# CÍRA: Center for iPS Cell Research and Application

### Center for iPS Cell Research and Application (CiRA)



CiRA's Goals in the first 10 years:

- 1. Establishment of basic technology and protect intellectual property rights
- 2. Creation of iPS cells for use in regenerative medicine
- 3. Conduct of preclinical and clinical studies
- 4. Development of therapeutic drugs using patient-derived iPS cells intellectual property

The Center for iPS Cell Research and Application (CiRA) was established in April 2010 as the world's first institution focusing on induced pluripotent stem cells (iPS cells). Dr. Shinya Yamanaka, who pioneered the research field of iPS cell technology, directs the institute.

Equipped with a cell processing facility and laboratory animal research facilities, CiRA is comprised of four research departments: Reprogramming Science, Cell Growth and Differentiation, Clinical Application and Regulatory Science. Twenty-eight principal investigators work here to develop medical and pharmaceutical applications for iPS cells.

www.cira.kyoto-u.ac.jp/e/



CiRA has now celebrated the second anniversary of its establishment. Supported by assistance from the Japanese government and encouragement from many individuals, their research activities are making steady progress, and the number of scientific and administrative staff has now grown to about 200 members from 120 when the center was established.









### Lecturer Kazutoshi Takahashi was awarded the NYSCF Robertson Prize

The New York Stem Cell Foundation (NYSCF), a non-profit organization conducting cutting-edge translational stem cell research in its laboratory in New York City and supporting research by stem cell scientists at other leading institutions around the world, awarded Lecturer Kazutoshi Takahashi, PhD, CiRA with the NYSCF – Robertson Prize for his extraordinary achievements in translational stem cell research. The announcement came just a day after Dr. Yamanaka and Sir John Gurdon were awarded the Nobel Prize in Physiology or Medicine.

Lecturer Takahashi, a postdoctoral researcher in Dr. Yamanaka's laboratory, has played an important role in the research on reprogramming of differentiated cells into iPS cells, especially in finding four initialization factor for establishing mouse iPS cells. He was the lead author of the paper published in 2006, *"Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors"*, which is a key research paper detailing the work of Dr. Yamanaka.

www.cira.kyoto-u.ac.jp/e/research/ktakahashi\_summary/



Kazutoshi Takahashi, Lecturer, Principal Investigator, CiRA

### Anacardic acid found to rescue certain ALS abnormalities in experimental drug screening assay using motor neurons from ALS patient-specific iPSCs

Associate Professor Haruhisa Inoue – CiRA [left] Researcher Naohiro Egawa – CiRA [right]

A research group at CiRA has successfully recapitulated amyotrophic lateral sclerosis (ALS) – associated abnormalities in motor neurons differentiated from induced pluripotent stem cells (iPSCs) obtained from patients with familial ALS, a late-onset, fatal disorder, also known as for Lou Gehrig's disease. In a drug screening assay using the disease model, the team further found that the chemical compound anacardic acid can rescue some ALS phenotypes *in vitro*.

www.kyoto-u.ac.jp/en/news\_data/h/h1/news6/2012/120802\_1.htm http://dx.doi.org/10.1126/scitranslmed.3004052





A control motor neuron (left) and a motor neuron derived from ALS patient-specific iPSCs (right) (COURTESY OF DR. HARUHISA INOUE'S LABORATORY)

### CiRA's Logo: The DesignConcept

The logo uses the letters C, i, R and an A to form a human figure representing the CiRA philosophy: "To realize research for people and the ideal of regenerative medicine." The four colors – blue, green, red and black – applied in the logo also symbolize the four defined factors used when first inducing iPS cells, as well as interaction among patients, researchers, clinicians and iPS cells.

