World Premier International Research Center Initiative (WPI)
Executive Summary (For Extension application screening)

Host Institution	Kyoto University	Host Institution Head	Hiroshi Matsumoto
Research Center	Institute for Integrated Cell-Material Sciences (iCeMS)	Center Director	Susumu Kitagawa

A. Progress Report of the WPI Center

I. Summary

In meeting expectations of the WPI program, iCeMS has achieved the status of a world-visible research center. A summary of accomplishments exemplifying this achievement is as follows:

1. **High level of science achieved:** (i) Outstanding research results on manipulation of gene expression, membrane compartments by Porous Coordination Polymers (PCP) and cell fates/cell-material interaction. (ii) **982** peer-reviewed papers, **212** (**22%**) of which are in journals with IF 10 or more, and **709** (**75%**) of which with co-authors outside of iCeMS.
2. **Interdisciplinary research pursued:** (i) iCeMS labs have synthesized a total of more than 1,500 materials and discovered a number of useful molecules that manipulate cell functions. (ii) Due to self-evaluation, 130 highly interdisciplinary and 205 interdisciplinary papers published, 94 (28%) of which have appeared in IF 10+ journals. (iii) iCeMS ranked 2nd among 6 WPI centers based on a bibliometric measure on interdisciplinarity proposed by *Porter & Rafols.*
3. **Eminent awards received: Nobel Prize** in Physiology or Medicine to Prof Yamanaka (2012); 2010 **Thomson Reuters Citation Laureate** to Profs Kitagawa and Yamanaka; Profs Heuser and Yamanaka elected to **U.S. National Academy of Sciences** (2011); and 89 other awards received.
4. **Biomaterials Science, a new international journal published:** Jointly with the UK-based Royal Society of Chemistry (RSC), 169 articles and 15 issues (as of the end of March 2014).
5. **External funding acquired:** JPY 5,492 million, 1.38 times greater than that supported by WPI (JPY 3,967 million) for the past three years.
6. **Entrepreneur startup company nurtured:** ReproCell now listed in JASDAQ Stock Exchange
7. **Internationalization and system reforms:** A variety of reforms undertaken in anticipation of MEXT's National University Reform Plan. Front runner and the testbed of Kyoto University system reforms such as **International Strategy, the 2 x 2020 initiative** (2013).
8. **CiRA spawned from iCeMS:** Differentiation with CiRA clarified and further collaboration as a sister institution promoted.

In January 2013, the iCeMS Director shifted from cell-biologist Prof Nakatsuji to materials scientist Prof Kitagawa, taking the institute to a higher level of cell-material integration. Under the strong leadership of Prof Kitagawa, iCeMS has clarified its research target as **"Manipulation of Cell Fundamentals by Synthetic Molecules."** The goal-oriented areas of investigation are clustered into three research pillars.

II. Items

1. Overall Image of Your Center

(a) iCeMS identity

The research goal/identity of iCeMS is the **"Integration of Cell and Material Sciences"**.

A critical review of ongoing collaborative projects, taking into consideration the end of the WPI

Program in FY2016, resulted in a tightened focus on the **Manipulation of Cell Fundamentals by Synthetic Molecules** that encompasses the following three research pillars.

i) Manipulation of Nucleus Information:
The nucleus memorizes and processes centralized information in the cell. We strive to elucidate the dynamics and mechanisms of chromatin organization and transcription regulation during cell differentiation as well as reprogramming. By doing so, we can develop synthetic functional molecules, including those with photoinducible properties, to visualize and manipulate nuclear information processing.

ii) Manipulation of Membrane Compartments:
Cellular membrane compartments mediate condensation and selection: inward and outward signaling cascades, energy conversion, and exchange of matter. We seek to understand the molecular mechanisms of these meso-domain reactions to develop molecular technologies for manipulating membrane functions by external stimuli such as light, magnetic field and heat.

iii) Manipulation of Cell Communication:
Differentiation of stem cells into multicellular tissues is regulated by the communication between cells alone and cells with materials. We seek to uncover underlying mechanisms and develop scaffolds by molecular scale design for reconstruction of functional cell architectures such as brain, muscle and germline tissues.

(b) Succession of the iCeMS Director from Prof Nakatsuji to Prof Kitagawa

At a research center such as iCeMS where the fields of study are particularly cross-disciplinary and evolving rapidly, an appropriate adjustment in the direction of the institute by shifting to a leader from a different background may aid in re-inspiring work across disciplines, and in nurturing a younger generation of scientists who are truly multidisciplinary minded and whose work will potentially lead to important new breakthroughs. With this in mind, Prof Kitagawa (materials scientist) replaced Prof Nakatsuji (cell biologist) as the director.

Effects of the succession are: (i) strengthening cell-material integration by a more materials science approach, (ii) strengthening interdisciplinary research by recruiting new world class professors (**R. Kageyama, M. Saitou, M. Tanaka and E. Sivaniah**), (iii) strengthening institute management, (iv) accelerating prioritized research topics and (v) quick decision making.

(c) Strengthening of collaboration with CiRA

In FY 2007, just after **Prof Yamanaka**'s discovery of human iPS cells, the iCeMS Director swiftly implemented his decision to create the Center for iPS Cell Research and Application under the auspices of iCeMS, marking a major advance in the effort to apply human stem cell research to the field of regenerative medicine.

Kyoto University established CiRA as the 14th university institute which is spawned from iCeMS on April 1, 2010, enabling it to freely develop clinical applications for regenerative medicine.

Differences between iCeMS' and CiRA's scientific approaches and goals, often a point of discussion in years past, are now sufficiently clear: **iCeMS incorporates iPS cells into its research combining cells and materials, while CiRA focuses on clinical applications of iPS cells.** In this context, six CiRA scientists have iCeMS affiliations, performing basic and multidisciplinary research related to iPS cells in conjunction with iCeMS colleagues.

2. Research Activities

(a) Representative results achieved

Twenty representative results have been achieved, the most outstanding three of which are as follows.

i) Manipulation of Nucleus Information:
Through interdisciplinary approaches (combinations of biology, physics, and chemistry), we are now able to successfully control gene expression for regulating cell fates. Collaborative research among iCeMS groups revealed that gene expression dynamics are important for the activity of transcription factors. Using a new light technology, we found that oscillatory expression of the transcription factor Ascl1 activates cell proliferation whereas sustained expression of Ascl1 promotes neuronal differentiation [*Science* 2013]. We also synthesized small molecules, `SAHA-PIPs', consisting of sequence-specific pyrrole-imidazole polyamides and the histone deacetylase inhibitor SAHA. One such compound successfully activates pluripotency genes in

mouse fibroblasts [*Sci Rep* 2012], while another induces germ cell genes [*Angew. Chem.-Int. Edit.* 2013].

ii) Manipulation of Membrane Compartments:
The collaboration among iCeMS researchers allows for the smooth transition from materials fabrications to cell biology investigations. The idea generated in iCeMS indeed stimulated chemists to produce porous coordination polymers (PCPs) with functions analogous to membrane compartments [*Angew. Chem. Int. Ed.* 2011, *Nat. Mater.* 2012, *Science* 2013, *Science* 2014]. In addition, newly synthesized photoactive PCPs that implement the light-triggered release of nitric oxide (NO) were integrated into cell culture substrates and iCeMS biologists are using them to control a localized cell stimulation system to investigate the roles of NO as intracellular and intercellular signaling molecules, thus moving towards gas biology applications [*Nat. Commun.* 2013].

iii) Manipulation of Cell Communication:
Multidisciplinary collaboration among iCeMS and other scientists generated outstanding outcomes in manipulating cell fates and cell-material interactions. For example, screening of chemical libraries and subsequent chemical synthesis identified small molecules that direct differentiation of pluripotent stem cells into cardiomyocytes [*Cell Reports* 2012] and late-stage pancreatic β-cells [*Nat. Chem. Biol.* 2014]. Combining cell biology and material sciences also revealed that the laminin fragment E8 greatly improves human ES/iPS cell culture for effective cell expansion [*Nat. Commun.* 2012]. iCeMS collaborations also identified a small molecule named `adhesamine' that promotes adhesion of cultured human cells [*Chem. Biol.* 2009], and later elucidated its mechanism of action [*J. Am. Chem. Soc.* 2013].

(b) Publications
iCeMS has published **982** peer-reviewed papers, **212** (**22%**) of which are in journals with IF 10 or more.

(c) Major grants obtained
iCeMS researchers acquired **JPY 8,995 million** of research funds in total since its establishment: 2,371 million from Grants-in-Aid for Scientific Research; 625 million from the Next-Generation Leading Research Funding Program; 5,037 million from sponsored research funding; and 962 million from other competitive research funding sources.

(d) Eminent awards received
31 iCeMS researchers have received 92 awards since the establishment of the institute. For the most outstanding awards, refer to A.I.3.

3. Interdisciplinary Research Activities

(a) Interdisciplinary Research results to date: Refer to A.I.2.

(b) Key Strategic Undertakings
We have gone through great lengths to promote interdisciplinary research. Major examples include: (i) director succession, (ii) 3 new PIs hired and 2 PIs not renewed, (iii) acceleration of prioritized research topics, (iv) annual iCeMS retreats for all research staff, (v) review articles on mesoscopic sciences and collaborative works (biology/chemistry and biology/physics) published, and (vi) Biomaterials Science, a new international journal published in collaboration with the UK-based Royal Society of Chemistry (RSC).

4. International Research Environment

(a) Research environment
Kyoto University provides a high-quality research environment at the main campus, consisting of about 11,000 m^2 of open lab and office space to foster interdisciplinary research. At the Katsura Lab (220m^2), collaborative work is conducted with 4 professors from the Graduate School of Engineering. At the Advanced Chemical Technology Center in Kyoto (**ACT Kyoto**, 595 m^2), research and development of gas science technology are conducted in line with one of Kyoto city's policies aimed at promoting the **academy-industry-government cooperation.**

(b) iCeMS prominent PIs from overseas

World-renowned Profs J. Heuser, Y. Chen, T. Hiiragi, K. Agladze and M. Tanaka have joined as PIs.

(c) iCeMS Kyoto Fellow and iCeMS Associate Kyoto Fellow

Since FY 2009 iCeMS has been attracting young, talented scientists worldwide with a total annual budget of 20–30 million yen and an opportunity to establish an independent research group. There are currently **6 fellows (including 4 from overseas).**

(d) Seminar tours for promotion

Seminar tours for promotion have been implemented since 2013 with the aim to evaluate the eligibility of a candidate for career advancement. The candidate visits three overseas institutions to conduct seminars and receive evaluations.

(e) Others

15 partner institutions established, 36 international symposia held, Overseas Researchers Support Office established (5 staff at present), iCeMS housing guarantor system launched, Overseas Visit Program for Young Researchers started(71 researchers visited)

5. Organizational Reforms

(a) Management under strong leadership of the Director

Top down decision making is determined by the **Executive Board** (the Director, two Deputy Directors, Chair of PI Meeting and Admin Director). Effects of strong leadership of the Director are: (i) promotion of interdisciplinary research areas; (ii) Acceleration of prioritized research topics; and (iii) quick decision making in personnel affairs and budget allocation

(b) System reforms achieved at iCeMS

There are a variety of system reforms being undertaken at iCeMS which cover internationalization, research support and management. These successful reforms are partially due to hiring professionals in international public relations and senior researchers experienced in industry. In addition, support from Innovation Management (IMG) and Science Communication (SCG) research groups have also played an important role in iCeMS system reforms.

(c) Ripple effects on Kyoto University management

Kyoto University has been going through great lengths to embody the **National University Reform Plan** under the leadership of President Matsumoto. iCeMS has been the front runner and testbed of these system reforms. The new paradigm created by iCeMS has been highly evaluated and has strongly influenced plans for reforms described below.

1. Kyoto University International Strategy (Formulated on September 2013)

Kyoto University has formulated a new international strategy, the **2x by 2020 Initiatives**. 2x by 2020 is the slogan of the new International Strategy by means of which Kyoto University aims to double its international indices in research, education and international service by the year 2020. Goals are clarified in terms of quantity and deadline as WPI missions.

2. Kyoto University administrative reform (Operational on July 2013)

Kyoto University has undertaken substantial administration reforms, such as the relocation and centralization of staff, new positions for supporting education and research, and implementation of rigorous evaluation and training systems to increase the efficiency of administration. iCeMS has become to support and accelerate internationalization far beyond iCeMS to the Graduate School of Advanced Integrated Studies in Human Survivability (*Shishu-Kan*) and the Institute for Liberal Arts Studies (ILAS), newly established in FY2013. In ILAS, more than one hundred overseas faculty are employed as tenured staff to teach classes in English.

iCeMS' wealth of experience in internationalization is anticipated to have a large impact on these new institutions. For example, 10 bilingual administrative staff members will be transferred to ILAS, some of whom are now receiving on the job training at iCeMS.

3. Kyoto University Research Administration (KURA)

KURA was established in 2012, and subsequently hired nearly 46 university research administrators (URAs). With its pioneering experience such as in its work with the IMG, iCeMS' Research Planning Section has been playing an important role in collaborating with KURA.

4. Personnel Management

Introduction of a new salary system including cross-appointment scheme is now under consideration and will be partially introduced to Kyoto University personnel management. Abolishment of retirement age has been implemented in other institutes such as CiRA and Shishu-kan, and will be expanded to other organizations.

6. Others

Kyoto University announced on May 21, 2013 its alliance with **"edX,"** making it the first Japanese university to take part in the non-profit educational consortium. The first course offered by Kyoto University's "*KyotoUx*" series is taught by iCeMS deputy director and Institute for Chemical Research **Prof Uesugi**, titled the "Chemistry of Life." The classes started in spring 2014 and student registration for the course is 20,269. Prof. Uesugi also provided the first "flipped class" in the long history of Kyoto University education. Joining edX will contribute towards raising the name recognition of iCeMS as well.

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Research Center	Institute for Integrated Cell-Material Sciences (iCeMS)	Center Director	Susumu Kitagawa

** Write your report within 30 pages. (The attached forms are in addition to this page count.) Keep the length of your report within the specified number of pages.*

Common Instructions:
** Please prepare this report based on the current (31 March 2014) situation of your WPI center.*
** Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.*

1. Overall Image of Your Center *(write within 2 pages including this page)*

Describe the Center's current identity and overall image. For centers that have had a change in their directors, describe that transition and the effects of the change.

- *On the sheets in Appendix 1, list the Principle Investigators, and enter the number of center personnel, a chart of the center's management system, a campus map showing the center's locations on the campus, and project funding.*

(a) Overall image of iCeMS

Since its establishment in 2007, iCeMS' identity has been perceived as unclear and too diverse. This perception may be due to the term "mesoscopic science" which we tried to create as a new interdisciplinary research field. While we believe that it is critical to look at mesoscopic domains lying between nano and macro realms to understand cells, we have not yet created a commonly shared perception of this term, even after numerous revisions. Thus, to avoid misunderstanding about iCeMS' present research goal, we will not emphasize the term "mesoscopic science" and instead, pursue the "Integration of Cell and Material Sciences" in mesoscopic domains.

Under the leadership of **Director Kitagawa**, a critical review of ongoing collaborative projects was carried out, taking into consideration the end of the WPI Program in FY2016, and resulted in a tightened focus on "**Manipulation of Cell Fundamentals by Synthetic Molecules** " that encompasses the following three research pillars.

(i) Manipulation of Nucleus Information:

The nucleus memorizes and processes centralized information in the cell. We strive to elucidate the dynamics and mechanisms of chromatin organization and transcription regulation during cell differentiation as well as reprogramming. By doing so, we can develop synthetic functional molecules, including those with photoinducible properties, to visualize and manipulate nuclear information processing.

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Cellular membrane compartments mediate condensation and selection: inward and outward signaling cascades, energy conversion, and exchange of matter. We seek to understand the molecular mechanisms of these meso-domain reactions to develop molecular technologies for manipulating membrane functions by external stimuli such as light, magnetic field and heat.

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(b) Succession of the iCeMS Director

1. Reason for the succession from Prof Nakatsuji to Prof Kitagawa

As its most visible "face", it is our understanding that the director of each WPI center should, to the extent possible, perform the duties of this office for the duration of the center's participation in the program. However, it is also worth considering that, especially at a research center such as the iCeMS where the fields of study are particularly cross-disciplinary and evolving rapidly, appropriate adjustment of the direction of the institute by shifting to a leader from a different background may aid in re-inspiring work across disciplines, and in nurturing a younger generation of scientists who are truly multidisciplinary minded and whose work will potentially lead to important new breakthroughs. With this in mind, Prof Kitagawa (materials scientist) replaced Prof Nakatsuji (cell biologist) as the director.

2. Effects of the succession

(i) Strengthening cell-material integration by a more material science approach

As described in 1-(a), under the leadership of Director Kitagawa, a critical review of ongoing collaborative projects was conducted, taking into consideration the end of the WPI Program in FY2016, resulting in a tightened focus on **"Manipulation of Cell Fundamentals by Synthetic Molecules"** that encompass the three research pillars.

(ii) Strengthening interdisciplinary research by recruiting new world-class PIs

In response to WPI Program Committee and Site Visit Working Group remarks questioning the strength of the institute's cell science team, we have taken measures to strengthen the lineup of researchers, such as with the inclusion of world-renowned Kyoto University scientists **Ryoichiro Kageyama** (Institute for Virus Research) and **Mitinori Saitou** (Graduate School of Medicine), University of Heidelberg Professor **Motomu Tanaka** and Cambridge University Assoc Professor **Easan Sivaniah**. In 2013, they joined iCeMS and have been allocated adequate lab space and postdoc researchers.

(iii) Strengthening institute management

Director Kitagawa is a specialist in materials science. Two deputy directors have been appointed to support his leadership role. One is a world-leading cell scientist **Ryoichiro Kageyama**, and the other is iCeMS Professor **Motonari Uesugi**, a highly-regarded chemical biologist in the United States and Japan with a solid track record of uniting cell-material research. The institute's new leadership team, strong in both international and interdisciplinary contexts, is well placed to lead iCeMS in this new phase of its unified study crossing the boundaries between cells and materials.

(iv) Acceleration of prioritized research topics

Under the new leadership, one of iCeMS startup grants was merged to prioritize research topics, aiming to accelerate outstanding projects nurtured by the startup grant in the areas of primary importance for multidisciplinary research, which are expected to yield results within two years in the highest quality scientific journals.

(v) Quick decision making

Under the leadership of Director Kitagawa, quicker decision-making has been carried out particularly in cases of promotion/termination of researchers and allocation of lab space and a budget for newly employed faculty.

2. Research Activities *(within 15 pages)*

2-1. Research results to date

Describe issues of a global level that the Center has challenged, and give the results. Select 20 representative results achieved during the period from 2007 through March 2014. Number them [1] to [20] and provide a description of each. Place an asterisk (*) in front of those results that could only have been achieved by a WPI center.

- *In Appendix 2, list the papers underscoring each research achievement (up to 40 papers) and provide a description of each of their significance.*

(a) Global level of science: challenge and achievement

Combining Kyoto University's established strengths in cell biology, chemistry, and physics, iCeMS has made ground-breaking contributions to the field of integrated cell-material science. Our overall proposition is the "Manipulation of Cell Fundamentals by Synthetic Molecules." Namely, we are focusing on three essential properties of cells, particularly mammalian stem cells: **(i) nuclear information, (ii) membrane compartments,** and **(iii) cell communication**. Interdisciplinary efforts among iCeMS researchers have uncovered a number of molecular mechanisms of cellular processes for elucidating the regulation of stem cell proliferation and differentiation, and of meso-domain reactions in membrane compartments, resulting in the design and discovery of new materials for the control of cell physiology. iCeMS researchers have synthesized or discovered over 1,500 chemical compounds to date, including novel and unique cell-manipulating compounds such as porous coordination polymers (PCP), SAHA derivatives, adhesamine, Kyoto Probe 1 (KP-1), and ferrocene-porphyrin-fullerene linked triad (FPFT). These world-class, prominent achievements are described in the following sections.

(b) Publication

iCeMS has published **982** peer-reviewed papers (articles, reviews and letters), **212** (**22%**) of which are in journals with IF 10 or more. **709** (**75%**) papers are with co-authors outside of iCeMS.

130 highly interdisciplinary and 205 interdisciplinary peer-reviewed papers, **94** (**28%**) of which have appeared in IF 10+ journals.

(c)Eminent awards received

Nobel Prize in Physiology or Medicine to Prof **Yamanak**a (2012); 2010 Thomson Reuters Citation Laureate to Profs **Kitagawa** and Yamanaka; Profs **Heuser** and Yamanaka elected to U.S. National Academy of Sciences (2011); and 89 other awards received.

(d) Representative results

I. Manipulation of Nucleus Information

***[I-1]**

Oscillatory control of factors determining multipotency and fate in mouse neural progenitors

This project enables gene expression control by light illumination to regulate stem cell differentiation [*Science* 2013]. Neural stem cells have multipotency to give rise to three different cell fates, neurons, oligodendrocytes, and astrocytes, but the precise mechanism of neural stem cell control remains to be determined. We generated bioluminescence and fluorescence reporters to monitor the expression dynamics of each cell fate determination factor. In collaboration with the iCeMS Center for Meso-Bio Single-Molecule Imaging (CeMI) microscopy specialists, we successfully revealed that the expression of these factors oscillates in neural stem cells, whereas the expression of one of them becomes sustained during cell fate choice. We developed a new optogenetic method to induce the oscillatory or sustained gene expression by changing the blue light illumination patterns, and showed that Ascl1/Mash1 activates neural stem cell proliferation when the expression oscillates, but induces neuronal differentiation when the expression is sustained. Thus, Ascl1/Mash1 has opposite functions depending on the expression dynamics.

