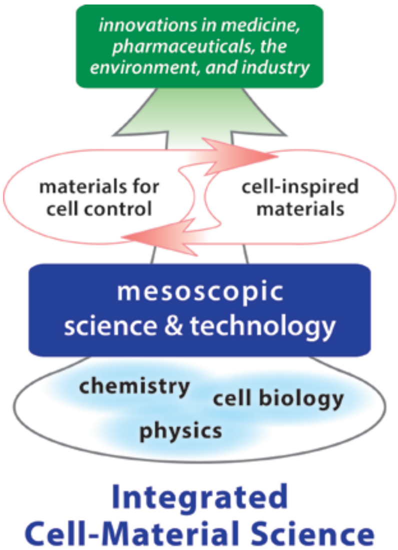
LARGE-SCALE PROJECTS

National Projects at Kyoto University

The promotion of large-scale research projects is a key policy of the Japanese government. Such projects are at the vanguard of academic research, coupling the most advanced technology and knowledge to pursue uncharted research frontiers. Kyoto University is commissioned to undertake several large-scale projects each year.

Making Ongoing Contributions to the Scientific Community

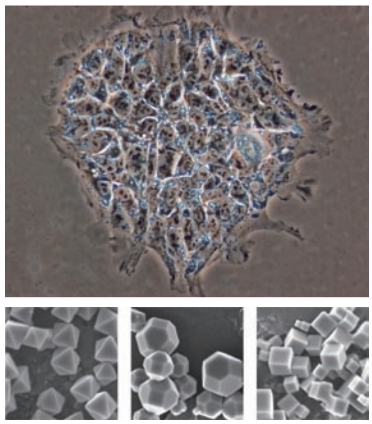
The Institute for Integrated Cell-Material Sciences (iCeMS)



Director: **Dr. Susumu Kitagawa**
Director of iCeMS/Profssor, Graduate School of Engineering
WEB www.icems.kyoto-u.ac.jp/

The Institute for Integrated Cell-Material Sciences (iCeMS) was founded in 2007 as part of a government program called the World Premier International Research Center Initiative (WPI) to recruit the best talent from around the world and drive the advancement of groundbreaking and interdisciplinary science. iCeMS is one of nine WPI centers throughout Japan and boasts eighteen world-renowned principal investigators, who are leading experts in cell biology, chemistry, and physics. Notably, Kyoto University Center for iPS Cell Research and Application (CiRA) director Dr. Shinya Yamanaka, the 2012 Nobel laureate in Physiology or Medicine, is an iCeMS scientific advisor. English is the official language of the center, and 30% of the research staff are from overseas.

The iCeMS is led by Director Susumu Kitagawa, and aims to bridge together synthetic materials and living cells. By focusing on a mesoscopic cellular environment, a realm between several and hundreds of nanometers, the institute strives to understand how processes in cells occur and then, harnessing this knowledge, specifically design materials to manipulate them. Three primary research areas include stem cells, cell membranes, and cellular energy storage. Stem cells are a promising area of regenerative medicine because they can essentially turn into any type of cell in the human body to replace damaged or diseased tissues. By understanding how stem cells function, materials could potentially be made to control them for medical applications. Meanwhile, the cell membrane is home to proteins that act as sentries for molecules that pass in and out of the cell. Breaking down how this trafficking is regulated may lead to synthesized materials for improving drug delivery. Lastly, energy is stored in specialized structures within cells and is used to create new molecules or deliver signals necessary for cell survival. Investigating how this process occurs may pave the way for the creation of novel materials capable of transporting and storing energy. Thus far, the high level of research conducted at iCeMS in these areas has led to publications in influential journals such as *Nature*, *Science*, and *Cell*. ↗



Cell and material sciences
Human embryonic stem cells (top) and mesoscopic crystals of porous coordination polymers with different morphology (bottom).