Idea: Lecturer Masato NAKAGAWA Design: Graphic Designer Akio OKUMURA



### Four Research Departments of CiRA



## Human iPS Cells Now Available through RIKEN BRC

Kyoto University has made the following iPS cells and relevant materials available to the scientific research community through the RIKEN BioResource Center (RIKEN), a public repository, for the benefit of scientific progress. The materials will be provided to non-profit academic research institutions solely for teaching and academic research purposes.

www.cira.kyoto-u.ac.jp/e/research/material\_1.html

### IP and Material Distribution for Commercial Uses

Requires a material transfer agreement (MTA) and patent license agreement with iPS Academia Japan, Inc., the company granted the rights to license the induced pluripotent stem cell (iPSC)-related patents from Kyoto University.

ips-cell.net/e/about/index.html

### **Department of Reprogramming Science**

iPSCs can be generated from ordinary somatic cells, such as skin cells, through the introduction of genes, proteins, or chemical compounds. They are able both to give rise to cells of any type in the body, and to proliferate indefinitely in culture. The event that causes differentiated cells to revert to an undifferentiated state of pluripotency is known as reprogramming. Led by Dr. Shinya Yamanaka, members of the Departments of Reprogramming Science are studying the mechanisms that underlie that process with the goal of developing even safer techniques for generating effective iPSCs.



### Human ES cells We senchymal stem cell Human IPS cells Furmar iP

### **Department of Cell Growth and Differentiation**

Led by Prof. Junya Toguchida, members of the Department of Cell Growth and Differentiation seek to develop methods for inducing pluripotent cells such as iPSCs and embryonic stem cells toward specific cell fates, such as mesenchymal tissue (bone, etc.) cells, cardiovascular lineages, neurons, and liver and pancreatic cells.

Using model organisms, they are also conducting preclinical studies on the safety and efficacy of somatic cells differentiated from iPSCs when transplanted into various tissues in the hopes of contributing to the development of effective iPS cell therapies.

### **Department of Clinical Application**

Members of the Department of Clinical Application generate iPSCs from somatic cells generously donated to the Center by patients afflicted with various genetic conditions, and use them to induce differentiation into various cell types as a platform for the study of disease etiology and mechanisms of pathology.

They further use patient-derived iPSCs in the search for and testing of candidate drug compounds and therapies. This division is led by Prof. Tatsutoshi Nakahata.



### **Department of Fundamental Cell Technology**

Lead by Dr. Yamanaka, the members of the Department of Fundamental Cell Technology investigate issues in the regulation and overseeing of research for the development of future therapies using iPSCs. In addition to overseeing the operations of the Facility for iPS Cell Therapy (FiT), which maintains and provides clinical-grade iPSCs, they also work to develop culture methods for the generation of cells of assured quality. They also provide technical and facilities support to other CiRA labs. The division strives to both establish reliable methods for iPS cell generation and maintenance within the institute, and to provide guidance for researchers around the world working with iPS cells.

# iCeMS: Institute for Integrated Cell-Material Sciences

# **The Vision:** mastering the chemical basis of cells, and synthesizing chemical materials to mimic cellular processes





All cellular processes can ultimately be comprehended as chemical events, and such a chemical understanding of cells should allow us to mimic cellular processes using chemical materials. Our institute seeks to illuminate precisely such a *chemical basis of cells*, creating compounds to control processes in cells such as **stem cells** (*materials for cell control*) in addition to sparking cellular processes to create chemical materials (*cell-inspired materials*). Combining Kyoto University's established strength in cell biology, chemistry, and physics to delve deeply into the mesoscale world lying at the boundary of materials and life, we are making a concerted effort, through interdisciplinary research, to ultimately create a new research field of integrated cell-material science.

### The Mesoscopic Domain: on the life/materials border





From left: iCeMS Director-Designate **Susumu Kitagawa**, well known for his original work on the design and development of porous coordination polymers/metal organic frameworks; iCeMS Director **Norio Nakatsuji**, Japan's pioneer in the establishment and distribution of human ES cell lines and a leader in ES/iPS cell-based drug discovery; CiRA Director and iCeMS PI **Shinya Yamanaka**, 2012 Nobel Laureate in Physiology or Medicine.