Our optogenetic technology developed in this study offers a novel way to control neural stem cell proliferation and neuronal differentiation, demonstrating its applicability to the regenerative medicine.

Underscoring paper: 1 [appendix 2-1]

***[I-2]**
Successful development of artificial genetic switches using DNA-based synthetic small molecules

Artificial transcriptional activators must encompass DNA recognition and functional modules involved in epigenetic activity, while allowing their natural counterparts to retain their ability to rewire transcriptional networks within a cell. Among the major classes of artificial transcriptional activators available for cellular reprogramming, small molecules get proclaimed to have better clinical prospects over natural DNA binding proteins, as they are mostly non-immunogenic. The Sugiyama lab synthesized a new class of dual-functional small molecules for genome engineering termed `SAHA-PIP' containing sequence-specific pyrrole-imidazole polyamides (PIPs) and the histone deacetylase inhibitor SAHA. A novel small molecule called **d** distinctively activated the pluripotency genes in mouse fibroblasts by triggering the epigenetic marks associated with transcriptionally permissive chromatin [*Sci Rep* 2012]. In human fibroblasts, a SAHA-PIP called **K** was shown to induce the typically conserved germ cell genes that regulate the meiotic process [*Angew. Chem.-Int. Edit.* 2013]. Subsequently, microarray studies and functional analysis revealed the remarkable ability of thirty-two distinct SAHA-PIPs to trigger the transcriptional activation of exclusive clusters of genes including KSR2, the obesity gene [*Sci Rep* 2014]. Taken together, our results represent a successful model of materials for cell control.

Underscoring papers: 2, 3, 4 [appendix 2-1]

[I-3]
Proof of concept for epigenetics-driven cancer development through artificial manipulation of epigenetic regulation

The technology for generating induced pluripotent stem cells (iPSCs) can be utilized to actively and globally manipulate the epigenetic regulation of differentiated cells. In this study, we have established an *in vivo* reprogramming system in which somatic cells can be reprogrammed into iPSCs in living mice [*Cell* 2014]. Interestingly, when incomplete reprogramming was induced in these mice, they developed tumors consisting of undifferentiated cancer cells. Importantly, no remarkable genetic mutations were observed in these tumors, and the cancer cells were readily reprogrammed into iPSCs with shorter latency and higher efficiency when compared with the process of reprogramming from normal somatic cells. Furthermore, kidney tumor-derived iPSCs contributed to chimeric mice and differentiated into apparently normal non-neoplastic kidney cells. Considering that iPSC derivation and the differentiation process are not accompanied by changes in genomic sequence, these findings indicate that the kidney cancer genome in this model supports normal kidney development, resulting in terminal differentiation into non-neoplastic kidney cells. It has been widely accepted that cancer arises primarily through accumulation of genetic mutations. Our results provided a proof of concept for epigenetics-driven cancer that is independent of genetic transformation, and suggest that particular types of cancer can arise mainly as a result of epigenetic disruption triggered by dedifferentiation.

Underscoring paper: 5 [appendix 2-1]

***[I-4]**
Identification of transcription factors sufficient for inducing the germ cell fate in epiblast cells in mice

This project offers a way to control germ cell fate by expressing appropriate transcription factors (TFs) *in vitro*. Through gene knockout studies, including ours, several TFs essential for primordial germ cell (PGC) specification have been identified, but TFs sufficient for PGC specification have been unknown due to a methodological limitation. By using an *in vitro* PGC specification system

that we have developed [*Cell* 2011; *Science* 2012], we explored TFs that may be enough to sufficiently confer germ cell fate on precursor cells, epiblasts. We found that overexpression of three TFs, *Blimp1*, *Prdm14*, and *Tfap2c* in epiblast-like cells (EpiLCs) is sufficient to rapidly and efficiently convert EpiLCs into PGC-like cells (TF-PGCLCs). Strikingly, overexpression of *Prdm14* alone was also sufficient to induce TF-PGCLCs, albeit at a low efficiency. Remarkably, upon transplantation into testes of neonatal mice lacking endogenous germ cells, TF-PGCLCs contributed to spermatogenesis and healthy offspring. Thus, this work provides a strong foundation for the TF-based control of gametogenesis *in vitro* [*Nature* 2013].

Underscoring papers: 6, 7, 8 [appendix 2-1]

***[I-5]**

Single molecule imaging and manipulation using meso-scale DNA origami structures

Various meso-scale DNA structures can be designed by the DNA origami method, and manipulation of the molecular movement on the DNA structures is now possible. Real-time observation of the dynamic movement of single molecules using high-speed atomic force microscopy (AFM) revealed various enzymatic reactions such as DNA methylation, repair, and recombination. The DNA frame system allowed for control of DNA methylation using the different tension of the substrate double-stranded DNAs (dsDNAs), and dynamic analysis of single enzyme was achieved using high speed AFM [*J. Am. Chem. Soc.* 2010]. Employing this method, structural changes of target DNA molecules including G-qaudruplex formation, duplex formation, and BZ transition were visualized at single molecule resolution. Manipulation of single molecules is also possible on the DNA structure. Using a mobile DNA molecule machine (DNA motor), the movement of the DNA motor was observed in the pathway of single-stranded DNA constructed on the DNA structure [*Nat. Nanotechnol.* 2011]. The DNA motor moved in a time-dependent manner, and the single molecule motion was visualized and analyzed in detail. Furthermore, the controlled movement of DNA motors to the multiple destinations were successfully achieved using the controllable gates on a branched pathway [*Nat. Nanotechnol.* 2012].

Underscoring papers: 9, 10, 11 [appendix 2-1]

II. Manipulation of Membrane Compartments

***[II-1]**

New single-molecule tracking methods elucidated the hierarchical meso-scale compartment architecture of the plasma membrane for signal transduction

iCeMS' Kusumi, Kiso, CeMI, NCBS-inStem, and Tanaka groups, as well as the iCeMS partner institutions, Purdue University and NCBS in India, have advanced the concept, in which signal transduction and ionic and molecular exchange functions of the plasma membrane (PM) are enabled by various meso-scale domains in PM. The team first improved single-molecule tracking methods, developing methods for world's fastest and longest tracking as well as simultaneous multi-species tracking [*Nat. Meth.* 2010; *J. Cell Biol.* 2013]. Using these methods, the team revealed that the PM is hierarchically organized by three-tiered meso-scale compartments: from the largest to smallest, (1) actin-induced membrane compartments, (2) raft domains existing within the actin-based compartments, and (3) dynamic protein complex domains [*Ann. Rev. Cell Dev. Biol.* 2012]. The team showed that G-protein-coupled receptors (GPCRs), the most important drug-development targets, are in dynamic equilibrium between monomers and homodimers, and by developing a single-molecule superquantitation method, it succeeded in fully characterizing the equilibrium, for the first time ever for any membrane molecules [*J. Cell Biol.* 2011]. The key roles of the transient dimers in GPCR function are now being elucidated. Furthermore, glycosylphosphatidylinositol-anchored receptors (GPI-AR), were found to form transient homodimers, which work as basic units for raft formation and function [*Nat. Chem. Biol.* 2012]. These studies were enabled by the close association of the team members, CeMI facilities, and financial support from iCeMS.

Underscoring paper: 12, 13, 14, 15, 16 [appendix 2-1]

***[II-2]**

Meso-scale raft domain architecture and function revealed by developing fluorescent ganglioside analogs

Gangliosides, which are glycolipids containing terminal sialic acids in their glyco chains, represent 3~10% of the plasma membrane (PM) polar lipids and are responsible for specific PM functions. Gangliosides are essential for the formation and signal transduction functions of the meso-scale raft domains. However, most data on these ganglioside functions are indirect, and as a result, how gangliosides are involved in these functions is largely unknown due to the non-availability of suitable fluorescent analogues of gangliosides. Here, the Kiso group, which leads the field of glyco-chain chemical synthesis, first established basic methods for chemically synthesizing gangliosides [*Angew. Chem.-Int. Edit.* 2011]. The iCeMS project team consisting of Kiso, Kusumi, CeMI, and NCBS-inStem groups successfully developed 6 fluorescent ganglioside analogs that behave like native gangliosides. Single-molecule tracking of these analogs in the PM of live cells is now revealing the formation of homo-dimer rafts and their specific interactions with several receptors. These results could be obtained as a result of the close association of iCeMS team members, CeMI facilities, and financial support from iCeMS.

Underscoring paper: 17 [appendix 2-1]

***[II-3]**
Mechanism of modulating membrane lipid distribution by lipid transporter

It is proposed that ABC proteins, such as ABCA1, ABCG1 and ABCG4, change distribution of membrane lipid compartments in the plasma membrane by moving lipid molecules and modulate cellular functions such as growth and migration. But their detailed mechanisms are not clear. The Ueda group, in collaboration with the Kusumi group, analyzed dynamics of ABCA1 on the plasma membrane via a single molecule imaging technique, and it was found that ABCA1 monomer-dimer interconversion occurs on the plasma membrane during functioning [*Proc. Natl. Acad. Sci. U. S. A.* 2013]. ABCA1 is involved not only in lipid transport but also in generating high-density lipoprotein (HDL, so-called good cholesterol) by loading excess cholesterol onto apolipoprotein A-I (apoA-I), a lipid acceptor in blood. This study suggests the physiological significance of converting the ABCA1 monomer to a dimer; the dimer serves as a receptor for two apoA-I molecules for the generation of HDL meso-scale particles. ABCA1 is important not only for quantity but also quality of HDL to prevent atherosclerosis. Novel lipid probes developed by the Kiso group [*Angew. Chem.-Int. Edit.* 2011] facilitate the visualization of changes of membrane lipid distribution. This study is an achievement of the integration of biology (Ueda), chemistry (Kiso) and physics (Kusumi) in iCeMS.

Underscoring paper: 17, 18 [appendix 2-1]

***[II-4]**
Mechanism of multi-drug transport by ABC proteins

Membranes define boundaries of a cell and cell compartments and separates the intra- from the extra compartmental environment. Transporters exchange materials via membranes, condense specific materials inside and eliminate nonessential, toxic materials. In this study, the Ueda group, in collaboration with the Kato group, revealed the functional mechanism of multidrug exporter MDR1, which eliminates various structurally unrelated toxic compounds from cells and maintains human health. This team first discovered a gene highly homologous to human *MDR1*, which Ueda identified from multidrug resistant cancer cells in 1986 (Cell, 1986), from unicellular eukaryote *Cyanidioschyzon merolae* and determined the structure of the protein at the highest resolution in the world [*Proc. Natl. Acad. Sci. U. S. A.* 2014]. The structure revealed i) how MDR1 takes hydrophobic toxic compounds into the protein, ii) how MDR1 recognizes various structurally unrelated compounds and iii) how MDR1 exports them out of cells. This study further led to the identification of new chemicals that serve as MDR1 substrates, by the Uesugi group [*Cell Reports* 2014].

Underscoring paper: 19, 20 [appendix 2-1]

***[II-5]**

A chemical probe that labels human pluripotent stem cells

Screening of fluorescent chemical libraries with human induced pluripotent stem cells (iPSCs) identified a fluorescent molecule (Kyoto probe 1 [KP-1]) that selectively labels human pluripotent stem cells [*Cell Reports* 2014]. Multidisciplinary collaborative analyses among iCeMS research groups revealed that the selectivity results primarily from a distinct expression pattern of ABC transporters in human pluripotent stem cells and from the transporter selectivity of KP-1. Expression of MDR1 (ABCB1) and ABCG2 (BCRP), both of which cause the efflux of KP-1, is repressed in human pluripotent stem cells. KP-1 may widely be used as a tool in the field of stem cell biology. This work was empowered by iCeMS and CiRA research groups including Uesugi (chemical biology), Ueda (ABC transporter biology), Nakatsuji (stem cell biology), Yamanaka (stem cell biology), Eto (hematology) and Inoue (neurology).

Underscoring paper: 20 [appendix 2-1]

***[II-6]**

Utilization of photoinduced charge-separated state of donor-acceptor linked molecules for regulation of cell membrane potential and ion transport

Ion channels transport ions selectively via membranes and play important physiological roles. The control of ion transport by light is an attractive strategy that allows targeted, fast control of precisely defined events in the biological membrane. The Imahori, Murakami, Mori, and Heuser groups have successfully controlled the membrane potential and ion transport across cell membranes by using ferrocene-porphyrin-fullerene linked triad molecules and light [*J. Am. Chem. Soc.* 2012]. Light irradiation led to the depolarization in the plasma membrane potential together with the inhibition of potassium ion flow across the membrane. The results provided unprecedented fundamental information on interactions between a photoinduced charge-separated state and biological membrane. More importantly, this is the first optogenetic method for intact cell membranes. Our strategy is potentially useful for controlling cell functions in a spatiotemporal manner, such as neuronal firing. Now we are trying to figure out the detailed mechanism of action in collaboration with cell biologists in iCeMS, and also synthesizing a variety of charge separation molecules based on more sophisticated molecular design to achieve reversible, stronger, and faster depolarization.

Underscoring paper: 21 [appendix 2-1]

***[II-7]**

Study on the generation of ultra-intense THz pulse sources and nonlinear spectroscopy

Rapid progress has recently been made in studying the "uncharted territory" of the terahertz electromagnetic spectrum. The Tanaka group in the CeMI is developing a method of imaging and manipulating cells using the terahertz pulse technology. With the femtosecond laser pulses in CeMI, they succeeded in developing the world's strongest terahertz radiation pulse source by using an optical rectification process [*Appl. Phys. Lett.* 2011]. This pulse source is the first ever with electric field strength of over 1 MV/cm, and its focused intensity is several tens of times larger than that obtained before by other research groups. They also used the source to produce important findings for the carrier multiplication process that plays a crucial role in high-speed transistors and photovoltaic devices [*Nat. Commun.* 2011]. These results are one of the leading works in the pioneering research field of terahertz non-linear spectroscopy, and are attracting worldwide attention. This technology is currently being applied to cell biology because the order of electric field generated by terahertz pulse (1 MV/cm = 100 mv/nm) is strong enough to locally manipulate the membrane potential of living cells. Such a non-invasive method to locally alter the membrane potential opens the door to further developments in the field of interdisciplinary cell-material sciences.

Underscoring papers: 22, 23, 24 [appendix 2-1]

***[II-8]**

Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform

Nitric oxide (NO) is an important signaling molecule that regulates a range of physiological and pathological processes including vascular smooth muscle relaxation and neurotransmission. The physical nature of gas, such as rapid diffusion, membrane permeability and high reactivity, is key for characterizing these molecules as a transmitter. However, due to these inherent properties, spatial and temporal delivery of this highly reactive free radical had proved challenging and attempts at single-cell stimulation by NO had not yet been achieved. The Kitagawa group synthesized new porous coordination polymers that release NO upon laser irradiation. Organizing a photoactive ligand into a three-dimensional porous structure increased its photoreactivity and NO release. Collaboration with the Chen and Wang groups achieved for the first time a precise and controlled delivery of NO at the cellular level via localized near-infrared two-photon laser activation. As confirmed by observing subsequent cell responses in terms of the variation in calcium concentrations, this unique approach provides a promising tool for better understanding the physiological role of NO [*Nat. Commun.* 2013]. Compared to conventional molecule-based photoactive compounds, the framework materials give a very high NO payload, leading to new research opportunities to unveil the secret role of NO, in particular, at the required high concentration.

Underscoring papers: 25 [appendix 2-1]

***[II-9]**
Structuring of porous coordination polymers in the mesoscale towards creation of cell-inspired materials

The simultaneous implementation of "selection" and "condensation" of matters is a basic factor to define the concept of compartmentalization in living cells. Here the Kitagawa group aimed to create such an integrated function by artificial materials called porous coordination polymers (PCPs). PCPs are crystalline porous materials possessing nanosized voids that efficiently trap small molecules or gases therein, meaning that this type of material inherently possess storage (condensation) and separation (selection) functions; however, the concept of integration for multiple functions via sequential processes has never been implemented. The Kitagawa group has been working on the structuring of PCPs and has developed several strategies to control the size [*Science* 2013] and morphology [*Nat. Mater.* 2012] of PCP crystals in the mesoscale and demonstrated novel functions. During the course of the studies, the group developed the synthetic strategy to fabricate core-shell type PCPs, in which one PCP covers the crystal of the other PCP and simultaneously implemented a integrated property of selectivity and storage; the shell with narrow pore selectively extracted cetane from its branched isomer (isocetane) and the core with large pores worked as a container to concentrate extracted cetane [*Angew. Chem.-Int. Edit.* 2011]. This first demonstration impacts not only on environmental and energy sciences but on the creation of a new material principle, cell-inspired materials.

Underscoring papers: 26, 27, 28 [appendix 2-1]

***[II-10]**
Self-Accelerating Gas Trapping in a Soft Nanoporous Crystal

Gas separation is a central subject in industry, and the discovery of a porous compound with high selectivity towards specific gas molecules is scientifically and technologically important. However, no break-through materials have been provided to date. We have focused on new soft porous coordination polymers, which are defined as those with adaptable pores that selectively uptake a specific guest species. The structural transformation of soft PCPs in response to physical or chemical stimuli [*Nat. Mater.* 2010] is key to excellent functions. Herein, the high selectivity towards carbon monoxide (CO) from a mixture with nitrogen (N_2), most competitive to CO, was achieved by the synergetic effect of the local interaction between the gas molecule and copper ion site upon a global transformation of the framework [*Science* 2014]. Thanks to this synergistic mechanism the gas molecules are trapped positive-allosterically (we call the highly allosteric gas trapping in PCP "self-accelerating process"), which is reminiscent of cellular functions, such as blood cells uptaking oxygen (O_2). This superb function could not be realized without

self-accelerating mechanism, opening up a new field of porous solid having cell-inspired functions.

Underscoring paper 29, 30 [appendix 2-1]

III. Manipulation of Cell Communication

*[III-1]
Establishment of an interdisciplinary approach for understanding principles and mechanisms governing neuronal shapes within cellular communities

Neurons in the brain arborize, forming highly-patterned dendritic processes to form efficient neural circuits. The complex tree of dendritic processes is specifically shaped to facilitate access to synaptic counterparts within the tissue. The Kengaku group demonstrated that the dendritic tree underwent dynamic remodeling influenced by neural activity of synaptic counterparts and physical interaction with other branches during postnatal maturation. Furthermore they demonstrated how a combination of dendrite dynamics sculpted the characteristic tree shape by utilizing live imaging of dendrite dynamics in conjugation with quantitative branch morphometry and computer-assisted simulations with the aid of the CeMI microscopy systems. From this they proved that branch retraction triggered by contacts between growing dendrites plays an important role in the intricate formation of non-overlapping dendrites [*Development* 2012]. Usingsimilar approaches, the Kengaku group along with collaborators identified the signals regulating the size of dendritic trees proportional to their external body size [*Sci Rep* 2014]. Through these studies we developed an interdisciplinary approach - utilizing cellular and molecular neurobiology and mathematical biology - for clarifying fundamental mechanisms of dendrite patterning in the developing brain. These studies were enabled by microscopy in the CeMI facilities.

Underscoring paper: 31, 32, 33 [appendix 2-1]

*[III-2]
Identification of a cis-acting element that localizes mRNA to synaptic compartments in neurons

The synapse is a structure between neurons through which a signal flows from one neuron to another. Synapses are typically formed between the axonal terminal of a neuron and the dendritic membrane of a target cell. Synaptic sites contain specific proteins that carry out the signaling processes. Neurons thus acquire mechanisms to deliver and localize functional proteins and messenger RNAs to synaptic compartments. This study identified the first known *cis*-element on mRNA that governs mRNA localization to synaptic compartments in neuronal dendrites [*Proc. Natl. Acad. Sci. U. S. A.* 2012]. Remarkably, the secondary structure of the element is an important determinant of localization rather than the RNA sequence itself, suggesting a new mechanistic concept of RNA subcellular localization. This discovery was made by a collaboration between groups of chemists at iCeMS and biologists at UCLA, who together examined local RNA residues both as micro building-blocks of molecular structures and as biological messengers for conveying synaptic functions.

Underscoring paper: 34 [appendix 2-1]

*[III-3]
Chemical tools for directed differentiation of pluripotent stem cells

Screening of chemical libraries and subsequent chemical synthesis identified small molecules that direct differentiation of pluripotent stem cells into cardiomyocytes [*Cell Reports* 2012] and late-stage pancreatic β-cells [*Nat. Chem. Biol.* 2014]. KY02111 induces highly efficient differentiation of functional ventricular and pace maker cardiomyocytes from human pluripotent stem cells. This molecule allowed a record-breaking, defined, cytokine- and xeno-free method for the large-scale production of human cardiomyocytes. This useful technology was made possible by combining expertise from four iCeMS groups: Nakatsuji (stem cell biology), Uesugi (chemical biology), Hauser (structural biology), and Yamamoto (molecular biology). On the other hand, the

discovery and analysis of promoters of late-stage differentiation into late-stage pancreatic β-cells was empowered by combining iCeMS chemical biology techniques and expertise from other researchers. Vesicular monoamine transporter 2 (VMAT2) inhibitors were identified as such promoters, suggesting roles of monoamine neurotransmitters in the maturation of pancreatic β-cells.

Underscoring paper: 35, 36, 37 [appendix 2-1]

***[III-4]**
Novel methods for adhesion and expansion of cells

Culturing human pluripotent stem cells originally required mouse feeder cells as a cell-adhesion substrates. Defined and xeno-free substrates are essential for clinical applications of human pluripotent stem cells. By combining technologies from cell biology and material sciences, the Nakatsuji group found that the laminin fragment E8 greatly improves culturing human ES/iPS cells, permitting single cell passaging for effective cell expansion [*Nat. Commun.* 2012]. On the other hand, by screening chemical libraries and subsequent chemical synthesis, the Uesugi group identified a small molecule named "adhesamine' that promotes adhesion and growth of cultured human cells [*Chem. Biol.* 2009]. Collaboration of Uesugi and Ueda groups revealed that the molecule cooperatively binds to heparan sulfate and induces its assembly, promoting clustering of heparan sulfate-bound syndecan-4 on the cell surface [*J. Am. Chem. Soc.* 2013]. The assembly-inducing molecule improved the viability and attachment of transplanted cells in mice. These new methods may contribute to increasing the overall general safety and efficacy of stem cell therapy or cell therapy.