The institute is also highly engaged in the international community, hosting several international symposia and seminars every year. More recently, iCeMS and the Royal Society of Chemistry launched a multi-disciplinary journal called *Biomaterials Science* to bring together research on the molecular and mesoscopic interactions of biomaterials and their potential applications. Since its inception, iCeMS has made significant contributions to the scientific community and continues to conduct cutting-edge research, which could have major implications for improving human well-being and the environment.

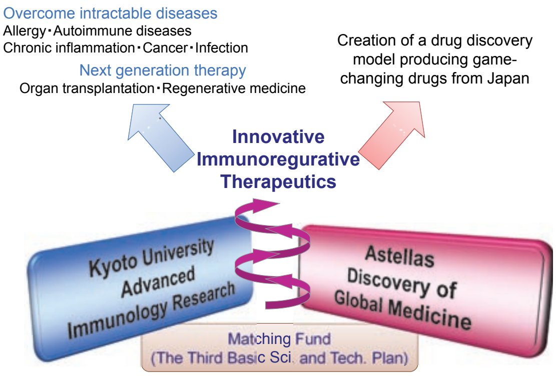
Best Drugs on Best Science

The Astellas Pharma-Kyoto University Project (AK Project)

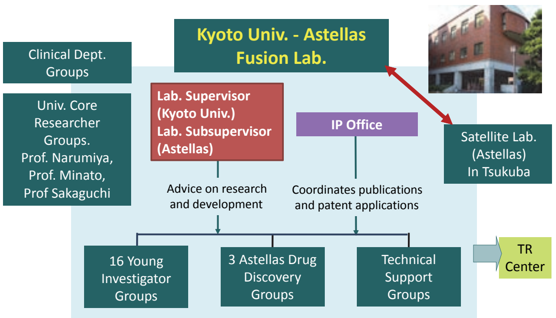
Project Leader: **Dr. Shuh Narumiya**

Professor, Graduate School of Medicine

WEB www.ak.med.kyoto-u.ac.jp (Japanese Only)



The Center for Innovation in Immunoregulative Technology and Therapeutics (The AK Project), an open innovation laboratory for drug discovery and development, was established in 2007 by Kyoto University and Astellas Pharma. The project is supported by a one to one matching fund from Astellas and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. The fund provides a total of 6 million dollars per year for the first three years and 15 million dollars per year for the next seven years. The AK Project aims to make innovative therapeutics to overcome intractable diseases in the immunology area, i.e. allergy, autoimmune diseases, chronic inflammation, cancer and infection, and to invent a drug discovery model in the post genome era capable of producing game-changing drugs in Japan.



The main site of the AK Project is the Fusion Laboratory, which occupies approximately 2000 m^2 from the basement to the third floor of Building B in the Medical School Campus of Kyoto University. There, sixteen groups led by young principal investigators (PIs), and three groups from Astellas work closely under the guidance of three key researchers from the Medical School, Prof. Shuh Narumiya, Prof. Nagahiro Minato and Prof. Shimon Sakaguchi. Each group carries out independent research to identify unique targets. A prominent feature of the AK project is collaboration with clinical departments, which search for biomarkers and verify the clinical significance of drug targets found in the Fusion Lab. There is a satellite laboratory located in the Astellas Research Institute in Tsukuba, which conducts high-throughput screening and compound optimization. Early clinical trials on drugs developed by the AK project are planned to be carried out at Kyoto University's Translational Research Center.

The AK Project is prominent in its integration of the medical school's basic and clinical medicine and industrial sector drug development technology. Basic scientists, clinicians and Astellas scientists form clusters in the Fusion Laboratory for each target disease to synergize their expertise. The members share clinical information and samples, knowledge on molecular mechanisms, and drug discovery skills. The AK Project has an intellectual property (IP) office in the Fusion Lab, and three IP managers handle all IP matters such as patent applications, publications, and contracts on-site. We have thus far successfully discovered twenty-three drug targets, filed twenty-two patent applications, and published more than 150 scientific papers. The project aims to simultaneously engage in excellent scientific research and drug discovery. Its motto is *Best Drugs on Best Science.*

Creation of Healthy Society

The Innovative Techno-hub for Integrated Medical Bio-imaging Project (CK project)

The CK project combines Kyoto University's integrated scientific-technological knowledge and excellent clinical research achievements with the Canon corporation's technical strengths in product development. Canon Inc. is a leader in the field of professional and consumer imaging equipment and information systems. Financially supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, the project was launched in 2006, and will last for ten years, concluding in 2015. Total budget from MEXT for the ten-year period is 11 billion JPY.