(as of December 2012)





### [News archive] Sir John Gurdon speaks at iCeMS

(Posted on the iCeMS website on November 29, 2010)

On November 26, 2010, **Sir John B. Gurdon**, FRS, professor at and founder of the Wellcome Trust/ Cancer Research UK Gurdon Institute at the University of Cambridge, visited Kyoto University's Institute for Integrated Cell-Material Sciences (WPI-iCeMS) to deliver a seminar on reprogramming of cell nuclei in eggs and oocytes.

Co-hosted with Kyoto University's Institute for Virus Research and Center for iPS Research and Application (CiRA), the seminar attracted over 100 iCeMS and other university department participants. During the course of the presentation, iCeMS Director Prof. Norio Nakatsuji, CiRA Director and iCeMS Dr. Shinya Yamanaka, and numerous young researchers engaged Prof. Gurdon in active discussions.

iCeMS Prof. Akihiro Kusumi, chief sponsor of the seminar, and Adj. Assoc. Prof. Kazuto Kato, who previously conducted post-doctoral research in the Gurdon lab at Cambridge, also made contributions to the debate.

Prof. Gurdon is likely best known for his work in the late 1950s and early 1960s showing that the nuclei of differentiated somatic cells retain the potential to develop into all cell types, a finding derived from experiments with South African clawed frogs (Xenopus laevis). In 2009 he received the Albert Lasker Basic Medical Award together with Dr. Yamanaka, for "discoveries concerning nuclear reprogramming, the process that instructs specialized adult cells to form early stem cells—creating the potential to become any type of mature cell for experimental or therapeutic purposes."



### About iCeMS and CiRA

Dr. Shinya Yamanaka, a principal investigator at the **Institute for Integrated Cell-Material Sciences (WPI-iCeMS)**, reported in November 2007 that his team had successfully generated induced pluripotent stem cells (iPS cells) from human skin cells. In January 2008, iCeMS Director Norio Nakatsuji appointed Dr. Yamanaka as founding director of the **Center for iPS Cell Research and Application (CiRA)**, which was established under the auspices of iCeMS in order to advance iPS cell research. In April 2010, Kyoto University re-established CiRA as a full-fledged university research institute, with Dr. Yamanaka as its founding director. Since that time, both institutes have continued to collaborate closely as sister institutes, with iCeMS aiming to integrate the cell and material sciences, contributing to the advancement of stem cell research such as with ES and iPS cells, and CiRA continuing its pioneering work in the areas of regenerative medicine and drug development using iPS cells.



### Fukui Institute for Fundamental Chemistry (FIFC)

The Fukui Institute For Fundamental Chemistry (FIFC) at Kyoto University was established on April 1, 2002. The FIFC is the successor to the Institute For Fundamental Chemistry (IFC), which was founded in 1984 in commemoration of the late Prof. Kenichi Fukui's Nobel Prize award in 1981, with the aim of promoting creative research in fundamental chemistry. The IFC was donated to Kyoto University in 2002, when it was renamed as the Fukui Institute for Fundamental Chemistry. The main objectives of the Fukui Institute for Fundamental Chemistry are to promote the philosophy of Prof. Fukui in science fields and to pursue fundamental concepts in theoretical and experimental chemistry.

The FIFC is comprised of two divisions, one lab, and three groups: The General Research Division, Theoretical Research Division, International Cooperation Laboratory, Morokuma Group, Sakaki Group, and Nagase Group. Through those divisions, the institute advances computer-aided research of materials science and theoretical chemistry.

The FIFC also offers a post-doctoral research program to encourage innovation by younger scientists in all fields of fundamental chemistry.





www.fukui.kyoto-u.ac.jp/

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### **FIFC Philosophy**

The FIFC has succeeded and developed Prof. Kenichi Fukui's philosophy of research, and aims to contribute to the progress of science throughout the world. Its goal is to lead world in terms of materials and related theories. They seek to be "the wellspring of wisdom."