Underscoring paper: 38, 39, 40 [appendix 2-1]

***[III-5]**
Generation of offspring from oocytes derived from in vitro primordial germ cell-like cells in mice

This project opens the way to generate oocytes with the capacity to contribute to healthy offspring from in vitro primordial germ cell-like cells (PGCLCs) induced from female embryonic stem cells (ESCs)/induced pluripotent stem cells (iPSCs) in mice. We have demonstrated that by using appropriate combinations of cytokines and culture conditions, male ESCs/iPSCs are induced into epiblast-like cells (EpiLCs) and then into PGCLCs, which, upon transplantation into testes of neonatal mice lacking endogenous germ cells, contribute to spermatogenesis and healthy offspring [*Cell* 2011]. Here, we next explored whether female PGCLCs bear the capacity to contribute to oogenesis and offspring. We induced female ESCs/iPSCs into EpiLCs and then into PGCLCs, and then aggregated PGCLCs with somatic cells isolated from embryonic ovaries to form reconstituted ovaries in culture. In reconstituted ovaries, PGCLCs showed gene expression changes indicative of oogonial differentiation, exhibited epigenetic reprogramming including X reactivation and erasure of imprints, and proceeded into the prophase I of meiosis. When transplanted under ovarian blusa of nude mice for four weeks, PGCLCs in reconstituted ovaries differentiated into oocytes at the germinal vesicle stage. Remarkably, these oocytes, through *in vitro* maturation and fertilization, contributed to healthy offspring. Thus, this work serves as a strong foundation for *in vitro* female gametogenesis [*science* 2012].

Underscoring papers: 6, 7 [appendix 2-1]

2-2. Research environment including facilities and equipment
Describe the degree to which the Center has prepared a research environment appropriate for a world premier international research center, including facilities, equipment and support systems, and describe the functionality of that environment.

(a) Facilities and equipment

Because Kyoto University is located in a cultural and sightseeing zone of a historical city, several amenity restrictions are being imposed that, combined with limited university campus space, prevent the construction of new buildings. As a result, although performing research "Under the

One Roof" — which is ideal for a WPI world research hub — is difficult to achieve, we are effectively utilizing research labs as shown below.

1. iCeMS Main Building and iCeMS Research Building

These buildings are conveniently located in Kyoto University's Main Campus, approximately 200 meters apart from each other, and together combine for 11,000 square meters of space. Most of the iCeMS researchers (115 researchers, 60%) make use of these buildings and the interdisciplinary research environment that is nurtured by open-lab and open-office space.

2. The iCeMS Center for Meso-Bio Single-Molecule Imaging (CeMI)

The Center for Meso-Bio Single-Molecule Imaging (CeMI) is located in iCeMS Research Building and contributes to joint research. Further details on P.14 2-4-(c).

3. Katsura Lab

Established in Kyoto University's Katsura Campus, 10km west of iCeMS Main Building, this lab has 220 square meters of space. Several joint research projects are conducted in collaboration with 4 professors from Graduate School of Engineering there. Details described on P.15 2-4-(e).

4. Advanced Chemical Technology Center in Kyoto (ACT Kyoto)

ACT Kyoto is a research and development center for chemical research, which is in line with one of the Kyoto city policies of promoting the academy-industry-government cooperation. iCeMS rents lab space (595 square meters) for research and development of gas science technology. Refer to P.17 2-6-1-(d).

(b) Support System

1. Startup grants to initiate cross-disciplinary collaboration

Small startup grants to initiate cross-disciplinary collaboration are provided to junior faculty and postdocs via "iCeMS Exploratory Grants for Junior Investigators," while the complementary "iCeMS Cross-Disciplinary Research Promotion Project" aids researchers in other departments of the university to start collaborative work with iCeMS researchers (the latter was expanded beyond the iCeMS as a result of a FY 2009 Site Visit suggestion). Refer to P.18 3-1-(c).

(million yen)

		2009	2010	2011	2012	2013	Total
Budget	Within iCeMS	49	76	67	34	n/a	227
	With other KU depts.	n/a	20.6	20.3	15.8	8.7	65.4
No. of granted projects	Within iCeMS	13	28	40	34	n/a	115
	With other KU depts.	n/a	19	15	15	9	58

2. Accelerating grants to promote outstanding projects

Following the startup phase, in FY 2013 iCeMS undertook a new initiative to accelerate outstanding projects in certain areas of institute-initiated projects. Granted projects are expected to yield results within two years in the highest quality scientific journals. Refer to P.2 1-(b)-2-(iv), P.25 5-1-(b)-2.

(million yen)

	2012 (prototype)	2013		Total
Budget	54	36	23	113
No. of granted projects	10	10	5	25

3. Support for overseas visit for young researchers

Since 2010, iCeMS has supported more than 70 young researchers in earning opportunities to visit world-class institutions, opening the door to further international collaborations and careers with financial support from JSPS. The priority of the program has been shifted to assisting researcher career development from simply boosting international collaboration, and the program has been run successfully by iCeMS own budget since FY 2013. Refer to P.24 4-4-(a).

(million yen)

	FY2009	FY2012	FY2011	FY2012	FY2013	Total
Budget	0.6	9.5	11	13	9	43.1
No. of granted researchers	1	10	15	27	18	71

4. Independent positions for young scientists worldwide

The iCeMS Kyoto Fellow position was established for young scientists worldwide with each fellow receiving a total annual budget of 20–30 million yen (including their own salary) and an opportunity to establish an independent lab group with a status of Assistant Professor or Research Associate. After their 5-year head-start at iCeMS, they are expected to continue and further their international scientific careers, or be promoted at Kyoto University. Such a process will help establish iCeMS as a prominent hub for building a global scientific career. There are presently 6 fellows (including 4 from overseas). Refer to P.21 4-1-2-(a).

5. Support for lab setup for new independent researchers

By absorbing the startup costs associated with setting up a laboratory environment for new independent researchers, iCeMS has demonstrated its commitment to helping these young researchers reach their full potential. Most notably, a startup fund equivalent to JPY 100 million, mainly covering equipment costs for a next generation optics system, was provided for Asst Prof Carlton, an iCeMS Kyoto Fellow, who was hired to further develop optical microscopy technology used to examine mesoscopic cellular architectures. Assoc Prof Sivaniah also benefited from a renovated laboratory with a startup fund of JPY 40 million.

6. Encouraging young researchers' participation in education

- **Teaching classes**

Young researchers participate in teaching that is important for their career development. 16 young researchers have already started to teach courses for undergraduate and graduate students at Kyoto University. Additionally, 2 new educational courses for undergraduates, both with participation from several young iCeMS researchers, have been prepared.

- **Co-Mentor Program**

iCeMS PIs officially affiliated with Graduate Schools and supervising graduate students may choose to assign other faculty members (including iCeMS Kyoto Fellows) as "co-mentors" to their students in order to provide additional advice and guidance. Co-mentors can obtain significant experience and expertise in teaching graduate students, which is important for their career development.

- **Promotion to a tenured position at the Institute for Liberal Arts and Sciences**

Kyoto University has launched the new institute as one of the international strategies where more than one hundred overseas faculty members are employed as tenured staff to teach classes in English. The faculty members are allocated a tenure position at their primary-graduate school/institute and serve to teach at the new institute. At present iCeMS faculty is not allowed to join this program due to the reason that iCeMS is a temporally established institute. We have to remove this restriction by utilizing a new system for faculty management described in Appendix 5.

7. Others

More than 60% of admin staff are bilingual. Open office and lab space foster an atmosphere for fusion and collaboration to take place between researchers. Refer to P.18 3-1-(e).

2-3. Competitive and other funding

Describe the results of the Center's researchers to date in securing competitive and other research funding.

- *In Appendix 2, describe the transition in acquiring research project funding, and note any external funding that warrants special arrangement*

(a) Obtained grants since its establishment

From FY2007 to FY2013, iCeMS researchers acquired a total of **JPY 8,995 million** in research funds: 2,371 million from Grants-in-Aid for Scientific Research; 625 million from the Next-Generation Leading Research Funding Program; 5,037 million from sponsored research funding; and 962 million from other competitive research funding sources. For the last three years, the amount iCeMS has acquired is **1.38 times** greater than the support from WPI.

(b) Outstanding efforts on competitive funding

1. Large scale projects

iCeMS scientists have acquired several large scale funding projects funded by Ministry of Economy, Trade and Industry's New Energy and Industrial Technology Development Organization (NEDO) and Japan Science and Technology Agency (JST). Details are described in Appendix 2-2.

2. The Cabinet Office's Funding Program for Next Generation World-Leading Researchers (NEXT) program

From iCeMS, 5 projects were selected (Profs Harada, Uesugi, and Kengaku, and Assoc Profs Sengoku, and Ueno), ranked 5th out of 209 recipient departments across Japan, next only to the graduate school of engineering at the University of Tokyo (9 projects), Tohoku University (8), Osaka University (6), and the Tokyo Institute of Technology (6).

3. Grants-in-Aid acquired by overseas researchers at iCeMS

iCeMS has held annual workshops on how to obtain grants in English, resulting in a consistent increase in the number of applications (240% in six years, 42 to 101) as well as an increase in the number of awarded grants to overseas researchers (From 1 to 12 in six years).

	FY2009	FY2010	FY2011	FY2012	FY2013	FY2014
No. of Application	42	39	60	65	84	101
No. of adoption	13	9	18	27	28	41
by overseas researchers	1	2	2	7	5	12

2-4. State of joint research

Describe the results of joint research conducted with other research organizations both in and outside Japan.

(a) National Centre for Biological Sciences (NCBS) and the Institute for Stem Cell Biology and Regenerative Medicine (inStem) in Bangalore, India

The iCeMS satellite lab in Bangalore on stem cell research and single molecule imaging was established in NCBS' new building, completed in June 2012. Assoc Prof Suzuki, for single molecule imaging, and Senior Lecturer Hasegawa, for stem cell research, conduct research activities there as group leaders. The research group published 11 papers, three of which appeared in journals with IF 10 or more.

- Full characterization of GPCR monomer-dimer dynamic equilibrium by single molecule imaging; *J. Cell Biol.* [IF 10.8] (2011)
- Dynamic Organizing Principles of the Plasma Membrane that Regulate Signal Transduction: Commemorating the Fortieth Anniversary of Singer and Nicolson's Fluid-Mosaic Model; *Annu. Rev. Cell Dev.Biol.* [IF 18.0] (2012)
- Transient GPI-anchored protein homodimers are units for raft organization and function; *Nat. Chem. Biol.* [IF 12.9] (2012)

The first paper from the Hasegawa lab in inStem-NCBS is expected to appear soon (a book chapter in press and a research paper manuscript under review). Their work at NCBS and inStem are highly regarded and the terms of their contracts have been extended.
Also refer to P.22 4-1-3-(a)-1 for further details in international activities.

(b) UCLA California NanoSystems Institute (CNSI)

iCeMS has been promoting active collaboration with CNSI as a partner institution since 2010. Research groups led by Profs Susumu Kitagawa and Omar Yaghi on porous materials, and Assoc Prof Ueno and Prof James Gimzewski on biomaterials STM and AFM have been conducting collaborative research. Furthermore research groups led by Prof Hashida, Prof Imahori and Assoc Prof Murakami and Prof Fuyuhiko Tamanoi have discussed future collaborations on drug delivery. These collaborations have already resulted in papers such as:

- Construction of Robust Bio-nanotubes using the Controlled Self-Assembly of Component Proteins of Bacteriophage T4; *Small* [IF 7.8] (2010)
- Delivery of Intact Transcription Factor Using Self-Assembled Supramolecular Nanoparticles; *Angew. Chem.-Int. Edit.* [IF 13.7] (2011)

Refer to P.22 4-1-3-(a)-2 for further details in international activities.

(c) The iCeMS Center for Meso-Bio Single-Molecule Imaging (CeMI)

CeMI was established to promote effective collaboration via the shared use of large scale and/or unique equipment among iCeMS researchers and collaborating scientists from other departments and organizations. CeMI-built stations are in operation: four, single fluorescent-molecule tracking (SFMT) stations, each with distinct and specific capabilities, including simultaneous three-color SFMT, photoactivation, and the world's fastest frame-rate at 10 kHz (all operable for live cells at 37°C in 5% CO_2 atmosphere); a terahertz near-field microscope with the world's fastest image acquisition rate (500Hz) and highest spatial resolution (λ /30) tracking (SFMT) stations.
Highlights of CeMI's achievements since its establishment include the following:

1. More than 100 papers were published by CeMI-affiliated labs including:
   - Cells Respond to Mechanical Stress by Rapid Disassembly of Caveolae; *Cell* [IF 32.0] (2011)
   - Oscillatory Control of Factors Determining Multipotency and Fate in Mouse Neural Progenitors; *Science* [IF 31.0] (2013)
   - Resonant and nonresonant control over matter and light by intense terahertz transients; *Nat. Photonics* [IF 27.3] (2013)
2. 332 users registered: 225 within the iCeMS, 81 from other Kyoto University departments, 26 from other universities.
3. 42 CeMI seminars were held (as part of the iCeMS Seminar series): 54 leading scientists in their fields were invited.
4. 128 CeMI training sessions were conducted: approximately 540 researchers attended training sessions on microscopy and imaging technology for a total of 313 days.
5. Accessibility was enhanced by daily consultation services from full-time CeMI staff and upgrading of imaging facilities based on iCeMS researchers' requests.

(d) Domestic satellite: the Faculty of Applied Biological Sciences, Gifu University

One domestic satellite laboratory was established at Gifu University in 2008, in order to add a world leader in glyco-chemistry. As an iCeMS PI, Prof Makoto Kiso collaborates and interacts with other members of the iCeMS in the area of glyco-technology and its application to cell biology. Since its establishment, over 250 carbohydrate derivatives were synthesized and a total of 36 papers have been published from the Kiso group. Representative papers in three main research domains are listed below.

<u>1. Chemical synthesis of glycolipids and carbohydrate important in cell membrane function</u>

- The Total Synthesis of the Neurogenic Ganglioside LLG-3 Isolated from the Starfish Linckia laevigata, *Angew. Chem.-Int. Edit.* [IF 13.7] (2011)
- A First Total Synthesis of Ganglioside HLG-2, *Chem.-Eur. J.* [IF 5.8] (2009)
- A First Total Synthesis of a Hybrid-Type Ganglioside Associated with Amyotrophic Lateral Sclerosis-Like Disorder, *Chem.-Eur. J.* [IF 5.8] (2011)
- The First Total Synthesis of Ganglioside GalNAc-GD1a, a Target Molecule for Autoantibodies in Guillain-Barre Syndrome, *Chem.-Eur. J.* [IF 5.8](2011)

<u>2. Sugar chain probe for elucidating the mechanism of recognition between proteins and carbohydrate</u>

- RCCrystal structure of botulinum neurotoxin type a in complex with the cell surface co-receptor GT1b - Insight into the toxin-neuron interaction, *PLoS Pathog.* [IF 8.1] (2008)
- Structures of Merkel Cell Polyomavirus VP1 Complexes Define a Sialic Acid Binding Site Required for Infection, *PLoS Pathog.* [IF 8.1] (2012)

3. Development of carbohydrate mimic that activates immune cells

- Design, Synthesis, and Structure-Affinity Relationships of Novel Series of Sialosides as CD22-Specific Inhibitors, *J. Med. Chem.* [IF 5.6] (2008)

(e) Katsura Lab

During the FY2011 Site Visit, one of the suggestions iCeMS received was to promote joint research in polymer chemistry. In response, iCeMS has opened a 220 m^2 shared-use laboratory on Kyoto University's Katsura campus, in collaboration with four professors from the university's Graduate School of Engineering at its core. Some notable progress has already being achieved, such as in the Imahori, Mori, and Murakami groups demonstration of effective control over cell functions utilizing the photoinduced charge-separated state for the first time, and the Kitagawa, Chen and Wang groups using a living cell made by the Mori group for working on a new PCP-based cell-stimulation platform that releases nitric oxide by photoactivation. Refer to P.11 2-2-(a)-3.

Representative papers from Katsura related labs.

- Utilization of Photoinduced Charge-Separated State of Donor-Acceptor-Linked Molecules for Regulation of Cell Membrane Potential and Ion Transport; *J. Am. Chem. Soc.* [IF 10.7] (2012)
- Photothermal Ability of Lanthanide Bis(naphthalocyanine) Dye and Inclusion into Modified High Density Lipoprotein Nanocarriers for Therapeutic Applications, *ACS Nano* [IF 12.0] (2013)
- Photothermal Ablation of Tumor Cells Using a Single-Walled Carbon Nanotube-Peptide Composite, *J. Control. Release* [IF 7.6] (2014)

(f) iCeMS collaborative papers

iCeMS has produced **924 peer-reviewed papers with an iCeMS affiliation** from 2007 to December 2013.

-21% (200) of those were published with co-authors affiliated with overseas institutes
-31% (289) with co-authors affiliated with Japanese institutes other than Kyoto University
-23% (220) with co-authors affiliated with other departments at Kyoto University
-11% (103) were co-authored within iCeMS

This demonstrates the institute's highly positive attitude towards collaborative research activities.

2-5. Appraisal by society and scientific organizations

Describe how society and/or scientific organizations in and outside Japan have recognized the Center's research achievements.

- *In Appendix 2, list the awards received and invitational lectures given by the Center's researchers.*

(a) Eminent awards received

As listed in Appendix 2, 31 iCeMS researchers have received 92 awards since the establishment of the institute. The most outstanding awards are as follows:

1. Nobel prize to Prof Yamanaka

iCeMS PI and CiRA Director Prof Yamanaka was awarded the 2012 Nobel Prize in Physiology or Medicine together with Sir John B Gurdon, University of Cambridge, for the discovery that mature cells can be reprogrammed to become pluripotent.

2. 2010 Thomson Reuters Citation Laureate to Profs Kitagawa and Yamanaka

iCeMS then Deputy Director Prof Kitagawa (Chemistry) and iCeMS PI and CiRA Director Prof Yamanaka (Physiology or Medicine) were awarded 2010 Thomson Reuters Citation Laureates. Laureates typically rank among the top one-tenth of one percent (0.1%) of researchers in their fields, based on citations of their published papers over the last two decades.

3. Profs Heuser and Yamanaka elected to U.S. National Academy of Sciences

iCeMS PI and Prof Heuser and iCeMS PI and CiRA Director Prof Yamanaka were elected as members of the U.S. National Academy of Sciences in May 2011.

(b) Distinguished talk invited

Director Kitagawa was invited to the Symposium Celebrating 125 Years of Angewandte Chemie (a journal with the highest IF in the field of chemistry, excluding review journals) in March 2013 as a speaker together with two Nobel laureates and several other leaders in the field. Invited talks were delivered to 2,000 audience members and broadcasted worldwide.

(c) World Stem Cell Summit

The iCeMS was actively involved in co-organizing and participating in the 2012 and 2013 World Stem Cell Summit, the second largest congress of stem cell research following JSSCR, held in Florida and San Diego, USA, attracting 2,500 visitors in two years from industry, academia, and government representing 40 countries. **Founding Director Nakatsuji** was invited to give the plenary for the third year in a row to an audience, which included experts in the stem cell and regenerative medicine fields. Other iCeMS' members gave poster presentations and were part of the awards evaluation committee.

(d) Outreach activities organized by Science Communication Group (SCG)

SCG, led by Specially-Appointed Prof Kato, have held hands-on iCeMS-CiRA joint stem cell classrooms for high school students and high school teachers since 2009. To date, 567 people have participated in this program. For these efforts, SCG received a Commendation for Science and Technology by MEXT in 2014. The concept of these activities was applied to science educational **TV programs by NHK.** Refer to P.17 2-6-2-(a).

2-6. Feeding research outcomes back into society

2-6-1. Applications of research results

Describe the applications created from research results, their effect in spawning innovation, intellectual properties (IPs) obtained, and joint research activities conducted with corporations, etc.

(a) Industrialization of research results

One of the successful examples of starting up and nurturing a business at iCeMS is **ReproCELL**. ReproCELL Inc. was established by an entrepreneur in 2003 with the goal of contributing to the health and welfare of the general public through the development of stem cell technologies and is now listed on the JASDAQ Stock Exchange. Many of ReproCELL's technologies were developed by **iCeMS Founding Director Nakatsuji**, a stem cell pioneer. ReproCELL develops diverse products, with an underlying theme that focuses on stem cell technology, to address the needs of researchers and clinicians. This product range encompasses reagents for ES/iPS cells and stem cell-derived functional cells.

(b) Patent acquisition

The present status of patent acquisition at Kyoto University's iCeMS for 2013 is as follows: Number of applications 65; PCT (Patent Cooperation Treaty) applications 7; and issued patents 6. The income from intellectual property of iCeMS from the year 2007 to 2013 has reached a total of JPY **6.6 million**. 1 million yen for MTA (Material Transfer Agreement): 5.6 million for licensing fees. SACI (Office of Society-Academia Collaboration for Innovation) will support patent-related issues and collect patent royalties.

*The License Fee income includes income from optional contracts only for iCeMS, and not those of license partners. Also, TLO contingent fee is not deducted from the amount.

(c) Collaborative work with industry

iCeMS has actively collaborated with industry. The total funding acquired by collaborative research for 161 projects has reached **JPY 194 million**. The number of projects and research funding have soared to 750% and 280%, respectively, in seven years.