Since 2012, Otsuka Pharmaceutical Co., Ltd., a pharmaceutical and nutraceutical company which seeks to contribute to better health for people worldwide, has participated in the project to accelerate the development of molecular imaging probes. The project involves 105 researchers, postdoctoral scholars, and medical doctors from Kyoto University, 125 researchers from Canon Inc., and 5 researchers from Otsuka Pharmaceutical Co., Ltd. The base institutions for the project are the Clinical Research Center (CRCMeD) on Kyoto University's Yoshida campus, the Int'tech Center on Katsura campus, the Kyoto University Hospital, and Canon Inc. in Shimomaruko, Tokyo.

The long-term aim of the project is the realization of new imaging-diagnosis techniques, including the development of innovative molecular imaging probes. Ultimately the program seeks to contribute to the creation of healthy society by promoting cutting-edge research and development, while fostering talented researchers in interdisciplinary research areas of medicine and engineering.

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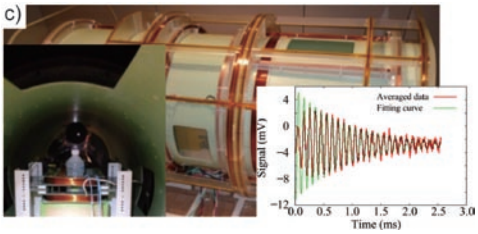

New imaging-diagnosis equipment

a) The research group's breakthrough in Optical Coherence Tomography (OCT), simultaneously bringing further improvements in resolution and imaging speed, is expected to lead to a high-level eye fundus diagnostic modality with the ability to detect signs of sight threatening diseases appearing on the fundi. b) The research group is investigating a novel technology which integrates ultrasound and optical imaging, and has started a clinical study of photoacoustic mammography (PAM) that enables the visualization of neovascular networks of cancer. c) The group is also planning to develop a small-scale MRI (magnetic resonance imaging) device using high-sensitivity optically pumped atomic magnetometers (AMMs) as detecting sensors, a small-scale MRI using AMMs that does not require superconducting magnets, and a new diagnostic system that can simultaneously observe biomagnetic and MR signals.

Toward Sustainable Development

Elements Strategy Initiative for Catalysts and Batteries (ESICB)

Director: **Dr. Tsunehiro Tanaka**

Professor, Graduate School of Engineering

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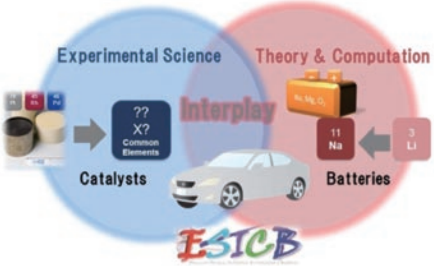
The industries of Japan depend on imports of rare earths and other rare metals which are key elements utilized in electronics, automobiles, information technologies, architecture, etc. The industries are facing a rise in the price of such materials, and a shortage of supply due to a rapid increase in the consumption and resource management policies of the countries which produce them, accompanied by global economic growth and the expansion of advanced industries.



The Ministry of Education, Culture, Sports, and Technology (MEXT) of Japan launched "Elements Strategy Initiative", ten-year national strategic research project to find alternative elements to replace the rare-metals in order to solve the problem of limited resource and strengthen Japanese industries. The project aims to develop rare-metal free materials in four research fields which are directly related to Japanese industrial competitiveness: magnetic materials, catalysts and batteries, electronic materials, and structural materials.

In 2012, Kyoto University was designated as two leading research centers of the Elements Strategy Initiative by the Japanese government; one is catalysts and batteries (ESICB), and the other is structural materials. (See the next article.)