### **Objectives of FIFC**

- Integrate the cutting-edge fundamental chemistry with related research fields.
- Formulate chemical theory for the next-generation.
- Perform highly original research.
- Support young scientists engaged in challenging research.

### Research

FIFC research ranges from theoretical chemistry to theoretical physics

- Theoretical/Computational Chemistry for Complex Systems
- Molecular Simulation of Liquids
- Theoretical/Computational Chemistry for Chemical Reactions
- Theoretical Solid State Chemistry
- Reaction Mechanisms of Metal Enzymes
- Electron Dynamics of Nano-materials
- Theoretical Simulation of Complex Molecules
- Research on Molecular Processes of Electronic Continuum States

Topics: Elements Strategy Initiative

Japan relies on imported rare earth and other rare metal elements which are utilized for advanced industries such as electronics, automotive, information technologies, architecture etc. The price of such materials is increasing and they are in short supply due to a rapid increase in demand and the influence of global economic growth and industrial expansion on the resource management policies of their countries of origin.

The Ministry of Education, Culture, Sports, Science and Technology (MEXT) launched the ten-year Elements Strategy Initiative as a national research program to investigate the substation of rare-metals with alternative abundant elements in order to solve such resource issues and strengthen Japanese industry. This project aims to develop rare-metal free materials in four research fields – magnetic materials, catalysts and batteries, electronic materials, and structural materials – which are directly related to Japanese industrial competitiveness.

In 2012, the Japanese government designated two research centers at Kyoto University as leading research centers for the initiative, one for catalysts and batteries, and the other for structural materials. Both centers operate based on Prof. Kenichi Fukui's philosophy of scientific research and pursue fundamental concepts in theoretical and experimental chemistry.



### **Elements Strategy Initiative for Catalyst and Batteries** (ESICB)

### Project Leader

Professor Tsunehiro Tanaka, Graduate School of Engineering Theoretical Research Division Supervisor, FIFC

This project aims to establish and advance elements science, develop rare-metal free catalysts and rechargeable batteries, and train young gifted scientists and engineers with the ultimate purpose of achieving sustainable development. The project is particularly concerned with elucidating the nanoscopic processes and phenomena of complex systems such as catalysts and batteries, and advancing the science describing complex systems through the interplay between theoretical and experimental sciences. It thereby seeks to develop rare-metal free catalysts and batteries by predicting new materials, and to foster young talented researchers.



www.esicb.kyoto-u.ac.jp/



### **Elements Strategy Initiative for Structural Materials** (ESISM)

Project Leader Professor Isao Tanaka, Graduate School of Engineering Ex-Director and Theoretical Research Division Supervisor, FIFC

The mission of this project is to advance the study and construction of new academic concepts for structural materials, develop industrial applications of research results, and foster young talented researchers to contribute to sustainable development.

Although they are generally a trade-off, the dual qualities of "strength" and "ductility" are essential for structural materials. They have achieved a breakthrough towards the ultimate material with both strength and ductility through multi-scale control of microstructures avoiding the use of rare metals. By combining leading-edge tools of theory and computation, and nano-analysis and advanced processing, they explore the frontier of structural materials science.



<u>esism.kyoto-u.ac.jp/en/</u>

# Yukawa Institute for Theoretical Physics

### History

The history of the Yukawa Institute for Theoretical Physics (formerly the Research Institute for Fundamental Physics) goes back to 1949, when Dr. Hideki Yukawa of Kyoto University received the first Nobel Prize awarded to a Japanese citizen. To commemorate this historic event, the president of Kyoto University proposed the establishment of a memorial hall on campus for Dr. Yukawa. In 1950, the Science Council of Japan issued a request to the central government for the allocation of special funding for the promotion of research into theoretical physics. Enthusiastic discussions among physicists all over the country ensued in support of the idea of establishing a new institution.