(d) New lab at Rakunan-shinto

As mentioned in P.11 2-2-(a)-4, iCeMS opened a new lab at the Advanced Chemical Technology Center in Kyoto (ACT Kyoto), located in Rakunan-shinto which is in the southern part of Kyoto City, 10 km from iCeMS Main building. Act Kyoto bridges industry, regional government and academia, and was selected as a Local Innovation Promoting Region by the regional activation program run by MEXT and METI. Here, iCeMS plays a leading role in local revitalization by promoting Kyoto Next-Generation Energy Systems Creation Strategy.

2-6-2. Achievements of Center's outreach activities

If the Center has conducted its own unique outreach activities, describe those worthy of special mention.

- *In Appendix 2, list and describe media coverage, press releases, and reporting.*

(a) Science Communication Group (SCG)

SCG has held "iCeMS Cafes" since 2008. The Cafe is designed as an outreach activity supporting iCeMS young researchers to gain experience in communicating with the public. In order to encourage young researchers who may be hesitant to join the cafe, SCG has provided an original "Dialogue skills Training Program" prior to the Cafe. As a result, nearly one hundred early-career researchers enthusiastically joined the events, and the program is now being used by Kyoto University and the JST's Center for Science Communication. Our outreach activities are expanding from one institute's challenge to a nation-wide practice for bridging researchers and the public.

(b) Social media utilization

iCeMS was **the first WPI institute to utilize social media** for effective science communication. At the 2014 Chicago AAAS meeting, iCeMS played a pivotal role in launching the official WPI facebook page to reach out to international audiences, where the use of social media is a common practice. During the four-day event, which attracted over 8,000 attendees from approximately 50 countries, the page count reached 765 views, obtaining 130 likes worldwide. This outreach medium became a standard platform for all WPI institutes to engage the public by posting notable events and research findings.

(c) Booths featuring hands-on activities

The iCeMS Science Communication Group and public relations section exhibited a booth that featured action figure crafting activities for participants at the Science Agora held in Tokyo in November, 2013. Through interpersonal communication, iCeMS promoted understanding of frontier research to over 450 participants over the course of two days. Similarly, iCeMS public relations exhibited a booth for high school students to learn about porous coordination polymers with the aid of magnetic objects at the WPI joint-symposium held in Sendai in December, 2013. The event attracted over 600 participants.

(d) edX Lectures

Prof Uesugi initiated a lecture series "Chemistry of Life" in April 2014 through a new online educational approach called "Massive Open Online Courses (MOOC)" offered by edX. This is the first lecture series provided by a Japanese University using edX.

edX is a non-profit educational consortium created by founding partners Harvard University and Massachusetts Institute of Technology (MIT) in 2012, and offers a variety of free interactive online classes from top-level universities in fields such as law, computer science, history and artificial intelligence. It is comprised of 27 schools including 15 recently added institutions, and boasts over 900,000 registered users worldwide. Refer to P.28 6-(b) for details.

3. Interdisciplinary Research Activities (within 3 pages)

3-1. State of Strategic (or "Top-down") Undertakings toward Creating New Interdisciplinary Domains

(a) Director succession

To take the institute to a higher level of cell-material integration, iCeMS decided to implement a more materials science approach under the leadership of Prof Kitagawa, to build upon the primarily cell science approach of iCeMS during the first five years under the leadership of Prof Nakatsuji. Mentioned in P.2 1-(b).

(b) New PIs hired

As stated in P.2 1-(b)-2-(ii), iCeMS has taken measures to strengthen its lineup of researchers, in response to WPI Program Committee and Site Visit Working Group remarks questioning the strength of the institute's cell science team. Three new PIs, Profs **Kageyama, Saitou, Tanaka and Assoc Prof Sivaniah** joined the iCeMS and were allocated adequate lab space and postdoc researchers.

(c) Startup grants for young researchers

As mentioned in P.11 2-2-(b)-1, iCeMS has provided two types of small startup grants to initiate interdisciplinary collaboration within the institute and within university. The grant for collaboration within the institute was merged into the **Accelerated Research Projects** for FY2013, marking a shift from the institute's startup phase into one focusing on promoting targeted research projects. Meanwhile the latter grant for collaboration within the university has been continued, albeit with a reduced total budget.

(d) Acceleration of prioritized research topics

Refer to P.2 1-(b)-2-(iv), P.11 2-2-(b)-2, P.25 5-1-(b)-2.

(e) Open-Offices and Open-Labs

Open laboratory and office space contributes to an environment suitable for adapting to dynamic research styles. For instance, even a short stay researcher would be able to drive joint research when visiting iCeMS immediately upon arrival. In addition, the Support Office for Common Use Equipment is contributing to this environment by making it increasingly more convenient for researchers to conduct experiments. Refer to P.12 2-2-(b)-7.

(f) Task forces established for interdisciplinary research

In order to promote interdisciplinary research and to focus its prioritized research areas, iCeMS has established appropriate task force teams, as called for by the situation and in a timely manner.

1. Cross-Disciplinary Research Task Force

Original and innovative cross-disciplinary collaborative projects integrating functional smart materials with living cells including stem cells were conducted among the Kitagawa, Imahori, Takano, Kiso, Chen, Kusumi, Ueda, Harada, Heuser, Kengaku, and Nakatsuji Labs. In 2012, every month many researchers including PIs and young researchers join to present research updates and to explore new areas for collaboration.

2. Future Challenge Task Force

This task force was established February 2014 to clarify the identity of iCeMS, an issue that has been raised in follow-up reports and at a meeting with the Program Director, Program Officer and representative of MEXT. This task force is also to identify challenging targets which the institute will achieve during the 5-year extension.

(g) Annual iCeMS retreats for all research staff

Annual iCeMS retreats have been held since 2009, for the purpose of sharing on-going, unpublished multidisciplinary research activities thorough poster presentations and short talks, including iCeMS researchers from the widest possible variety of backgrounds. This once-a-year opportunity has contributed significantly to the generation of new collaborations and the acceleration of on-going multidisciplinary projects. Numbers of attendees and poster presentations have increased by 253% (83 to 210) and 379% (39 to 148) in five years.

(h) Review articles on mesoscopic sciences published

In order to raise the name recognition of mesoscopic science, we have published several review papers.

- Function and regulation of ABCA1-membrane meso-domain organization and reorganization; *FEBS J* [IF 4.3] (2011)
- Hierarchical mesoscale domain organization of the plasma membrane; *Trends Biochem Sci* [IF 13.1] (2011)
- Fundamental and functional aspects of mesoscopic architectures with examples in physics, cell biology, and chemistry; *Crit Rev Biochem Mol Biol* [IF 5.6] (2011)
- Control over Flexibility of Entangled Porous Coordination Frameworks by Molecular and Mesoscopic Chemistries; *Chem. Lett.* [IF 1.6] (2013)

In addition to these individual review papers, Wiley's Biotechnology Journal special issue on the July 2011 Heidelberg-Kyoto multi-disciplinary symposium — "Crossing Boundaries: Stem Cells, Materials, and Mesoscopic Sciences" — was published in June 2012.

(i) Biomaterials Science, a new international journal published in collaboration with the UK-based Royal Society of Chemistry (RSC)

In January 2012, iCeMS began an important new project to contribute to the further development of cell-material integration research as well as mesoscopic sciences by launching a new international journal, Biomaterials Science, in collaboration with RSC. 169 articles and 15 issues have appeared in the online journal as of the end of March 2014.

(j) Strengthening the iCeMS Center for Meso-Bio Single-Molecule Imaging (CeMI)

Refer to P.11 2-2-(a)-2, P.14 2-4-(c).

(k) Joint work with the domestic satellite: Gifu University

Refer to P.14 2-4-(d).

(l) Collaboration with the Katsura Lab

Refer to P.11 2-2-(a)-3, P.15 2-4-(e).

3-2. State of "Bottom-up" Undertakings from the Center's researchers toward Creating New Interdisciplinary Domains

Young researchers are voluntarily conducting various kinds of Cross-disciplinary activities.

(a) iCeMS International Seminars

iCeMS has hosted 160 seminars, conducted in English, since its inception in 2007. Eighty seven percent of these seminars have featured speakers from overseas institutes representing 22 countries. Average 31 researchers joined the seminars.

(b) Young Scientists' Colloquia & Happy Hour Series

This is a cross-disciplinary series of informal scientific talks and social gatherings, which are open to all scientists interested in attending a casual forum for exchanging ideas and getting to know other researchers. The idea for the colloquia was born out of a series of informal Friday happy hours initiated by the iCeMS Kyoto Fellows. Since 2012, ten colloquia have been held, attracting an average of 21 researchers.

(c) iCeMS Science 101

This is an informal monthly meeting, organized by postdocs, to facilitate communication among young scientists who are starting their careers and coming from diverse research backgrounds. It serves as a tutorial for general education rather than specific research studies and provides a foundation for researchers to conduct interdisciplinary studies. Four evening meetings have been held since it was launched in October 2013, attracting an average of 17 attendees.

3-3. Results of research in fused research fields

Describe the Center's record and results by interdisciplinary research activities.

- *In Appendix 3, list the main papers published (up to 20 papers) on the Center's interdisciplinary research and provide a description of each of their significance.*

(a) Overall evaluation

Due to self-evaluation, the institute has produced 130 highly interdisciplinary and 205 interdisciplinary peer-reviewed papers, 94 (28%) of which have appeared in IF 10+ journals.

In order to evaluate more quantitatively, we applied the established bibliometric measure proposed by Porter & Rafols, and analyzed interdisciplinary indices of iCeMS research, comparing them with those of other WPI centers. Indices consist of **Integration** (the average interdisciplinarity of ***cited*** papers ***by*** each publication from a WPI-institute and **Diffusion** (the average interdisciplinarity of ***citing*** papers ***to*** each publication from a WPI-institute). iCeMS Integration and Diffusion indices are 0.598 and 0.527 respectively which are both 2nd among 6 WPI centers.

(b) Representative results of interdisciplinary research

20 representative papers are described in Appendix 3. Three outstanding interdisciplinary research results are as follows.

(i) Manipulation of Nucleus Information:

We now successfully control gene expression by interdisciplinary methods (combinations of biology, physics, and chemistry) to regulate cell fates. Collaborative research among iCeMS groups revealed that gene expression dynamics are important for the activity of transcription factors. Using a new light technology, we showed that oscillatory expression of the transcription factor Ascl1 activates cell proliferation whereas sustained expression of Ascl1 promotes neuronal differentiation [*Science* 2013]. We also synthesized small molecules, SAHA-PIP, consisting of sequence-specific pyrrole-imidazole polyamides and the histone deacetylase inhibitor SAHA. One such compound successfully activates pluripotency genes in mouse fibroblasts [*Sci Rep* 2012], while another induces germ cell genes [*Angew. Chem.-Int. Edit.* 2013].

(ii) Manipulation of Membrane Compartments:

The collaboration among iCeMS researchers allows for the smooth transition from materials fabrications to cell biology investigations. The idea generated in iCeMS indeed stimulated chemists to produce a new material concept 'cell-inspired materials' and the Kitagawa group synthesized several porous coordination polymers (PCPs) with functions similar to compartmentalization concept [*Angew. Chem.-Int. Edit.* 2011, *Nat. Mater.* 2012, *Science* 2013, *Science* 2014]. Furthermore, newly synthesized photoactive PCPs that implement the light-triggered release of nitric oxide (NO) was integrated into cell culture substrates and iCeMS biologists are using them to control a localized cell stimulation system to investigate the roles of NO as intracellular and intercellular signaling molecules, thus towards gas biology applications [*Nat. Commun.* 2013].

(iii) Manipulation of Cell Communication:

Multidisciplinary collaboration among iCeMS and other scientists generated outstanding outcomes in manipulating cell fates and cell-material interactions. For example, screening of chemical libraries and subsequent chemical synthesis identified small molecules that direct differentiation of pluripotent stem cells into cardiomyocytes [*Cell Reports* 2012] and late-stage pancreatic β-cells [*Nat. Chem. Biol.* 2014]. A combination of cell biology and material sciences also revealed that the laminin fragment E8 greatly improves human ES/iPS cell culture for effective cell expansion [*Nat. Commun.* 2012]. iCeMS collaborations also identified a small molecule named "adhesamine' that promotes adhesion of cultured human cells [*Chem. Biol.* 2009] and revealed its mechanism of action [*J. Am. Chem. Soc.* 2013].

4. International Research Environment (within 4 pages)

4-1. International Circulation of Best Brains
4-1-1. Center's record of attracting and retaining top-world researchers from abroad
Describe the participation of top-world researchers as PIs and the residing of joint researchers at the Center.

- *In Appendix 4, give the number of overseas researchers among all the Center's researchers, and the yearly transition in their numbers.*

(a) iCeMS prominent PIs from overseas

1. **Prof John Heuser**: an internationally recognized authority on electron microscopy, was named a National Academy of Sciences Member in May 2011.

2. **Prof Yong Chen**: a research director of CNRS at the Ecole Normale Supérieure of Paris, contributed to a number of European research projects.

3. **Prof Motomu Tanaka**: a professor of University of Heidelberg, an internationally recognized authority on Biological Physics, received the Philipp Franz von Siebold Prize in 2013.

4. **Prof Konstantin Agladze**: USA-based Russian Biophysicist left to join MIPT (Moscow Institute of Physics and Technology).

5. **Prof Takashi Hiiragi**: Highly regarded Developmental Biologist, hired from Max-Planck Institute for Molecular Biomedicine, left to join EMBL (The European Molecular Biology Laboratory) after 5 years at iCeMS.

(b) Visitors

There are many world-renowned scholars who have visited for short stays, not exceeding three months, to conduct joint research.

4-1-2. Employment of young researchers at the Center and their job placement after leaving the Center

Describe the Center's employment of young researchers, including postdoctoral researchers, and the positions they acquire after leaving the Center.

- *In Appendix 4, enter the following:*
  - *The state of international recruitment for postdoctoral researchers, applications received, and selections made*
  - *The percentage of postdoctoral researchers from abroad*
  - *The positions that postdoctoral researchers acquire after leaving the Center*

(a) iCeMS Kyoto Fellows and iCeMS Associate Kyoto Fellows hired

Since FY 2009 iCeMS has been attracting young talented scientists worldwide with a total annual budget of 20–30 million yen and an opportunity to establish an independent research group. A total of 96 candidates, which consist of 70% from overseas scientists, have applied for the positions. There are presently **6 fellows (including 4 from overseas)** selected after rigorous screening of highly qualified candidates. Refer to P.12 2-2-(b)-4.

(b) Young researchers hired

	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013	Total
Associate Professor	2	4	2	1	2	0	3	14
Senior Lecturer	0	2	3	1	1	0	1	8
Assistant Professor	3	4	9	6	6	3	8	39

Research Associate	8	35	53	36	24	29	32	217
Total	13	45	67	44	33	32	44	278

Numbers of iCeMS Kyoto Fellow and iCeMS Associate Kyoto Fellow are included in total numbers.

(c) Promotion and transfer of young researchers

Since its establishment, 15 young researchers (Assoc Prof, Sen Lec, Asst Prof, Research Associate) have been promoted at iCeMS and are actively engaged in research activities.

- 1 Associate Professor → Professor in FY 2012
- 1 Senior Lecturer → Associate Professor in FY 2012
- 1 Assistant Professor → Associate Professor in FY 2013
- 12 Research Associates → Assistant Professors since FY 2009

148 of 165 (90%) scientists who left iCeMS have found new positions inside and outside of Japan, and 32 (19%) have relocated overseas. To address the issue of brain circulation abroad, we initiated a new Seminar Tour program in 2013 — in addition to the overseas visits program — to encourage young and promising researchers to turn their attention to international opportunities.

4-1-3. Overseas satellites and other cooperative organizations

- *In Appendix 4, describe the state of the Center's agreements concluded with overseas satellites and other cooperative organizations.*

(a) Partner institutions

The number of iCeMS' partner institutions as of the end of FY2013 was 15. To date, a variety of academic exchanges have taken place which have resulted in raising the name recognition of iCeMS. Here we introduce 3 institutions which produce fruitful scientific outcomes such as publishing jointly papers.

1. National Centre for Biological Sciences (NCBS) and the Institute for Stem Cell Biology and Regenerative Medicine (inStem) in Bangalore, India

As described at P.22 2-4-(a), two of iCeMS scientists have been conducting international research activities in NCBS and inStem. In FY2012, iCeMS and NCBS won an international research grant between India and Australia (JPY 20 million over 2 years) together with the University of Melbourne. Senior Lecturer Hasegawa was appointed to an invited editor of Stem Cell International.

Their works at NCBS and inStem are highly evaluated and their contract terms are extended by 2015.

2. UCLA California NanoSystems Institute (CNSI), USA

The iCeMS has been promoting active collaboration with CNSI since 2010. Research groups led by Profs Susumu Kitagawa and Omar Yaghi on porous materials; Assoc Prof Takafumi Ueno and Prof James Gimzewski on biomaterials STM and AFM; and Prof Mitsuru Hashida, Prof Hiroshi Imahori and Assoc Prof Tatsuya Murakami and Prof Fuyuhiko Tamanoi on drug delivery have been conducting collaborative research.

In 2011, Prof Omar Yaghi, the CNSI coordinator of the collaboration, moved to the University of California, Berkeley, and in 2012 Prof Takafumi Ueno, the coordinator on the iCeMS side, transferred to Tokyo Institute of Technology. Afterwards, new collaborative research was discontinued.

However, iCeMS has been actively taking part in the International Symposium on NanoBiotechnology (see 4-2), which was inaugurated by CNSI in 2007. Refer to P.14 2-4-(b).

3. Heidelberg University, Germany

First formed in 2011, the Japanese-German University Presidents' Conference (German-Japanese HeKKSAGOn Universities Consortium, consisting of Heidelberg University, Göttingen University, Karlsruhe Institute of Technology, Tohoku University, Osaka University, and Kyoto University) continues to meet annually. Kyoto University works especially closely with Heidelberg University in the area of cell-material integration, resulting in the Heidelberg-Kyoto joint symposium "Crossing Boundaries: Stem Cells, Materials, and Mesoscopic Sciences" held in Heidelberg in July 2011.
On March 30, 2012, Prof Nakatsuji and Prof Anthony Ho of SFB 873 continued their collaboration by co-organizing a session of the 2nd Japanese-German Presidents' Conference put on by HeKKSaGOn.

Prof Nakatsuji gave a lecture for a summer school held at Heidelberg University from September 17-26, 2012. It was the first summer school of the Japanese-German network HeKKSaGOn, and the title was "Crossing Borders: Unraveling Principles of Life with Quantitative Tools". The 2nd HeKKSaGOn summer school will be held at Karlsruhe Institute of Technology in September 2014, and Prof Kusumi will give a lecture for the school.

As a concrete result of these collaborations, **Prof M Tanaka** of Heidelberg was appointed as an iCeMS PI beginning in FY2013.

In addition, Kyoto University has established an overseas office on Heidelberg University Campus on May, 2014. Kyoto University allocates an administrative staff in the office to promote cooperation among the HeKKSaGOn Consortium.

4-2. Center's record of holding international symposia, workshops, research meetings, training meetings and others

- *In Appendix 4, describe the main international research meetings held by the Center.*

For the main international research meetings held by iCeMS, see Appendix 4-6. Some major symposia are as follows

(a) Heidelberg-Kyoto joint symposium "Crossing Boundaries: Stem Cells, Materials, and Mesoscopic Sciences"

As mentioned above, the Heidelberg-Kyoto joint symposium "Crossing Boundaries: Stem Cells, Materials, and Mesoscopic Sciences" was held in Heidelberg in July 2011. 34 speakers from the iCeMS joined the meeting and the number of participants totaled 296. This symposium featured mesoscopic sciences of cell-material integration, an area which Heidelberg University and Kyoto University work especially closely with each other.

(b) Kick-off Symposium for Biomaterials Science

As stated in P.19 3-1-(i), iCeMS launched a new international journal, Biomaterials Science, in collaboration with RSC and, together, held a joint kick-off symposium for the journal Biomaterials Science in Kyoto in March 2013. 13 speakers from iCeMS joined the workshop, and the total number of attendees was 157. It also included remarks by WPI Program Director Dr Toshio Kuroki, iCeMS Founding Director Nakatsuji, and Managing Editor Niamh O'Connor. Several members of the editorial board delivered presentations, along with members of the iCeMS Academic Advisory Committee.

(c) Japan-France workshop on nanotematerials co-hosted by 4 WPI institutes

Four World Premier International Research Center Initiative (WPI) institutes and France's National Center for Scientific Research (CNRS) co-hosted the 10th annual workshop on nanomaterials between Japan and France in Kyoto in June 2013. Four speakers from iCeMS joined the workshop, and the total number of attendees was 82. The workshop has been promoting

researchers from both countries to exchange scientific ideas, foster interdisciplinary collaborations, and forge new connections since 2000.

(d) International Symposium on Nanobiotechnology

The symposium series was initiated in 2007 by the California NanoSystems Institute (CNSI) of the University of California, Los Angeles and the Center for NanoBio Integration (CNBI) at the University of Tokyo. iCeMS has joined this symposium since 2010 as one of the core members. The 8th symposium will be held in Beijing in October 2014.

4-3. System for supporting the research activities of overseas researchers
Describe the Center's preparations to provide an environment conducive for overseas research to concentrate on their work, including for example living support in various languages or living support for their families.

(a) Overseas Researchers Support Office

The Overseas Researchers Support Office was established in FY2009 to assist foreign researchers in quickly and smoothly adapting not only to their new research environment but also to their new lives in Japan. They specifically provide assistance with immigration procedures, residence status updates, housing arrangements and other matters related to daily life.