The ESICB is devoted to establishing and deepening the science of elements, developing rare-metal free catalysts and rechargeable batteries, and training gifted young scientists and engineers to work towards sustainable development. In particular, the ESICB elucidates the 'nanoscopic' processes and phenomena of the complex systems such as catalysts and batteries and deepen the science describing such complex systems through the interplay between the theoretical and experimental sciences. Thereby, the ESICB seeks to develop rare-metal free catalysts and batteries by prediction of new materials as well as foster talented young researchers throughout the project.

Strength and Toughness are Fundamental

Elements Strategy Initiative for Structural Materials (ESISM)

Director: **Dr. Isao Tanaka**
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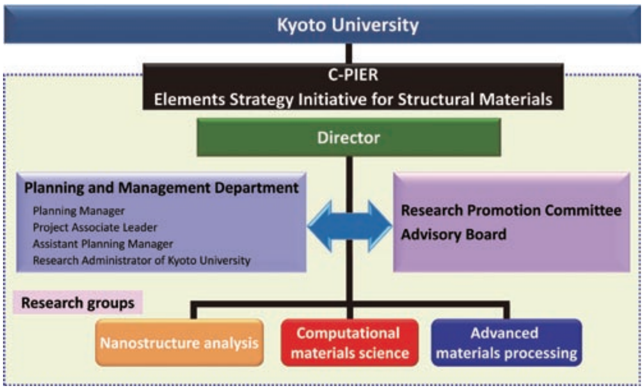
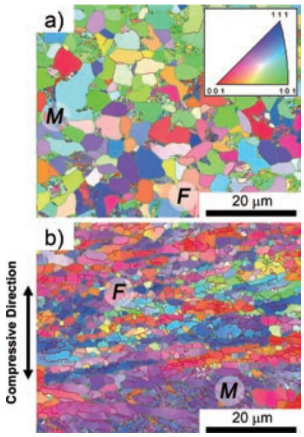


Even in the modern era of science and technology, it has been shown through natural disaster and nuclear meltdown that Japan's social systems are, as ever, exceedingly frail. Indeed, some have even lost trust in science and technology themselves. To win back public trust and develop a new strategy for the growth of Japan, it is essential to employ the power of science and technology to reinforce social infrastructure and secure a high degree of reliability. For this purpose, not only in massive structures and transportation systems, but also in medicine, communications, energy conversion, energy storage and the environment, it is necessary to study the performance of structural materials under normal steady-state conditions, and also their dynamic characteristics: responses to sporadic changes in stress patterns, electrical and magnetic fields, or chemical environments. In short, it is required to have a correct understanding of all manners of "deformation and fracture" phenomena, and information that can be used to ensure dependable service over the entire design lifespan. It is this notion—structural materials, in the broad sense—that has such a strong bearing on the safety and robustness of social infrastructure in every way.



Electron Backscatter Diffraction (EBSD) orientation maps
a) statically transformed ferrite. b) dynamically transformed ferrite in an Fe-6Ni-0.1C alloy.

In structural materials, both of strength and toughness are required. This is fundamental. Strength, or resistance to deformation, allows producing materials that are light and compact. Toughness, or resistance to fracture, allows producing materials that are dependable. Generally, however, there is a tradeoff between the two—what is strong is brittle, what is tough is weak. But does it have to be this way? Is there any way that can produce the ultimate frontier material, not through the addition of rare alloying elements, but rather through structural control, from electrons and atoms at one extreme to macrostructures at the other, with new tools ranging from electron theory to state-of-the-art metrology? The mission of Elements Strategy Initiative for Structure Materials (ESISM) at Kyoto University is expressed as three points: 1) Through fundamental research, to deepen our understanding of structural materials and develop new conceptualizations; 2) To support efforts toward the industrial application of our findings; 3) To nurture talented researchers and other personnel capable of sustaining the development of Japan into the future. Necessary for this mission are not only the untiring efforts of our members, but also an unfettered exchange of views and opinions, including a broad dialogue with society at large and a free association with professional colleagues at home and abroad.