The Yukawa Hall was inaugurated in 1952 and in the following year (1953) it was renamed the Research Institute for Fundamental Physics (RIFP). Dr. Yukawa was appointed as the first director, and led the institute until his retirement in 1970.

The RIFP was a new type of national research center for theoretical physics, its facilities available for collaborative use by the entire community of theoretical physicists in Japan. Many physicists participated in the organization of topical workshops and international conferences at RIFP, and stayed at the institute for certain periods to work in collaboration with their peers. Those traditions are still maintained by the Yukawa Institute.

A major expansion took place in 1990 when the entire academic staff of the Research Institute for Theoretical Physics (RITP) of Hiroshima University moved to the RIFP. At the time of the unification, RITP had ten academic staff members and its research area had expanded to include cosmology, general relativity, field theory, and particle theory. As a result of the unification, the institute was reinstituted as a Joint Research Laboratory attached to Kyoto University. Although the Japanese name of the institute, *Kisobutsurigaku Kenkyujo*, remained unchanged, its English name was changed to the Yukawa Institute for Theoretical Physics (YITP) in memory of Dr. Hideki Yukawa.

In 2008, Toshihide Maskawa, the seventh director of the institute was awarded the Nobel Prize in Physics.



Yukawa Hall and the statue of Dr. Yukawa



Hideki Yukawa, seated at the center, and his colleagues. To his right are S. Tomonaga and S. Sakata. A picture taken in 1954 in front of the entrance of the Yukawa Hall.



Nobel Prize Diploma for Dr. Maskawa



### Research Groups

### **High Energy Physics Group**

The goal of high energy physics is to elucidate the basic constituents of matters and the laws that govern their dynamics. This group aims at the understanding of fundamental laws of nature that lies beyond the Standard Model. Current research fields include: superstring theory, quantum gravity, quantum field theory and particle phenomenology.

### **Condensed Matter Physics Group**

All matters are aggregates of numerous particles interacting with each other in various manners. This group aims at elucidating complex movements or states which do not appear until particle systems form a group or their dynamic temporal changes. Furthermore, it aims to elucidate the mode of material movement and dynamic changes in phase structure in non-equilibrium open systems including biological systems. Current research fields include: solid state physics and advanced statistical dynamics.

### International Exchange

The YITP is one of the most important hubs of international collaboration in the field of theoretical physics in Japan. Since 1978, the YITP has held regular annual international conferences. Among those events, the Yukawa International Seminar (YKIS) has the longest history, and each year is attended by approximately 100 participants from Japan and 40 from overseas.

The YITP has hosted a number of visiting professors and short-term visitors from abroad. They collaborate with Japanese researchers and play an important role in enhancing theoretical physics research in Japan. During their time at the YITP, the visiting professors give special lectures and assist with the education of graduate students at Kyoto University.

### **Nuclear Theory Group**

The study of nuclear structure and nuclear interactions constitutes one of the traditional research areas of the institute. Yukawa's meson theory played a historical role in research programs at the Institute. Current research fields include: nuclear many-body physics and quark-hadron many-body.

### Astrophysics Group

This group studies cosmological and astrophysical structures under extreme conditions, based on general relativity, quantum field theory and/or string theory as well as on experimental and observational data, making full use of computer simulations when necessary. Current research fields include: the early universe, high energy astrophysics, numerical relativity and gravitational waves, and higher dimensional spacetime and gravity.

### **Program for Quark-Hadron Physics**

In 2007, a program for a long-term international workshop on quark-hadron physics was adopted as a special education and research project by the government of Japan. Since its adoption, two or three long-term (one to three months) workshops have been held annually on a variety of themes related to quark-hadron physics.



Yukawa International Seminar 2011 (YKIS2011)