(b) iCeMS Housing Guarantor System launched

For enhancing the international environment of the institute, iCeMS launched a Housing Guarantor System in October 2012 to fulfill the role of guarantor when international scientists lease housing for mid- to long-term stays. Joint guarantors are often requested for leases, a custom that has been a persistent barrier for researchers from overseas who have difficulty finding a Japanese guarantor at the time of their arrival. iCeMS has partnered with several cooperative housing agencies in the area in order to improve the move-to-Japan experience.
The numbers of past guarantees include 1 in FY2012 and 8 in FY2013.

4-4. Others
Describe the Center's policy for sending Japanese researchers overseas to gain international experience, and give examples of how the Center is working to create career paths for its researchers within a global environment of researcher mobility.

(a) The iCeMS-JSPS Overseas Visit Program for Young Researchers

The iCeMS-JSPS Overseas Visit Program for Young Researchers has been implemented since 2010 with aims to 1) provide opportunities for young iCeMS researchers to conduct research at overseas institutes, 2) to strengthen participants' international competitiveness, and 3) to enhance iCeMS' role as an international hub for researchers in related fields. To date, 71 researchers have earned opportunities to visit world-class institutions, opening the door to further international collaborations and careers. Since FY2013, the priority of the program has shifted to career development in contrast to simply boosting international collaboration efforts, and has been successfully run using iCeMS own budget. Also see P.11 2-2-(b)-3.

(b) Seminar tours for promotion

Seminar tours for promotion have been implemented since 2013 to evaluate the eligibility of a candidate for career advancement. The candidate visits three overseas institutions to conduct seminars, and examiners at each institution make evaluations with an international perspective. Based on these evaluations, the Executive Board carefully considers and reaches a final decision. In FY2013 four candidates went on seminar tours, two of which were promoted in the end. For this seminar tour, the overseas visit program described above can be utilized.

5. Organizational Reforms (within 3 pages)

5-1. Decision –making system in the center

Describe the strong leadership that the director is giving the Center's operation and its effect, and the division of roles and authority between the Center and its host institution.

(a) Management under strong leadership of the Director

Top down decision-making is made by the Executive Board (the Director, two Deputy Directors, PI Chairman and Admin Director) about matters related to personnel affairs, budget and management — excluding university level management matters and appointment of the iCeMS Director (directly appointed by the President). Refer to Appendix 1-3 and P.25 5-1-(a).

(b) Effect of strong leadership of the Director

1. Promotion of interdisciplinary research areas

Because initiating interdisciplinary research and getting breakthroughs in science are challenging, strong leadership by the Director is critical for success. Particularly, in the early stages after iCeMS' inauguration, **Founding Director Nakatsuji** was dedicated to exploring collaborations with many iCeMS' members and establishing an interdisciplinary research environment.

2. Acceleration of prioritized research topics

In **Accelerated Research Projects** initiated in 2013, **Director Kitagawa** takes initiatives to decide on the research topics. With his strong leadership, quick decision-making and prioritized budget allocation have been successfully achieved (Refer to P.11 2-2-(b)-2). Also as described in 1, his decisive leadership has made iCeMS research mission more transparent.

3. Quick decision making

Under the leadership of the Director, decision-making is faster, particularly in the cases of promotion/termination of researchers and allocation of lab space and budget.

5-2. Arrangement of administrative support staff and effectiveness of support system

Describe the assignment of the Center's administrative support staff who have English language and other specialized skills, effort made in establishing the support system, and the system's effectiveness.

(a) Professionals hired in International Affairs and Planning

iCeMS has hired professionals with a wealth of experience in international public relations at overseas and Japanese public sectors and Master of Professional Studies in Strategic Public Relations holder, at the International Affairs and Planning Section for internationalization of iCeMS. In addition, the institute hired a public relations University Research Administrator (URA) to enhance the global visibility of iCeMS. The URA has a PhD and is able to comprehend and communicate the institute's scientific findings to the general public.

(b) Professionals hired in Research Planning

Two senior researchers are employed in the Research Planning Section to oversee the management of large-scale projects, support the acquisition of new large-scale project funds, and advance open innovation with industry via the Open Innovation Task Force and Industrial Advisory Committee (Refer to Appendix 1-3). In addition, a URA has been hired by iCeMS to improve the procurement of external funding in the form of grants.

(c) Industry-government-academia collaboration management by the Innovation Management Group (IMG)

IMG, led by Assoc Prof Sengoku, is exploring novel modes, models, and methods for advancing innovation management in order to realize the promise of leading edge inventions and discoveries for society. IMG has been conducting social implementation initiatives for advanced cross-sector

partnerships by designing new and improved collaboration systems between public and private sectors. These initiatives are being conducted in partnership with Kyoto SMI (Smart Materials & Innovation), a satellite NPO and subsidiary of the WPI-iCeMS.

(d) Public outreach by the Science Communication Group (SCG)

SCG initiated numerous outreach efforts, such as science cafés, hands-on iCeMS-CiRA joint stem cell classrooms, hands-on exhibitions at science festivals hosted by the Cabinet Office (two days in March 2013), and lectures for middle and high school students (more than 5 times in FY2012). SCG offered a "Dialogue Skills Training Program" for young iCeMS' scientists. This program has been adopted by the Center for Science Communication of the Japan Science & Technology Agency (JST) as its communication program for scientists. Refer to P. 16 2-5-(d), P.17 2-6-2-(a).

5-3. System reforms advanced by WPI program and their ripple effects
Concisely itemize the system reforms made to the Center's research operation and administrative organization, and describe their background and results. Describe the ripple effects that these reforms have on the host institution. (Describe the ripple effects on other institutions.)

(a) System reforms achieved at iCeMS

There are a variety of system reforms being undertaken at iCeMS, some of which are listed below.

1. Internationalization

(i) Use of English as the official language; (ii) Global recruitment and over 30% overseas researchers; (iii) Strengthening of International Public Relations and Oversea Affairs and Planning staff, (iv) Establishment of the Overseas Researchers Support Office, (v) Over 50% English-speaking administration staff; (vi) Active MoU exchange with 15 world-renowned partner institutions; (vii) 29 international symposia held; (viii) 160 international seminars; (ix) International journal newly published (Biomaterials Science with RSC); (x) English-language workshops on obtaining competitive grants

2. Interdisciplinary research support and open collaboration with industries

(i) Open office and open lab policies; (ii) Establishing Research Planning Section, Innovation Management Group (IMG) and Science Communication Group (SCG); (iii) Collaboration with KURA, (iV) Establishing Industrial Advisory Board; (v) Outreach activities , (v) Annual retreats

3. Management

(i) Director decision making; (ii) Merit-based salary system; (iii) Hiring not limited by the retirement age; (iv) Budget allocation on prioritized researches; (v) Strict and fair personnel strategy; (vi) Cooperative management with researchers by various committees

(b) Ripple effects on Kyoto University management

Kyoto University is making a great effort to embody the **National University Reform Plan** under the leadership of President Matsumoto. iCeMS has been the front runner and the testbeds of these system reforms. The new paradigm created by iCeMS has been high evaluated and has strongly influenced plans for these Kyoto University reforms described below.

1. Kyoto University international strategy (Formulated on September 2013)

Kyoto University has formulated a new international strategy, the 2x by 2020 Initiatives. 2x by 2020 is the slogan of the new International Strategy by means of which Kyoto University aims to double its international indices in research, education and international service by the year 2020. Goals are clarified in terms of quantity and deadline as WPI missions.

2. Kyoto University level administrative reform (Operational on July 2013)

Kyoto University has undertaken substantial administration reforms, such as the relocation and centralization of staff, new positions for supporting education and research, and implementation of rigorous evaluation and training systems to increase the efficiency of administration. iCeMS

has become to support and accelerate internationalization far beyond iCeMS to the Graduate School of Advanced Integrated Studies in Human Survivability (*Shishu-Kan*) and the Institute for Liberal Arts Studies (ILAS), newly established in FY2013. In ILAS, more than one hundred of oversea faculty are employed as tenured staff to teach classes in English.

iCeMS' rich accumulated experience in internationalization is anticipated to have a large impact on these new institutions. For example, 10 bilingual administrative staff are allocated to ILAS, some of whom are now on the job training at iCeMS.

3. Kyoto University Research Administration

KURA (Kyoto University Research Administration) was established at the university in 2012, and subsequently hired nearly 46 university research administrators (URAs). With its pioneering experience such as in its work with the Innovation Management Group, iCeMS' Research Planning Section has been playing an important role in collaborating with KURA.

4. Personnel management

Introduction of a new salary system including cross-appointment scheme is now under consideration and will be partially introduced into Kyoto University's personnel management. Abolishment of the retirement age has been implemented in other institutes such as CiRA and Shishu-kan and will be expanded to other organizations.

5-4. Support by Host Institution

The following two items concern the support that the host institution provides the Center, including those items of support that it committed to at the time of the initial project proposal submittal or in its revised commitment following the project's interim evaluation. Describe the functional measures that the host institution has taken to sustain and advance the Center's project.

5-4-1. Record of host institution support and its effects

- *In Appendix 5, describe the concrete measures being taken by the host institution.*

Kyoto University declared at the time of the initial project proposal to secure measures to support iCeMS research activities, and has secured them. Refer to Appendix 5.

5-4-2. Position of the Center within the host institution's mid-term plan

- *To Appendix 5, attach the cover sheets of the host institution's "Mid-term objectives" and/or "Mid-term plan" and parts of these documents related to the WPI Center.*

Kyoto University launched, in September 2013, a plan to establish the **International Center for Emerging Science** as one of the International Strategies **"2x by 2020"**. If the 5-year extension is allowed, the present iCeMS (modified as stated in 1) will continue to be the main institute of the new center. If not allowed or after the 5-year extension finishes in FY2021, iCeMS will be retained as scale-down version of its present state. Refer to Progress Plan Application.

5-5. Others

Describe efforts advanced to foster young researchers (e.g., start-up funding, autonomous research environment) and to enlist female researchers.

- *In Appendix 5, give the transition in the number of female researchers.*

iCeMS has taken the following efforts to foster young researchers.

(a) Startup grants to initiate cross-disciplinary collaboration: P.11 2-2-(b)-1, P.18 3-1-(c)
(b) Acceleration of outstanding projects: P.2 1-(b)-2-(iv), P.11 2-2-(b)-2, P.25 5-1-(b)-2
(c) Support for overseas visit for young researchers: P.11 2-2-(b)-3, P.24 4-4
(d) Independent positions for young scientists worldwide: P.12 2-2-(b)-4, P.21 4-1-2-(a)

6. Others

- *In addition to the above 1-5 evaluation items, only if there is anything else that deserves mention regarding the center project's progress, please note it.*

(a) Strengthening collaboration with CiRA

In FY 2007, just after **Prof Yamanaka**'s discovery of human iPS cells, iCeMS Director swiftly implemented his decision to create the Center for iPS Cell Research and Application under the auspices of iCeMS, marking a major advance in the effort to apply human stem cell research to the field of regenerative medicine.

Reflecting on the progress made in the field as well as answering public expectations, Kyoto University established CiRA as the 14th university institute outside of iCeMS on April 1, 2010, enabling it to freely develop clinical applications for regenerative medicine.

Differences between iCeMS' and CiRA's scientific approaches and goals, often a point of discussion in years past, are now sufficiently clear: **iCeMS incorporates iPS cells into its research, combining cells and materials, while CiRA focuses on clinical applications of iPS cells.** In this context, six CiRA scientists have iCeMS affiliations, performing basic and multidisciplinary research related to iPS cells in conjunction with iCeMS colleagues. Moreover, CiRA PI and iCeMS Professor Yamada and CiRA PI and iCeMS Kyoto Fellow Yamamoto both engage in the management of this institute as participants in iCeMS Board of PI meetings.

(b) Asian Chemical Biology Initiative

iCeMS has been serving as the headquarters of the Asian Chemical Biology Initiative. This program, sponsored by JSPS "Asian CORE Program" since 2011 (5-year term), aims to establish Asian research hubs that conduct world-class research, and foster outstanding young researchers. This initiative is being orchestrated by iCeMS **Prof Uesugi** in cooperation with institutions in Asia, including Seoul National University, Tsinghua University and National University of Singapore. The main goals of this initiative are as follows.

1. To establish a world-visible core of "Chemical Biology originating from Asian countries" led by Japan's initiatives.
2. To recruit talented graduate students from emerging Asian countries to Chemical Biology. More than 70 Asian chemical biology professors from Japan, Korea, China, Singapore, Hong Kong and India have already joined this initiative. Since the launch of this initiative, more than 100 international students have applied for interviews to study in Japan.

(c) Kyoto University joined edX program

Kyoto University announced on May 21, 2013 its alliance with "edX," making it the first Japanese university to take part in the non-profit educational consortium created by founding partners Harvard University and Massachusetts Institute of Technology (MIT) in 2012.
edX offers a variety of free interactive online classes from top-level universities in fields such as law, computer science, history and artificial intelligence. Through its expanding network, edX is comprised of 27 schools including 15 recently added institutions, and boasts over 900,000 registered users worldwide.

Taught by iCeMS Deputy Director **Prof Uesugi**, the "Chemistry of Life" is the first course offered by Kyoto University's "KyotoUx" series. In addition to being a complete 15-week course with homework assignments and quizzes, the teaching staff developed a new educational approach called the "Kyoto Method" for teaching chemistry students, and may be one day utilized by other edX courses. The classes started in spring 2014 and student registration for the course is 20,269. Prof Uesugi also provides the first "flipped class" in the long history of Kyoto University's education.

It is worth noting that Tokyo University's IPMU offered a short 4-week course as part of another MOOC, called Coursera, which was taught by Director Hitoshi Murayama.

7. Center's Response to Results of FY2013 Follow-up (including Site Visit Results)

** Describe the Center's Response to Results of FY2013 Follow-up. Note: If you have already provided this information, please indicate where in the report.*

Directorship has been smoothly shifted to Dr. Kitagawa, who presented the second mission of iCeMS, cell-inspired materials. Although the new director emphasized the significance of mesoscopic science, the terminology and the line of thinking did not create a commonly shared impression among the site visit members.

As described in 1, the root of the problem is caused by the term "mesoscopic science" which is well known to physicists but not to biologists. As one of the four missions of WPI is to "create new interdisciplinary domains", iCeMS has set up an ambitious research goal i.e. "establish mesoscopic science" and has been making every effort to reach it.

The vision has been criticized as being too diverse and ambiguous, leading us to revise it several times after iCeMS' establishment upon receiving valuable suggestions and advice from Program Committee, Site Visit WG and iCeMS Advisory Board members. While we believe that it is critical to look at mesoscopic domains lying between nano and macro realms to understand cells, we have not yet created a commonly shared perception of this term, even after numerous revisions. Thus, to avoid misunderstanding about iCeMS' present research goal, we will not emphasize the term "mesoscopic science" and instead, pursue the "Integration of Cell and Material Sciences" in mesoscopic domains.

Based on this, our biggest concern is that identity of iCeMS has not been clearly defined yet. We understand the significance of cell-inspired materials but are afraid that the incorporation of the new theme will broaden the topics more diffusively. In other words, research topics appear to be a little too diversified in areas related to cell biology, stem cells, membrane structures, chemistry and physics.

As described in 1, under the leadership of Director Kitagawa, a critical review of ongoing collaborative projects was conducted toward the end of the WPI Program in FY2016, resulting in a tightened focus on **Manipulation of Cell Fundamentals by Synthetic Molecules** covering the following three research pillars.

- Manipulation of Nucleus Information
- Manipulation of Membrane Compartments
- Manipulation of Cell Communication

At the FY2013 Program Committee meeting, Director Kitagawa proposed the other focal area "***cell-inspired materials***" which leans more heavily on materials science. Accepting the Program Committee's advice mentioned above, iCeMS has decided not to include "cell-inspired materials" at present as one of its research targets and will postpone it as future challenging research during the 5-year extension period.

In addition, as for the administration, a robust and concrete future plan for the institute by Kyoto University headquarters is keenly required.

Kyoto University announced in September 2013 the plan to establish the **International Center for Emerging Science** as one of its International Strategies.

If the 5-year extension is awarded, iCeMS in its current state will continue to be the main institute of the new center. However, If not allowed or after the 5-year extension finishes in FY2021, iCeMS will be retained as scale-down version of its present state (iCeMS beyond WPI).

The organization of the iCeMS beyond WPI together with financial and personnel support from the host institution have been tentatively agreed upon with current President Matsumoto, whose term will end in September 2014. However, plans have not been fixed because they require input from the next Kyoto University President. Nonetheless, a formal planning committee to establish the International Center for Emerging Science has already begun and submitted an interim report on the basic framework of the new center. The final report will be formally approved at the Dean and Directors Meeting no later than the end of FY2014. Structural details of the new center and the iCeMS beyond WPI will be finalized under the leadership of the new president before FY2016 when the third mid-term goal period starts. Refer to Progress Plan Application.

** All of Impact Factors indicated in this report are cited form Thomson Reuters 2012 Journal Citation Reports. **

World Premier International Research Center Initiative (WPI)

1. FY 2013 List of Principal Investigators

NOTE:
・Underline names of investigators who belong to an overseas research institution. Place an asterisk (*) by names of investigators considered to be ranked among world's top researchers.
・In case of researchers not listed in the latest report, attach "Biographical Sketch of a New Principal Investigator".

<Results at the end of FY2013>

Principal Investigators Total: 18

Name (Age)	Affiliation (Position title, department, organization)	Academic degree, specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Center Director Kitagawa, Susumu* (62)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Coordination Chemistry	75%	15%		10%	Oct. 1, 2007	Usually stays at the institution.	
Nakatsuji, Norio* (64)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Stem Cell Biology	40%	50%	5%	5%	Oct. 1, 2007	Usually stays at the institution.	
Imahori, Hiroshi* (52)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Organic Chemistry	80%	10%		10%	Oct. 1, 2007	Usually stays at the institution.	
Uesugi Motonari* (47)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Chemical Biology	80%	10%		10%	Oct. 1, 2007	Usually stays at the institution.	

<Results at the end of FY2013>

Principal Investigators Total: 18

Name (Age)	Affiliation (Position title, department, organization)	Academic degree, specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Ueda, Kazumitsu* (60)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Cellular Bio-chemistry	80%	10%		10%	Oct. 1, 2007	Usually stays at the institution.	
Kiso, Makoto* (66)	Professor, Gifu University	Ph.D. Glycotechnology	80%	10%		10%	Oct. 1, 2007	Joins a video conference from Gifu University once a month. Usually stays at Gifu University satellite.	
Kusumi, Akihiro* (61)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Single-Molecule Cell Biophysics	80%	10%		10%	Oct. 1, 2007	Usually stays at the institution.	
Kengaku, Mineko* (47)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Developmental Neurobiology	90%	10%			Oct. 1, 2008	Usually stays at the institution.	
Sugiyama, Hiroshi* (57)	Professor, Graduate School of Science, Kyoto University	Ph.D. Chemical Biology	15%	5%	70%	10%	Apr. 1, 2008	Participates at the 20% effort level. 80% devoted to the Graduate School of Science.	

<Results at the end of FY2013>

Principal Investigators Total: 18

Name (Age)	Affiliation (Position title, department, organization)	Academic degree, specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Tanaka, Koichiro* (51)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Terahertz Optical Science	90%	10%			Apr. 1, 2008	Usually stays at the institution.	
Hashida, Mitsuru* (62)	Professor, Graduate School of Pharmaceutical Sciences, Kyoto University	Ph.D. Drug Delivery Systems	40%	10%	40%	10%	Jan. 1, 2008	Participates at the 50% effort level. 50% devoted to the Graduate School of Pharmaceutical Sciences.	
Harada, Yoshie* (54)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Ph.D. Single-Molecule Physiology	90%	10%			Mar. 1, 2008	Usually stays at the institution.	
Chen, Yong* (57)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University Research Director, Ecole Normale Supérieure, CNRS	Ph.D. Nanobiotechnology	30%	10%	50%	10%	Mar. 1, 2008	Participates in the institution at the 40% effort level. (Frequency of visits to Japan: 5 times and 82 days in FY 2013	

Yamanaka, Shinya* (51)	Professor, CiRA, Kyoto University	M.D. Stem Cell Biology	4%	1%	75%	20%	Oct. 1, 2007	Participates at the 5% effort level. 95% devoted to the CiRA.	