Regulation and Reconstitution of the Totipotent Epigenome

JST Strategic Basic Research Programs (ERATO) "SAITOU Totipotent Epigenome"

Research Director: **Dr. Mitinori Saitou**

Professor, Graduate School of Medicine

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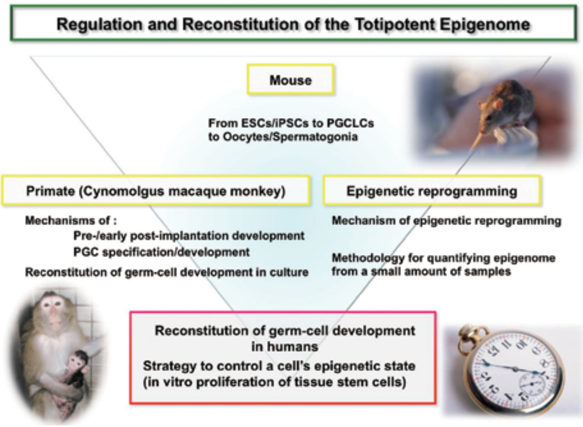
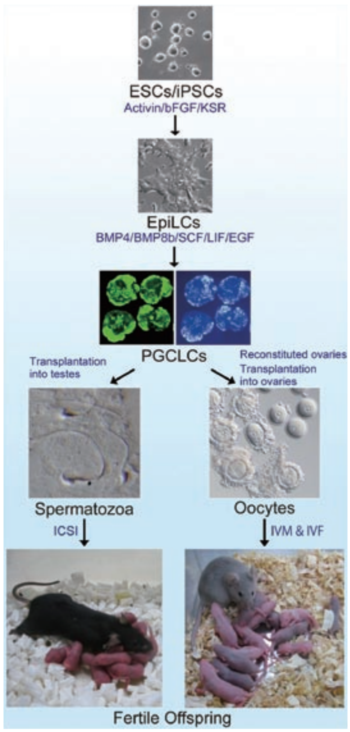


Totipotency refers to the ability of a cell to differentiate into all cell lineages and to form individuals. In mammals including humans, only zygotes and their immediate descendants (blastomeres in 2-cell and 4-cell embryos) bear the totipotency. During subsequent development, although embryonic cells lose their totipotency, primordial germ cells (PGCs), the precursors both for oocytes and spermatozoa, initiate a program for re-acquiring totipotency, in part through the process called epigenetic reprogramming. Understanding of the genetic and epigenetic mechanisms for the acquisition of totipotency in the germ line is of key importance in biomedical science and in regenerative medicine.

Using the mouse and a non-human primate (cynomolgus macaque monkey) as model organisms, this project explores the genetic and epigenetic regulation in germ cells, early embryos and stem cells, aiming for the regulation and reconstitution in vitro of germ cell development and ultimately, totipotency. Prof. Saitou and his colleagues succeeded in inducing mouse embryonic stem cells (ESCs)/induced pluripotent stem cells (iPSCs) into epiblast-like cells (EpiLCs), which were in turn induced into PGC-like cells (PGCLCs) with capacity for both spermatogenesis and oogenesis. This work is a major breakthrough, which allows the generation of PGCLCs in a relatively large number (~10^6) and provides a foundation for the reconstitution of whole germ cell development in vitro. Thus, the knowledge obtained by this project will provide a foundation for clarification of the mechanisms for infertility, congenital diseases and some genetic disorders, as well as for development of a method for stem/progenitor cell proliferation.