<Results at the end of FY2013>

Principal Investigators Total: 18

Name (Age)	Affiliation (Position title, department, organization)	Academic degree, specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Heuser, John* (71)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University Professor, Washington University School of Medicine	M.D. Biophysics	50%		40%	10%	Nov. 16, 2009	Participates in the institution at the 50% effort level. (Frequency of visits to Japan: 4 times and 155 days in FY 2013)	
Kageyama, Ryoichiro* (57)	Professor, Institute for Virus Research, Kyoto University	M.D. Ph.D. Developmental Biology	15%	10%	65%	10%	Feb. 2, 2013	Participates at the 25% effort level. 75% devoted to the Institute for Virus Research.	
Saitou, Mitinori* (43)	Professor, Graduate School of Medicine, Kyoto University	M.D. Ph.D. Germ Cell Biology	15%	5%	70%	10%	Jan. 16, 2013	Participates at the 20% effort level. 80% devoted to the Graduate School of Medicine.	
Tanaka, Motomu* (43)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	M.D. Ph.D. Biological Physics	40%		50%	10%	Apr. 1, 2013	Participates at the 40% effort level. (Frequency of visits to Japan: 7 times and 116 days in FY2013)	

Researchers unable to participate in project in FY2013

Name	Affiliation (Position title, Department, Organization)	Starting date of project participation	Reasons	Measures taken
Agladze, Konstantin* (58)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University	Jan. 7, 2008	Expiration of the contract term and moved to MIPT, Russia	Hired new PIs
Hiiragi, Takashi* (45)	Professor, Institute for Integrated Cell-Material Sciences, Kyoto University Group Leader, European Molecular Biology Laboratory (EMBL)	Apr. 1, 2008	Expiration of the contract term and moved to EMBL, Germany.	Hired new PIs

Biographical Sketch of a New Principal Investigator in FY 2013

Name (Age)	Tanaka, Motomu (43)
Current affiliation (Position title, department, organization)	Program-Specific Research Center Professor, Institute for Integrated Cell-Material Sciences, Kyoto University
Academic degree, specialty	Habilitation in Experimental Physics, Technical University Munich (2005) PhD in Physical Chemistry, Kyoto University (1998)

Research and education history

1989-1993 B.S. Physical Chemistry, Kyoto University, Japan

1993-1995 M.S. Department of Molecular Engineering, Kyoto University

1995-1998 PhD, Department of Molecular Engineering, Kyoto University

1998-2001 Postdoc (JSPS, Humboldt Fellow), Department of Physics, Technical University Munich

2001-2005 Independent Group Leader (Emmy Noether Fellow),
Department of Physics, Technical University Munich

2001 Visiting Scholar, Department of Chemical Engineering, Stanford University

2004 Invited Lecturer, Department of Physics, Kyoto, University

2005 Habilitation in Experimental Physics, Technical University Munich

2005- Professor, Physical Chemistry of Biosystems, Institute of Physical Chemistry,
University of Heidelberg

2007- Faculty (joint appointment), Faculty of Physics and Astronomy, University of Heidelberg

2007- Faculty, The Hartmut Hoffmann-Berling International Graduate School of Molecular and Cellular Biology, University of Heidelberg

2013- Professor (HeKKSaGOn professorship), Institute for Integrated Cell-Material Sciences, Kyoto University

Achievements and highlights of past research activities *(Describe qualifications as a top-caliber researcher if he/she is considered to be ranked among the world's top researchers.)*

- Design of quantitative cell surface models (polymer-supported membranes)

- Quantifying the impact of surface saccharides on mechanics by using off-specular neutron scattering

- Localization of ions and elements at biological interfaces in Å accuracy using X-ray evanescent fluorescence

- Impacts of cooperativity in cell adhesion and spreading using artificial mesoscopic domains

- Unraveling characteristic spatio-temporal patterns from stochastic dynamics in diseases and development

- Dynamic changes in cell micro-environments using smart materials for regulating the cell fate

Achievements

(1) International influence *a) Guest speaker, chair, director, or honorary member of a major international academic society in the subject field, b) Holder of a prestigious lectureship, c) Member of a scholarly academy in a major country, d) Recipient of an international award(s) , e) Editor of an influential journal etc.*

Pleanary Lectures

Invited Talk, Gordon Research Conference "Biofunctional Interfaces", September 2008, Aussois (France).

Plenary Lecture, Euromembrane Congress, September 2009, Montpellier (France).

Invited Speaker, Kick-Off Symposium RIKEN-MPI Center "Chemical System Biology", March 2012, Dortmund (Germany).

European Congress in Colloid and Interface Science, September 2012, Malmö (Sweden).

Award

Emmy Noether Fellowship, German Science Foundation (2001)

Bronze Medal, Fonds der Chemischen Industrie (2006)

Philipp Franz von Siebold Prize, Humboldt Foundation (2014)

Advisory Board

Scientific Council, Institute Laue Langevin, Biological Physics (2009 - 2012)

Scientific Council, European Synchrotron Radiation Facility, Soft Condensed Matter (2012 -)

(2) Receipt of large-scale competitive fundings *(over past 5 years)*

Collaborative Research Center (SFB 873), German Science Foundation, (2010 - 2018)

Collaborative Research Center (SFB 1129), German Science Foundation (2014 - 2018)

Helmholtz Program "BioInterface", Helmholtz Association (2010 - 2015)

Basic Research Grant (KIBAN A), JSPS (2014 - 2017)

Scientific Research in Innovative Area (Shingakujutsu), JSPS (2014 - 2016)

(3) Article citations *(Titles of major publications, and number of citations.)*

Tanaka, M. and E. Sackmann, *Polymer-Supported Membranes as Models of the Cell Surface.* Nature, 2005. **437**: p. 656-663. **Citation: 573**

Sackmann, E. and M. Tanaka, *Supported membranes on soft polymer cushions: Fabrication, characterization and applications.* Trends Biotechnol., 2000. **18**(2): p. 58-64. **Citation: 376**

Hillebrandt, H., G. Wiegand, M. Tanaka, and E. Sackmann, *High electric resistance polymer/lipid composite films on indium-tin-oxide electrodes.* Langmuir, 1999. **15**(24): p. 8451-8459. **Citation: 149**

Schneck, E., T. Schubert, O.V. Konovalov, B.E. Quinn, T. Gutsmann, K. Brandenburg, R.G. Oliveira, D.A. Pink, and M. Tanaka, *Quantitative determination of ion distributions in bacterial lipopolysaccharide membranes by grazing-incidence X-ray fluorescence.* Proceedings of the National Academy of Sciences, 2010. **107**(20): p. 9147-9151. **Citation: 23**

Yoshikawa, H.Y., F.F. Rossetti, S. Kaufmann, T. Kaindl, J. Madsen, U. Engel, A.L. Lewis, S.P. Armes, and M. Tanaka, *Quantitative Evaluation of Mechanosensing of Cells on Dynamically Tunable Hydrogels.* Journal of the American Chemical Society, 2011. **133**(5): p. 1367-1374. **Citation: 42**

(4) Others *(Other achievements that indicate qualification as a top-caliber researcher, if any.)*

Member (PI), Canadian Centre of Excellence "Advanced Food and Material Network" (2006 - 2009)

German Coordinator, EU FP7 "SoftActive"

Guest Editor "Material Science of Supported Membranes" Material (2012)

Academic Director, German-Japanese Summer School "Princiles of Life with Quantitative Tools", September 2012, Heidelberg (Germany)

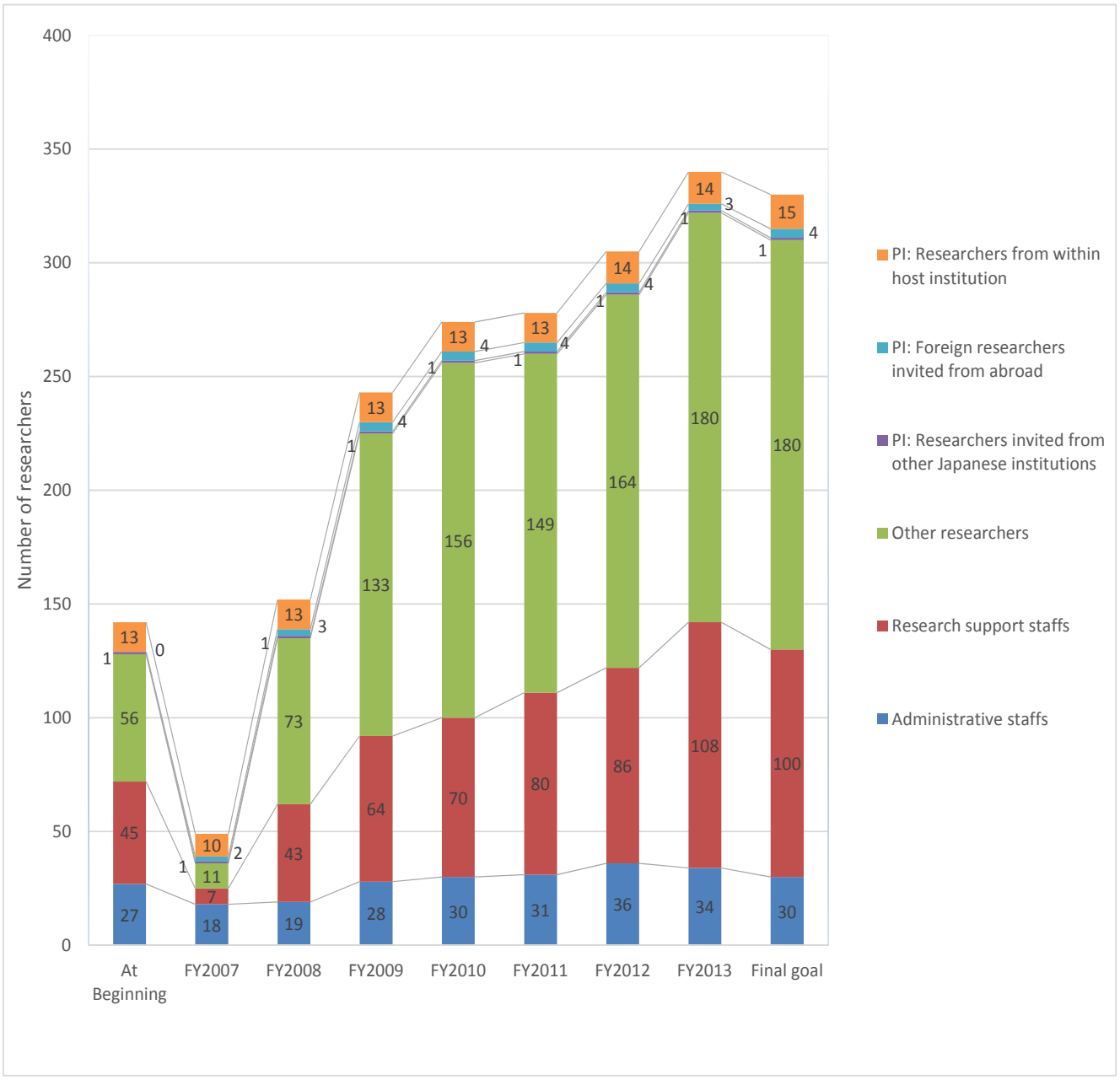
Guest Professor, Department of Physics, Kyoto University (2012)

Organized more than 20 International Symposiums and Workshops

World Premier International Research Center Initiative (WPI)

2. Annual transition in the number of Center personnel

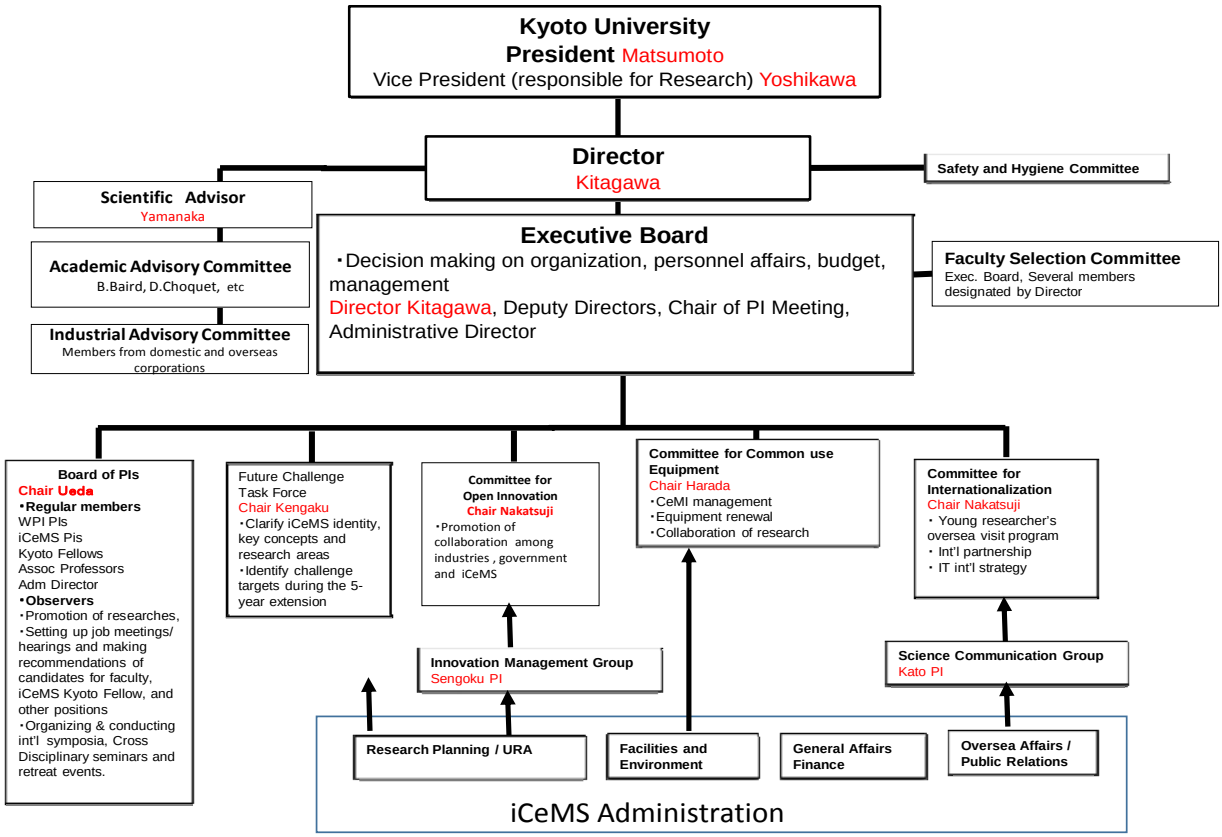
*Make a graph of the annual transition in the number of center personnel since the start of project.



World Premier International Research Center Initiative (WPI)

3. Diagram of management system

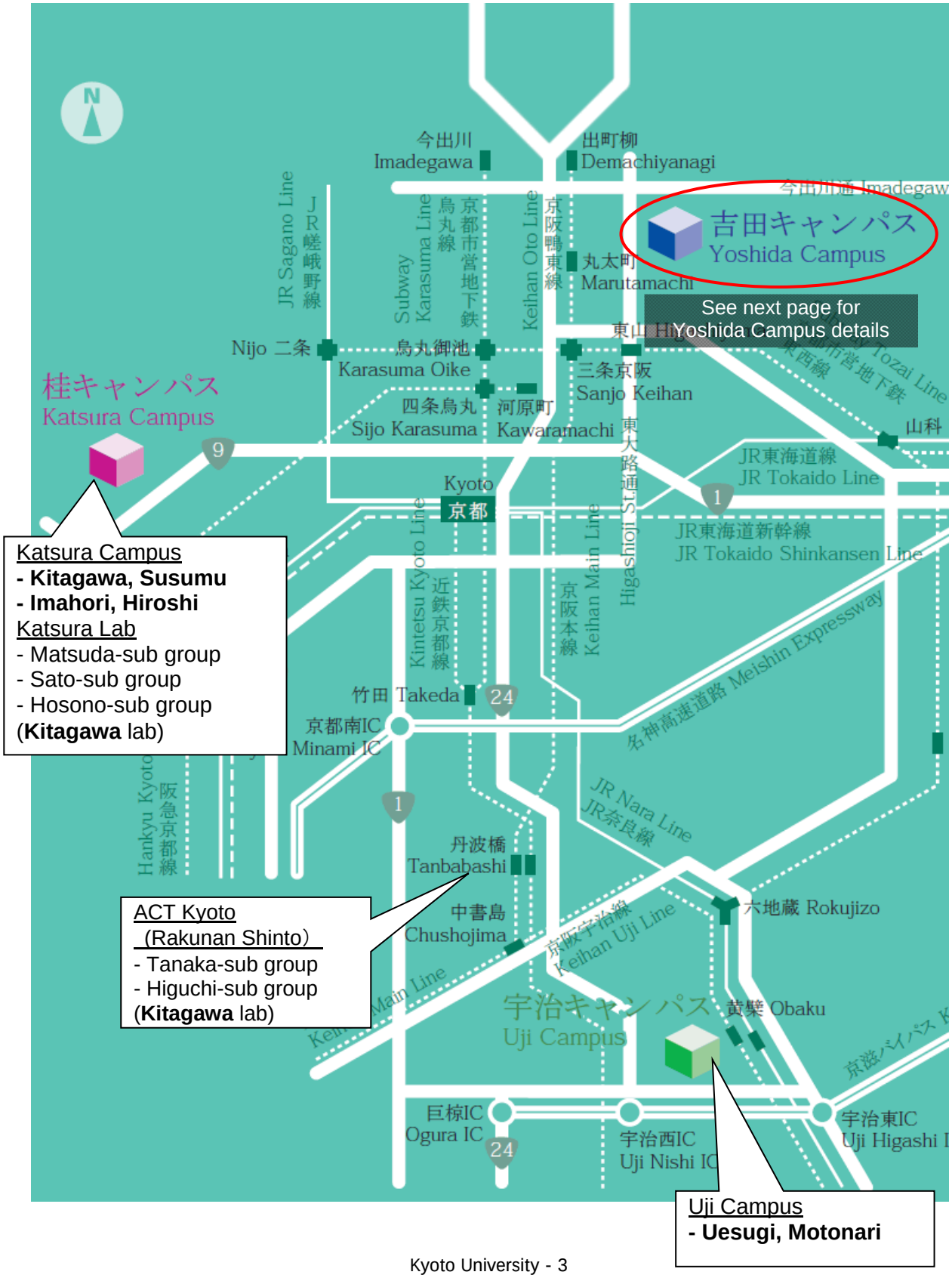
1. Top down decision making by Executive Board
   The board consists of the Director, two Deputy Directors, Chair of PI Meeting and Admin Director. Meetings are held twice a month, and the Director makes top-down decisions on matters related to personnel affairs, budget and other management issues.
2. Board of PIs
   The board consists of PIs, Associate Professors and iCeMS Kyoto fellows. PI meetings are held monthly to share important management information and to set up job seminars and make recommendations of candidates for faculty and other positions.
3. Management support by various committees
   Committees include Future Challenge Task Force, Open innovation, Facilities Management, CeMI Management and Internationalization.
4. Scientific Advisor
   Nobel Prize winner Prof Yamanaka contributes valuables suggestions from a broader point of view.
5. Academic and Industrial Advisory Boards
   The Academic Board consists of world renowned professors (researchers from 8 overseas and 2 domestic institutions). The board meetings, held three times to date, contribute valuable comments on research activities conducted at iCeMS. The Industrial Advisory Board (managers from 3 overseas and 3 domestic industries) was established in 2013 to promote further collaboration with industries.



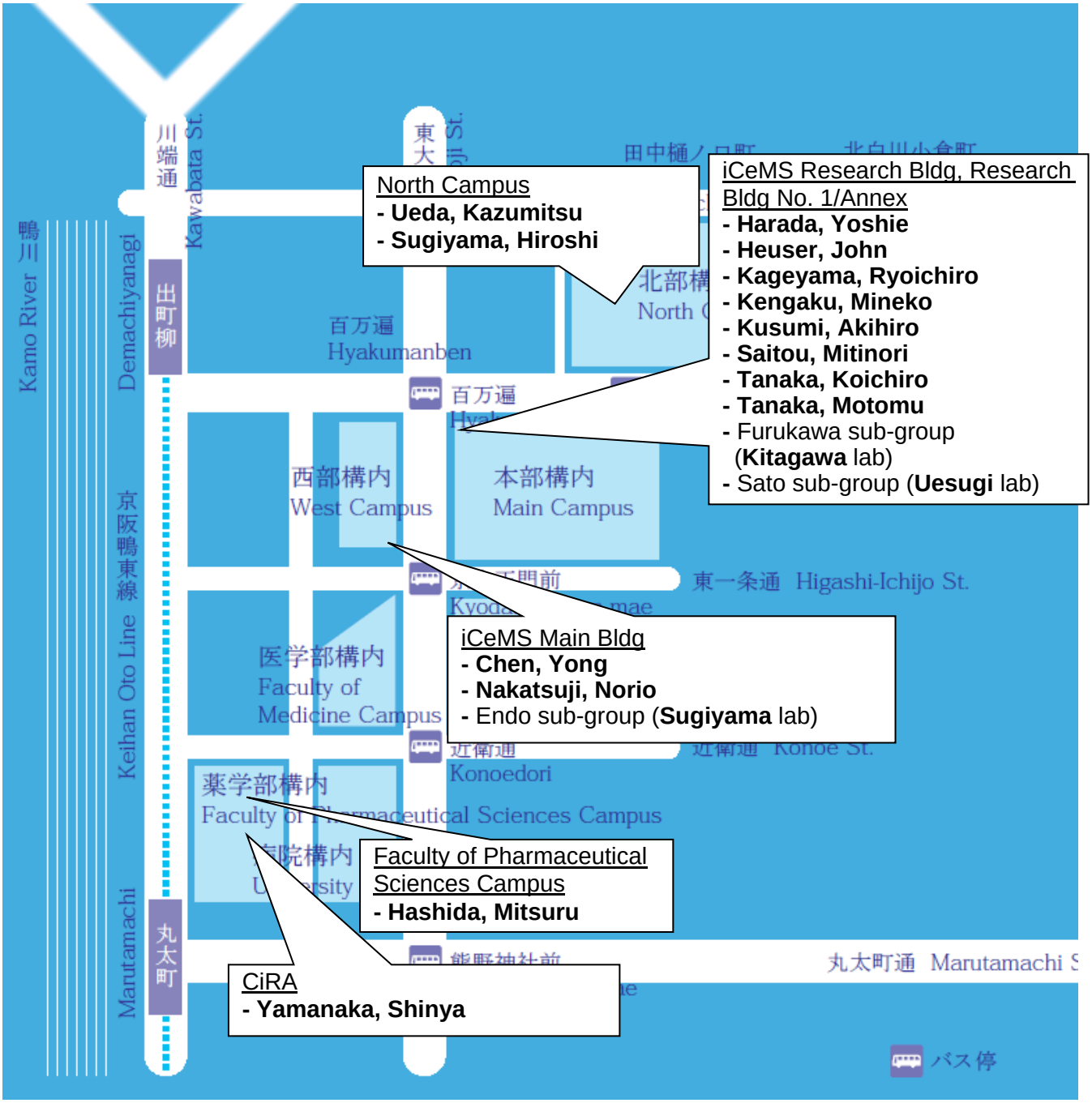
World Premier International Research Center Initiative (WPI)

4. Campus map

- Please draw a simple map of the campus showing where the main office and principle investigator(s) are located.