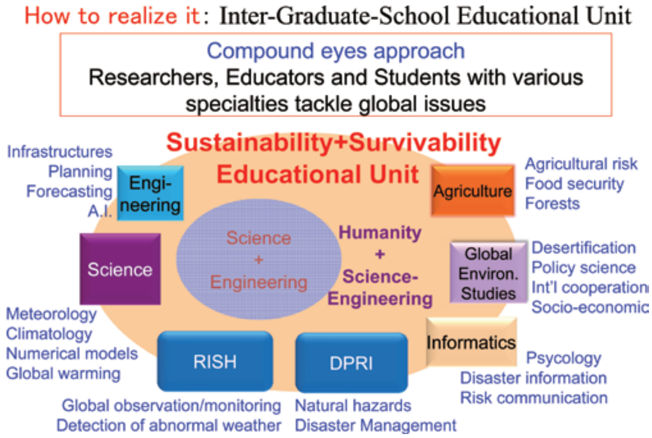


ESCs: embryonic stem cells, iPSCs: induced pluripotent stem cells, EpiLCs: epiblast-like cells, PGCLCs: primordial germ cell-like cells, ICSI: intracytoplasmic sperm injection, IVM: in vitro maturation, IVF: in vitro fertilization, PC: principle component.

Sustainability/Survivability Science for a Resilient Society Adaptable to Extreme Weather Conditions

The Global COE - ARS Program

Leader: **Dr. Kaoru Takara**
Professor, Disaster Prevention Research Institute
WEB 133.3.251.107/index.php?id=3



The GCOE-ARS Program (Global Center of Excellence — Adaptation and resilience in a sustainable/survival society to extreme weather and water conditions) focuses on adaptation to climate change impacts, such as extreme weather and subsequent water-related hazards that seriously affect people and societies around the world, such as cyclones, storms, floods, droughts, and sea level rise.

In order to confront those serious problems, the GCOE-ARS Program has been providing innovative education and research opportunities by operating an interdisciplinary graduate school education system (Educational Unit) under the Center for Promotion of Interdisciplinary Education and Research (C-PIER) since April 2010. This effort is anticipated to produce young world leaders, who will have the expertise to deal with global climate issues in coming decades. The Educational Unit is composed of five graduate schools (Global Environmental Studies, Science, Engineering, Informatics and Agriculture) and two research institutes: the Disaster Prevention Research Institute (DPRI) and the Research Institute for Sustainable Humanosphere (RISH).

This COE Program implements two research activities:

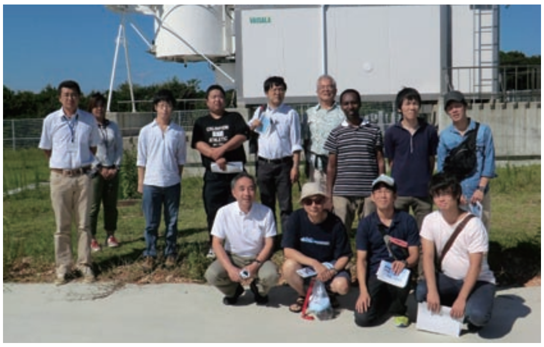
Theme 1: Science-Engineering Interdisciplinary Research on the Monitoring and Prediction of Extreme Weather, Water Cycle and Disaster Contingency

Theme 2: Integrated Social-Natural Sciences Research Towards the Creation of a Sustainable Society Adaptable to Global Environmental Change

Under these research themes, young graduate students can join field-based research projects in partner countries in Asia, Oceania, and Africa to further their own scientific purposes, as well as build their capacities in various technological, social, and international skills for adaptation strategies for current and future global environmental changes. So far, ten students have graduated from the program: four from Japan, and the others are from Bangladesh, Brazil, Cambodia, India, Indonesia, and the Philippines.

The program has established an international network covering major international organizations such as UNESCO (United Nations Educational, Scientific and Cultural Organization) and the WMO (World Meteorological Organization), as well as research sites and institutions in Fiji, India, Indonesia, Malaysia, Thailand, Vietnam, Niger, Egypt, France, the UK, and USA.

The GCOE-ARS Program produces annual reports. Selected research outcomes are published in the Special Issue of the *Journal of Disaster Research on Sustainability/Survivability Science for a Resilient Society Adaptable to Extreme Weather Conditions*, **8** (1), 2013.



In front of the automatic radiosonde observation system in the Shionomisaki site of the Japan Meteorological Agency