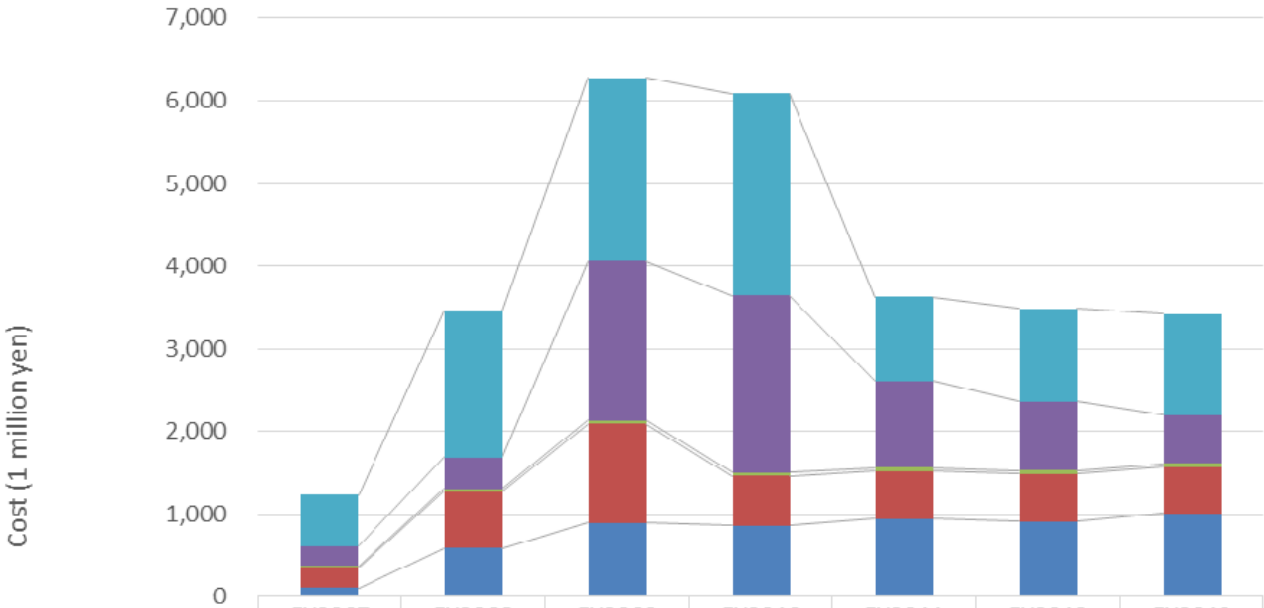
Yoshida Campus



World Premier International Research Center Initiative (WPI)

5. Annual transition in the amounts of project funding

*Make a graph of the transition in the number of overall project funding.



	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013
Research Projects	618	1,774	2,217	2,437	1,015	1,129	1,219
Equipment	237	384	1,924	2,140	1,051	831	585
Travel	24	27	46	45	46	42	44
Project Activities	241	687	1,194	600	575	574	565
Personnel	111	590	894	862	943	913	1,007

6. FY2013 Project Expenditures (the exchange rate used: 1USD= 100JPY)

Overall project funding

Cost Items	Details	Costs (10,000 dollas)
Personnel	Center director and Administrative director	35
	Principal investigators (no. of persons: 18)	178
	Other researchers (no. of persons: 89)	545
	Research support staffs (no. of persons: 80)	129
	Administrative staffs (no. of persons: 46)	120
	Total	1,007
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons:)	
	Cost of dispatching scientists (no. of persons: 33)	63
	Research startup cost (no. of persons: 28)	180
	Cost of satellite organizations (no. of satellite organizations: 1)	50
	Cost of international symposiums (no. of symposiums: 2)	1
	Rental fees for facilities	24
	Cost of consumables	39
	Cost of utilities	53
	Other costs	155
	Total	565
Travel	Domestic travel costs	10
	Overseas travel costs	23
	Travel and accommodations cost for invited scientists (no. of domestic scientists: 44) (no. of overseas scientists: 23)	6
	Travel cost for scientists on secondment (no. of domestic scientists: 6) (no. of overseas scientists: 10)	5
	Total	44
Equipment	Depreciation of buildings	124
	Depreciation of equipment	461
	Total	585
Other research projects	Projects supported by other government subsidies, etc.	39
	Commissioned research projects, etc.	677
	Grants-in-Aid for Scientific Research, etc.	503
	Total	1,219
Total		3,420

Ten thousand dollars

WPI grant	1,334
Costs of establishing and maintaining facilities	14
Renovation of Research building	4
Others	10
Cost of equipment procured	136
Draft chamber	4
Others	132

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (no. of persons:)	
	Other researchers (no. of persons: 2)	
	Research support staffs (no. of persons: 7)	
	Administrative staffs (no. of persons:)	
	Total	44
Project activities		3
Travel		2
Equipment		1
Other research projects		23
Total		73

7. FY2013 WPI Grant Expenditures (the exchange rate used: 1USD= 100JPY)

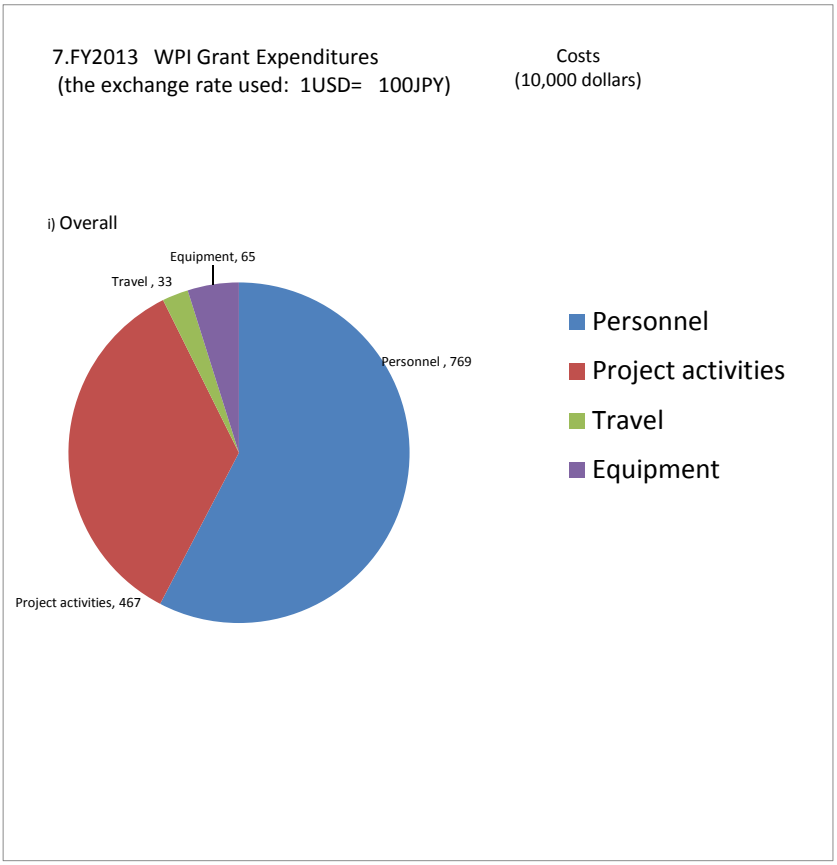
i) Overall expenditures

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	16
	Principal investigators (no. of person : 18)	68
	Other researchers (no. of person:89)	517
	Research support staffs (no. of person:77)	125
	Administrative staffs (no. of person:17)	43
	Total	769
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of person)	
	Cost of dispatching scientists (no. of person : 33)	63
	Research startup cost (no. of person : 28)	180
	Cost of satellite organizations (no. of satellite organization : 1)	50
	Cost of international symposiums (no. of symposiums : 2)	1
	Rental fees for facilities	22
	Cost of consumables	21
	Cost of utilities	44
	Other costs	86
	Total	467
Travel	Domestic travel costs	7
	Overseas travel costs	15
	Travel and accommodations cost for invited scientists (no. of domestic scientists:43) (no. of overseas scientists:23)	6
	Travel cost for scientists on secondment (no. of domestic scientists:4) (no. of overseas scientists:10)	5
	Total	33
Equipment	Cost of equipment procured	65
	Total	65
Total		1334

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (0)	
	Other researchers (2)	
	Research support staffs (7)	
	Administrative staffs (0)	
	Total	44
Project activities		3
Travel		2
Equipment		1
Total		50

7.FY2013 WPI Grant Expenditures (the exchange rate used: 1USD= 100JPY)



World Premier International Research Center Initiative (WPI)

1. List of papers underscoring each research achievement

** List papers underscoring each research achievement listed in the item 2-1 "Research results to date" (up to 40 papers) and provide a description of the significance of each (within 10 lines).*
** For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. If a paper has many authors, underline those affiliated with the Center.*
** If a paper has many authors (say, more than 10), all of their names do not need to be listed.*
** Place an asterisk (*) in front of those results that could only have been achieved by a WPI center.*

***I-1. Oscillatory control of factors determining multipotency and fate in mouse neural progenitors**

*1. Imayoshi, I; Isomura, A; Harima, Y; Kawaguchi, K; Kori, H; Miyachi, H; Fujiwara, T; Ishidate, F; Kageyama, R; Oscillatory Control of Factors Determining Multipotency and Fate in Mouse Neural Progenitors; *Science* 342, 1203-1208 (2013) [IF 31.0]

This project enables gene expression control by light illumination to regulate stem cell differentiation. Neural stem cells have multipotency to give rise to three different cell fates, neurons, oligodendrocytes, and astrocytes, but the precise mechanism of neural stem cell control remains to be determined. We here generated bioluminescence and fluorescence reporters to monitor the expression dynamics of each cell fate determination factor. In collaboration with CEMI microscopy specialists, we revealed that the expression of these factors oscillates in neural stem cells, whereas the expression of one of them becomes sustained during cell fate choice. By using a new optogenetic method, we successfully showed that oscillatory expression of the proneural factor Ascl1 activates neural stem cell proliferation, whereas sustained expression of Ascl1 induces neuronal differentiation.

***I-2. Successful development of artificial genetic switches using DNA-based synthetic small molecules**

2. Pandian, GN; Nakano, Y; Sato, S; Morinaga, H; Bando, T; Nagase, H; Sugiyama, H; A synthetic small molecule for rapid induction of multiple pluripotency genes in mouse embryonic fibroblasts; *Sci Rep* 2, 544 (2012) [IF 2.9]

Cellular reprogramming involves the genome-wide remodeling of chromatin and small molecules affecting the chromatin landscape have been shown to reactivate the endogenous pluripotency network in place of transcription factor transduction. The Sugiyama lab synthesized a new class of targeting small molecule termed, SAHA-PIP containing sequence-specific pyrrole-imidazole polyamides (PIPs) and histone deacetylase inhibitor SAHA. Genome-wide gene analysis revealed that a SAHA-PIP called δ induced multiple pluripotency-associated genes via site-specific chromatin modifications and initiated cellular reprogramming by switching "ON" the complex transcriptional gene network. This article got highlighted in STEM CELLS PORTAL as a study destined to make an impact on stem cell research and clinical studies.

3. Han, L; Pandian, GN; Junetha, S; Sato, S; Anandhakumar, C; Taniguchi, J; Saha, A; Bando, T; Nagase, H; Sugiyama, H; A Synthetic Small Molecule for Targeted Transcriptional Activation of Germ Cell Genes in a Human Somatic Cell; *Angew. Chem.-Int. Edit.* 52, 13410-13413 (2013) [IF 13.7]

In this study carried out in human fibroblasts, we identified that a SAHA-PIP called K was capable of triggering unusual transcriptional activation of the typically conserved PIWI gene that regulates the meiotic process. This first ever report on a germ cell gene switch is a successful

representative model that substantiates the scope of iCeMS, which aims to achieve `materials for cell control`. This paper was selected as a `Hot paper` by the editor for the importance of this work in a rapidly evolving field of high current interest.

*4. Pandian, GN.; Taniguchi, J; Junetha, S; Sato, S; Han, L; Saha, A; AnandhaKumar, C; Bando, T; Nagase, H; Vaijayanthi, T; Taylor, R; Sugiyama, H; Distinct DNA-based epigenetic switches trigger transcriptional activation of silent genes in human dermal fibroblasts; *Sci Rep* 4, 3843 (2014) [IF 2.9]

Artificial transcriptional activators must encompass both DNA recognition and functional modules to retain the capability of their biological counterparts and rewire misregulated transcriptional networks. In this study, we demonstrate through microarray studies about the remarkable ability of thirty-two distinct SAHA-PIPs to trigger the transcriptional activation of exclusive clusters of genes including KSR2, the obesity gene. Our proof-of-concept study demonstrates the possibility to develop this kind of DNA-based epigenetic switches as `iCeMS developed materials` for controlling the transcription of silent genes associated with cell fate and/or the genes of therapeutic importance. This paper got highlighted in various portals including one in GEN News titled, `Install Epigenetic Switches to Give Silent Genes a Voice`.

I-3. Proof of concept for epigenetics-driven cancer development through artificial manipulation of epigenetic regulation

5. Ohnishi, K; Semi, K; Yamamoto, T; Shimizu, M; Tanaka, A; Mitsunaga, K; Okita, K; Osafune, K; Arioka, Y; Maeda, T; Soejima, H; Moriwaki, H; Yamanaka, S; Woltjen, K; Yamada, Y; Premature Termination of Reprogramming In Vivo Leads to Cancer Development through Altered Epigenetic Regulation; *Cell* 156, 663-677 (2014) [IF 32.0]

It is widely accepted that cancer develops through accumulation of genetic mutations. Taking advantage of iPSC technology, this paper provided a proof of concept that cancer can arise predominantly through altered epigenetic regulations.

*I-4. Identification of transcription factors sufficient for inducing the germ cell fate in epiblast cells in mice

*6. Hayashi, K; Ohta, H; Kurimoto, K; Aramaki, S; Saitou, M; Reconstitution of the mouse germ cell specification pathway in culture by pluripotent stem cells.; *Cell* 146, 519-532 (2011) [IF 32.0]

This work demonstrates the reconstruction of the mouse germ cell specification pathway in culture using pluripotent stem cells. Embryonic stem cells (ESCs)/induced pluripotent stem cells (iPSCs) are induced into epiblast-like cells (EpiLCs) and then into primordial germ cell-like cells (PGCLCs) with capacity to contribute to spermatogenesis and healthy offspring. This work serves as a robust foundation for in vitro gametogenesis from pluripotent stem cells.

*7. Hayashi, K; Ogushi, S; Kurimoto, K; Shimamoto, S; Ohta, H; Saitou, M; Offspring from Oocytes Derived from in Vitro Primordial Germ Cell-like Cells in Mice; *Science* 338, 971-975 (2012) [IF 31.0]

This paper reports the generation of healthy offspring from oocytes derived from in vitro primordial germ cell-like cells induced from embryonic stem cells or induced pluripotent stem cells in mice. This work was selected as one of the 10 breakthrough achievements in 2012 by Science.

*8. Nakaki, F; Hayashi, K; Ohta, H; Kurimoto, K; Yabuta, Y; Saitou, M; Induction of mouse germ-cell fate by transcription factors in vitro; *Nature* 501, 222-226 (2013) [IF 38.6]

This paper reports the identification of transcription factors that are sufficient to induce, upon in vitro epiblast-like cells generated from embryonic stem cells, primoridial germ cell-like cells with capacity for spermatogenesis.

***I-5. Single molecule imaging and manipulation using meso-scale DNA origami structures**

*9. Endo, M; Katsuda, Y; Hidaka, K; Sugiyama, H; Regulation of DNA Methylation Using Different Tensions of Double Strands Constructed in a Defined DNA Nanostructure; *J. Am. Chem. Soc.* 132, 1592-1597 (2010) [IF 10.7]

A novel strategy for regulating an enzymatic DNA modification reaction has been developed by employing a designed nanoscale DNA scaffold "DNA frame". Tense and relaxed double-stranded DNAs (dsDNA) were incorporated into the DNA frame, and the effect of tension for the methyltransfer reaction was investigated. High-speed atomic force microscope (AFM) imaging revealed the different dynamic movement of methylase complexes on tense and relaxed dsDNAs. AFM analysis and biochemical analysis revealed that the methylation preferentially occurred in the relaxed dsDNA. The results indicate the importance of the structural flexibility for bending of the duplex DNA during the methyltransfer reaction.

*10. Wickham, SFJ; Endo, M; Katsuda, Y; Hidaka, K; Bath, J; Sugiyama, H; Turberfield, AJ; Direct observation of stepwise movement of a synthetic molecular transporter; *Nat. Nanotechnol.* 6, 166-169 (2011) [IF 31.1]

A DNA transportation system with a mobile DNA nanomachine (DNA motor) was constructed on a DNA origami surface. The track with multiple ssDNAs (stators) was introduced onto the DNA origami tile to observe the movement of a DNA motor strand. Time-dependent movement of the motor strand along the motor track was observed. Furthermore, the stepwise movement of the motor strand was directly visualized by high-speed AFM. The detailed AFM analysis revealed that the distance of the motor-strand movement corresponded to the distance between the adjacent stators, indicating that the movement occurred stepwise on the track.

*11. Wickham, SFJ; Bath, J; Katsuda, Y; Endo, M; Hidaka, K; Sugiyama, H; Turberfield, AJ; A DNA-based molecular motor that can navigate a network of tracks; *Nat. Nanotechnol.* 7, 169-173 (2012) [IF 31.1]

To control the programmable movement of the DNA motor strand, a branched track was constructed on the DNA origami tile, and three branching points and four final destinations were created. The block strands were introduced at both sides of the branching points to control the direction of the DNA motor. When the specific block strands were removed by the corresponding release strand, the motor strand moved to reach the final destination, which was observed using AFM and the fluorescence quenching method. The DNA motor can be precisely delivered to the defined destination by following the programmed instructions.

***II-1. New single-molecule tracking methods elucidated the hierarchical meso-scale compartment architecture of the plasma membrane for signal transduction**

*12. Tanaka, KAK; Suzuki, KGN; Shirai, YM; Shibutani, ST; Miyahara, MSH; Tsuboi, H; Yahara, M; Yoshimura, A; Mayor, S; Fujiwara, TK; Kusumi, A; Membrane molecules mobile even after chemical fixation; *Nat. Methods* 7, 865-866 (2010) [IF 23.6]

Chemical crosslinking has been extensively used for immobilizing membrane-associated molecules and cytoskeletal molecules in optical and electron microscopy in virtually all the biomedical fields. We critically reevaluated this method, and reported that under general crosslinking conditions, membrane molecules are hardly immobilized, and described new methods useful for many membrane proteins.

*13. Nishimura, H; Ritchie, K; Kasai, RS; Morone, N; Sugimura, H; Tanaka, K; Sase, I; Yoshimura, A; Nakano, Y; Fujiwara, TK; Kusumi, A; Biocompatible fluorescent silicon nanocrystals for single-molecule tracking and fluorescence imaging; *J. Cell Biol.* 202, 967-983 (2013) [IF 10.8]

Fluorescence microscopy is used extensively in cell biological and biomedical research, but it is plagued by three major problems with the presently available fluorescent probes: photobleaching, blinking, and large size. In this research, these problems have been basically solved by developing biocompatible, red-emitting silicon nanocrystals (SiNCs) with a 4.1-nm hydrodynamic diameter, conjugated to biomolecules precisely at a 1:1 ratio, which neither blinked nor photobleached for at least 5 h. Using the SiNCs, it became possible for the first time to observe the internalization process of receptor molecules at the single-molecule level and to reveal the micron-scale mosaicism in the plasma membrane.

*14. Kusumi, A; Fujiwara, TK; Chadda, R; Xie, M; Tsunoyama, TA; Kalay, Z; Kasai, RS; Suzuki, KGN; Dynamic Organizing Principles of the Plasma Membrane that Regulate Signal Transduction: Commemorating the Fortieth Anniversary of Singer and Nicolson's Fluid-Mosaic Model; *Annu. Rev. Cell Dev.Biol.* 28, 215-250 (2012) [IF 18.0]

In this review, we tried to synthesize our current biological, chemical, and physical knowledge about the plasma membrane to provide new fundamental organizing principles of this structure that underlie every molecular mechanism that realizes its functions. Special attention was paid to signal transduction function and the dynamic aspect of the organizing principles. We propose that the cooperative action of the hierarchical three-tiered mesoscale (2–300 nm) domains is critical for membrane function and distinguishes the plasma membrane from a classical Singer-Nicolson-type model.

*15. Kasai, RS; Suzuki, KGN; Prossnitz, ER; Koyama-Honda, I; Nakada, C; Fujiwara, TK; Kusumi, A; Full characterization of GPCR monomer-dimer dynamic equilibrium by single molecule imaging; *J. Cell Biol.* 192, 463-480 (2011) [IF 10.8]

The G-protein-coupled receptors (GPCRs) represent the largest superfamily in human genome and more than half of the drug development cost is now spent for drugs that can modulate the GPCR functions. However, the exact mechanism for its function remains unknown. We found a GPCR forms transient homodimers, with a lifetime of 90 ms, and succeeded in fully characterizing its monomer-dimer dynamic equilibrium, first time ever for any membrane molecules. This work is important in GPCR research as well as in the methodology development for determining the dynamic equilibrium in the membrane.

*16. Suzuki, KGN; Kasai, RS; Hirosawa, KM; Nemoto, YL; Ishibashi, M; Miwa, Y; Fujiwara, TK; Kusumi, A; Transient GPI-anchored protein homodimers are units for raft organization and function; *Nat. Chem. Biol.* 8, 774-783 (2012) [IF 13.0]

The sterol-dependent mesoscale domains in cellular membranes, called raft domains, have been controversial, including their very existence. In this work, advanced single-molecule tracking developed in the Kusumi and CeMI groups revealed the interactions among some of the most rudimentary units from which rafts may originate (glycosylphosphatidylinositol-anchored

receptors [GAR] and cholesterol), clarifying that lipid- and protein-based interactions jointly contribute to form the transient GAR homodimer rafts in the plasma membrane. These homodimer rafts act as the basic units for generating more stable signaling rafts and their signal transduction activities. Understanding these interactions helps to develop long-evolving and still debated models of raft domains.

***II-2. Meso-scale raft domain architecture and function revealed by developing fluorescent ganglioside analogs**

*17. Tamai, H; Ando, H; Tanaka, HN; Hosoda-Yabe, R; Yabe, T; Ishida, H; Kiso, M; The Total Synthesis of the Neurogenic Ganglioside LLG-3 Isolated from the Starfish Linckia laevigata; *Angew. Chem.-Int. Edit.* 50, 2330-2333 (2011) [IF 13.7]

This paper describes the first total synthesis of highly neuritegenic glycolipid LLG-3 which was found in starfish and the first demonstration of neuritegeneration induced by the synthetic LLG-3. To achieve the first total synthesis, the most crucial, common issue in glycolipid syntheses, that is, the chemical conjugation of sugar chain (glycan) and lipid was mainly addressed. As a result, an expedient approach to the glycolipid framework has been successfully established, which was designated as glucosyl ceramide cassette approach, in this study. In addition, a reliable method for constructing complex sialic acid-containing glycan has been developed. By harnessing the two important synthetic methods, the target molecule has been successfully synthesized. This innovation provided the core technology of glycolipid synthesis, which allowed us to develop a wide spectrum of fluorescent ganglioside probes for single molecule imaging of lipid raft.

***II-3. Mechanism of modulating membrane lipid distribution by lipid transporter**

*18. Nagata, KO; Nakada, C; Kasai, RS; Kusumi, A; Ueda, K; ABCA1 dimer-monomer interconversion during HDL generation revealed by single-molecule imaging; *Proc. Natl. Acad. Sci. U. S. A.* 110, 5034-5039 (2013) [IF 9.7]

The generation of high-density lipoprotein (HDL), one of the most critical events for preventing atherosclerosis, is mediated by the ATP binding cassette protein A1 (ABCA1) located on the plasma membrane. Using single-molecule tracking, we found that ABCA1 forms a dimer as it accumulates cholesterol in/around the ABCA1molecule, where two molecules of apoA1 is recruited and form a pair, presumably during the process of receiving the accumulated cholesterol from ABCA1, and eventually making a nascent HDL. This was achieved by close collaboration between Ueda and Kusumi groups, which was made possible by iCeMS.

***II-4. Mechanism of multi-drug transport**

*19. Kodan, A; Yamaguchi, T; Nakatsu, T; Sakiyama, K; Hipolito, CK; Fujioka, A; Hirokane, R; Ikeguchi, K; Watanabe, B; Hiratake, J; Kimura, Y; Suga, H; Ueda, K; Kato, H; Structural basis for gating mechanisms of a eukaryotic P-glycoprotein homolog; *Proc. Natl. Acad. Sci. U. S. A.* 111, 4049-4054 (2014) [IF 9.7]

MDR1 exports various hydrophobic chemicals in an ATP-dependent manner and determines their absorption and distribution in the body, and is involved in multidrug resistance (MDR) in tumors. To understand the mechanism of the multidrug transport is important for designing drugs of good bio-availability and efficient cancer chemotherapy. Ueda group, in collaboration with Kato group, determined the high-resolution crystal structures of a eukaryotic MDR1 homolog and revealed the detailed architecture. The structure revealed i) how MDR1 takes hydrophobic toxic compounds into the protein, ii) how MDR1 recognizes structurally unrelated various compounds and iii) how MDR1 exports them out of cells.

***II-5. A chemical probe that labels human pluripotent stem cells**

*20. Hirata, N; Nakagawa, M; Fujibayashi, Y; Yamauchi, K; Murata, A; Minami, I; Tomioka, M; Kondo, T; Kuo T; Endo, H; Inoue, H; Sato, S; Ando, S; Kawazoe, Y; Aiba, K; Nagata, K; Kawase, E; Chang, Y; Suemori, H; Eto, K; Nakauchi, H; Yamanaka, S; Nakatsuji, N; Ueda, K; Uesugi, M; A chemical probe that labels human pluripotent stem cells; *Cell Reports* 6, 1165-1174 (2014) [IF n/a]

Screening of fluorescent chemical libraries with human induced pluripotent stem cells (iPSCs) identified a fluorescent molecule (Kyoto probe 1 [KP-1]) that selectively labels human pluripotent stem cells. Our mechanistic analyses indicated that the selectivity results primarily from a distinct expression pattern of ABC transporters in human pluripotent stem cells and from the transporter selectivity of KP-1. KP-1 may widely be used as a tool in the field of stem cell biology.

***II-6. Utilization of photoinduced charge-separated state of donor-acceptor linked molecules for regulation of cell membrane potential and ion transport**

*21. Numata, T; Murakami, T; Kawashima, F; Morone, N; Heuser, JE; Takano, Y; Ohkubo, K; Fukuzumi, S; Mori, Y; Imahori, H; Utilization of Photoinduced Charge-Separated State of Donor-Acceptor Linked Molecules for Regulation of Cell Membrane Potential and Ion Transport; *J. Am. Chem. Soc.* 134, 6092-6095 (2012) [IF 10.7]

We have successfully controlled the membrane potential and ion transport across the PC12 cell membrane by using ferrocene– porphyrin– fullerene triad molecules, cell penetrating high density lipoprotein (HDL), This is the first optogenetic method utilizing the photoinduced charge-separated state of D–A-linked molecules on the intact cell membrane.

***II-7. Study on the generation of ultra-intense THz pulse sources and nonlinear spectroscopy**

*22. Hirori, H; Doi, A; Blanchard, F; Tanaka, K; Single-cycle terahertz pulses with amplitudes exceeding 1 MV/cm generated by optical rectification in LiNbO3; *Appl. Phys. Lett.* 98, 91106 (2011) [IF 3.8]

In 2002, Hebling et al. theoretically devised a tilted-pulse-front pumping scheme for efficiently generating THz pulses using $LiNbO_3$ crystals. However, the scheme's complexity and noncollinear propagation geometry, where the angle between the propagation directions of the THz radiation and the pump pulse are not equal, have stymied researchers seeking to generate and focus the THz pulse in an optimal way. In this study, the best condition for the optimal pump-to-THz conversion efficiency can be found by the optical calculation. The generated pulse source is the first ever with electric field strength of over 1 MV/cm, and its focused intensity is several tens of times larger than that obtained before by other research groups.

23. Hirori, H; Shinokita, K; Shirai, M; Tani, S; Kadoya, Y; Tanaka, K; Extraordinary carrier multiplication gated by a picosecond electric field pulse; *Nat. Commun.* 2, 594 (2011) [IF 10.0]

The study of carrier multiplication has become an essential part of many-body physics and materials science as this multiplication directly affects nonlinear transport phenomena, and has a key role in designing efficient solar cells and electroluminescent emitters and highly sensitive photon detectors. Here we show that a 1-MV/cm electric field of a terahertz pulse, unlike a DC bias, can generate a substantial number of electron–hole pairs, forming excitons that emit near-infrared luminescence. The bright luminescence associated with carrier multiplication suggests that carriers coherently driven by a strong electric field can efficiently gain enough

kinetic energy to induce a series of impact ionizations that can increase the number of carriers by about three orders of magnitude on the picosecond time scale.

24. Kampfrath, T; Tanaka, K; Nelson, KA; Resonant and nonresonant control over matter and light by intense terahertz transients; *Nat. Photonics* 7, 680-690 (2013) [IF 27.3]

Electromagnetic radiation in the terahertz (THz) frequency range is a fascinating spectroscopic tool that provides resonant access to fundamental modes, including the motions of free electrons, the rotations of molecules, the vibrations of large molecules such as proteins and DNAs, and the relaxations of polar liquids such as water. As a result, THz waves have been extensively used to probe such responses with high sensitivity. However, owing to recent developments in high-power sources, scientists have started to abandon the role of pure observers and are now exploiting intense THz radiation to engineer transient states of matter. This Review provides an overview and illustrative examples of how the electric and magnetic fields of intense THz transients can be used to control matter and light resonantly and non-resonantly.

***II-8. Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform**

*25. Diring, S; Wang, DO; Kim, C; Kondo, M; Chen, Y; Kitagawa, S; Kamei, K; Furukawa, S; Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform; *Nat. Commun.* 4, 2684 (2013) [IF 10.0]

Nitric oxide (NO) is one of the most investigated gasotransmitters, having important roles in numerous signaling events as well as therapeutic potentials. However, the development of releasing systems that allow spatial and temporal control over the delivery remains challenging. Collaboration among iCeMS scientists generated a new photoactive porous coordination polymer, which allows for a controlled release of nitric oxide upon light irradiation. Organizing a photoactive ligand into a three-dimensional porous structure induced a drastic increase in the photoreactivity and in the amount of released NO. The technology permitted a precisely controlled delivery of NO at the cellular level via localized near-infrared two-photon laser activation. This unique approach provides a tool for better understanding the physiological role of NO.

***II-9. Structuring of porous coordination polymers in the mesoscale towards creation of cell-inspired materials**

*26. Reboul, J; Furukawa, S; Horike, N; Tsotsalas, M; Hirai, K; Uehara, H; Kondo, M; Louvain, N; Sakata, O; Kitagawa, S; Mesoscopic architectures of porous coordination polymers fabricated by pseudomorphic replication; *Nat. Mater.* 11, 717-723 (2012) [IF 35.8]

This paper describes a method for the formation of mesoscopic architectures made of PCPs with designed morphology in both two and three dimensions. Inspired by geological processes, this method relies on the replacement of a sacrificial metal oxide priory shaped via a sol-gel procedure by an analogous PCP architecture. In particular, the replication of macroporous alumina aerogels resulted in a PCP architecture with hierarchical porosity in which the hydrophobic micropores of the PCP and the mesopores/macropores inherited from the parent aerogels synergistically enhanced the material's selectivity and mass transfer for water/ethanol separation.

27. Sakata, Y; Furukawa, S; Kondo, M; Hirai, K; Horike, N; Takashima, Y; Uehara, H; Louvain, N; Meilikhov, M; Tsuruoka, T; Isoda, S; Kosaka, W; Sakata, O; Kitagawa, S; Shape-Memory

Nanopores Induced in Coordination Frameworks by Crystal Downsizing; *Science* 339, 193-196 (2013) [IF 31.0]

Flexible porous coordination polymers change their structure in response to molecular incorporation but recover their original configuration after the removal of guest. We demonstrated that crystal downsizing of twofold interpenetrated frameworks regulates the structural flexibility and induces a framework shape-memory effect. In addition to the two structures that contribute to the sorption process (that is, a closed phase and a guest-included open phase), we isolated an unusual, metastable open dried phase when downsizing the crystals to the mesoscale, and the closed phase was recovered by thermal treatment. The successful isolation of two interconvertible empty phases, the closed phase and the open dried phase, provided switchable sorption properties with or without gate-opening behavior.

28. Hirai. K; Furukawa. S; Kondo, M; Uehara, H; Sakata, O; Kitagawa. S; Sequential functionalization of porous coordination polymer crystals; *Angew. Chem. Int. Ed*. 50, 8057-8061 (2011) [IF 13.7]

Chemists fabricate materials by integrating two or more distinct chemical functionalities into a single platform, leading to a multifunctional property that conventional single-phase material can never achieved. We introduce the concept of compartmentalization utilized in living cells into porous coordination polymers (PCPs) and synthesized the materials that simultaneously implement two key properties of compartmentalization: selection and condensation. We developed the synthetic strategy to grow a shell PCP on the surface of a core PCP to fabricate a core-shell PCP crystal, in which the shell totally covers the core. Using the shell with narrow pores and the core with large pores, we realized an integrated property of selectivity and storage; the shell selectively extracted cetane molecules from its branched isomer (isocetane) and the core worked as a container to concentrate extracted cetane.

***II-10. Self-Accelerating Gas Trapping in a Soft Nanoporous Crystal**

*29. Sato, H; Kosaka, W; Matsuda, R; Hori, A; Hijikata, Y; Belosludov, RV; Sakaki, S; Takata, M; Kitagawa, S; Self-Accelerating CO Sorption in a Soft Nanoporous Crystal; *Science* 10, 167-170 (2014) [IF 31.0]

Carbon monoxide (CO) is a central resource for industry, and the discovery of a porous compound with high selectivity toward CO is scientifically and technologically important. The Kitagawa group developed a new soft nanoporous crystalline material that selectively adsorbs CO with adaptable pores, along with the first crystallographic evidence that CO molecules can coordinate with Cu2+ ions. The unprecedented high selectivity was achieved by the synergetic effect of the local interaction between CO and accessible metal sites and a global transformation of the framework. This transformable crystalline material enabled the separation of CO from a mixture with nitrogen, a gas that is the most competitive to CO. The dynamic and efficient molecular trapping and releasing system is reminiscent of sophisticated biological systems such as heme proteins.

30. Sato, H; Matsuda, R; Sugimoto, K; Takata, M; Kitagawa, S; Photoactivation of a nanoporous crystal for on-demand guest trapping and conversion; *Nat. Mater.* 9, 661-666 (2010) [IF 35.8]

The discovery of a new porous compound with unique properties is scientifically and technologically important. However, the functional species used in this context are limited to those that are sufficiently inert to not spoil the porous structures. In this work, the Kitagawa group showed a new strategy to achieve a crystalline porous material with the pore surface regularly decorated with highly reactive 'bare' nitrenes that are photonically generated from stable 'dormant' precursors at will. The bare triplet nitrenes were accessible to and reacted with adsorbed oxygen or carbon monoxide molecules, which showed not only activation of the pore

surface, but also a high probability of chemical trapping and conversion of guest molecules by light stimulation on demand.

***III-1. Establishment of an interdisciplinary approach for understanding principles and mechanisms governing neuronal shapes within cellular communities**

31. Yamada, M; Yoshida, Y; Mori, D; Takitoh, T; Kengaku, M; Umeshima, H; Takao, K; Miyakawa, T; Sato, M; Sorimachi, H; Wynshaw-Boris, A; Hirotsune, S; Inhibition of calpain increases LIS1 expression and partially rescues in vivo phenotypes in a mouse model of lissencephaly; *Nat. Med.* 15, 1202-U132 (2009) [IF 22.9]

LIS1 is a causal gene for a genetic brain malformation type I lissencephaly. Kengaku group and coworkers proposed a new therapeutic approach for this disease using a calpain inhibitor that inhibited LIS1 proteolysis and rescued abnormal brain formation in Lis1 heterozigous mutant mice.

32. Fujishima, K; Horie, R; Mochizuki, A; Kengaku, M; Principles of branch dynamics governing shape characteristics of cerebellar Purkinje cell dendrites; *Development* 139, 3442-3455 (2012) [IF 6.2]

Branch patterns of neuronal dendrites greatly vary depending on their function in the neural circuit. In this paper, we analyzed dynamics of dendritic arborization in developing neurons by live-imaging and quantitative morphometry. Using a combination of molecular biology and mathematical modeling, Kengaku group identified an important contribution of contact-mediated branch retraction in the formation of non-overlapping dendrites.

*33. Shimono, K; Fujishima, K; Nomura, T; Ohashi, M; Usui, T; Kengaku, M; Toyoda, A; Uemura, T; An evolutionarily conserved protein CHORD regulates scaling of dendritic arbors with body size; *Sci Rep* 4, 4415 (2014) [IF 2.9]

Most organs scale proportionally with body size through regulation of individual cell size and/or cell number. Insects grown under a mild starvation condition scale down the neuronal size in proportion to the decreased body size. These neurons preserve the branching complexity of the arbor, but scaled down the entire arbor, making a "miniature". Kengaku group identified a gene regulating the neuronal size regardless of the body size. The results indicate that dendritic growth and branching are controlled by partly separate mechanisms.

***III-2. Identification of a cis-acting element that localizes mRNA to synaptic compartments in neurons**

*34. Meer, EJ; Wang, DO; Kim, S; Barr, I; Guo, F; Martin, KC; Identification of a cis-acting element that localizes mRNA to synapses; *Proc. Natl. Acad. Sci. U. S. A.* 109, 4639-4644 (2012) [IF 9.7]

mRNA localization and regulated translation can spatially restrict gene expression to each of the thousands of synaptic compartments formed by a single neuron. While cis-acting RNA elements have been shown to direct localization of mRNAs from the soma into neuronal processes, less is known about signals that target transcripts specifically to synapses. We have identified a 66-nucleotide element in the 5'UTR of sensorin that is necessary and sufficient for synaptic mRNA localization. Mutational and chemical probing analyses reveal a role for secondary structure in this process.

***III-3. Chemical tools for directed differentiation of pluripotent stem cells**

*35. Minami, I; Yamada, K; Otsuji, TG; Yamamoto, T; Shen, Y; Otsuka, S; Kadota, S; Morone, N; Barve, M; Asai, Y; Tenkova-Heuser, T; Heuser, JE; Uesugi, M; Aiba, K; Nakatsuji, N; A small molecule that promotes cardiac differentiation of human pluripotent stem cells under defined, cytokine- and xeno-free conditions; *Cell Reports* 2, 1448-1460 (2014) [IF n/a]

A multidisciplinary collaboration among Nakatsuji, Uesugi, and Heuser groups discovered, through chemical library screening and organic synthesis, a small molecule that boosts cardiomyogenesis. The discovery of the molecule named KY02111 led to a novel, defined method to induce differentiation of functional ventricular and pace maker cardiomyocytes at high efficiency from human pluripotent stem cells including ES and iPS cell lines. This cytokine- and xenon-free method is currently considered as the most suited technology for production of human cardiomyocytes for clinical application.

*36. Minami, I; Yamada, K; Otsuji, TG; Yamamoto, T; Shen, Y; Otsuka, S; Kadota, S; Morone, N; Barve, M; Asai, Y; Tenkova-Heuser, T; Heuser, JE; Uesugi, M; Aiba, K; Nakatsuji, N; A Small Molecule that Promotes Cardiac Differentiation of Human Pluripotent Stem Cells under Defined, Cytokine- and Xeno-free Conditions; *Cell Reports* 2, 1448-1460 (2012) [IF n/a]

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37. Sakano, D; Shiraki, N; Kikawa, K; Yamazoe, T; Kataoka, M; Umeda, K; Araki, K; Mao, D; Matsumoto, S; Nakagata, N; Andersson, O; Stainier, D; Endo, F; Kume, K; Uesugi, M; Kume, S; VMAT2 identified as a regulator of late-stage beta-cell differentiation; *Nat. Chem. Biol.* 10, 141-148 (2014) [IF 13.0]

Cell replacement therapy for diabetes mellitus requires cost-effective generation of high-quality, insulin-producing, pancreatic β cells from pluripotent stem cells. Screening of a chemical library identified reserpine and tetrabenazine (TBZ), both vesicular monoamine transporter 2 (VMAT2) inhibitors, as promoters of late-stage differentiation of Pdx1-positive pancreatic progenitor cells into Neurog3 (referred to henceforth as Ngn3)-positive endocrine precursors. VMAT2-controlled monoamines, such as dopamine, histamine and serotonin, negatively regulated β-cell differentiation. When ES cell-derived β cells were transplanted into AKITA diabetic mice, the cells reversed hyperglycemia. This work provides a basis for the understanding of β-cell differentiation and its application to a cost-effective production of functional β cells for cell therapy.

III-4. Novel methods for adhesion and expansion of cells

*38. Miyazaki, T; Futaki, S; Suemori, H; Taniguchi, Y; Yamada, M; Kawasaki, M; Hayashi, M; Kumagai, H; Nakatsuji, N; Sekiguchi, K; Kawase, E; Laminin E8 fragments support efficient adhesion and expansion of dissociated human pluripotent stem cells; *Nat. Commun.* 3, 1236 (2012) [IF 10.0]

Culture of human pluripotent stem cells originally required mouse feeder cells as a cell-adhesion substrate. Defined and xeno-free substrate is essential for clinical application of human pluripotent stem cells. Cell adhesion molecule laminin is one of such currently used substrate. However, it is a very large molecule that can be denatured easily, making disadvantages in quality control, production cost and handling. Nakatsuji group and others found that the laminin

fragment E8 can support human ES/iPS cell culure much better than the whole laminin molecule. This technology enabled single cell passaging for more effective cell expansion. This work may contribute to various applications of human ES/iPS cells.

39. Yamazoe, S; Shimogawa, H; Sato, S; Esko, JD; Uesugi, M; A Dumbbell-Shaped Small Molecule that Promotes Cell Adhesion and Growth; *Chem. Biol.* 16, 773-782 (2009) [IF 6.2]

During an image-based phenotype screening of a chemical library, Uesugi group noted a small molecule that boosts the adhesion and growth of human cells. Chemical and cell biological experiments suggest that the diaryldispirotripiperazine derivative (adhesamine) targets selective cell-surface glycosaminoglycans, especially heparan sulfate, for increasing cell adhesion and growth. Adhesamine induces apparently normal cell adhesion accompanied by organized actin structures and activation of focal adhesion kinase and ERK1/2 mitogen-activated protein kinases. Adhesamine may be useful as a cell-attaching reagent for cell engineering and basic cell biology.

*40. Takemoto, N; Suehara, T; Frisco, HL; Sato, S; Sezaki, T; Kusamori, K; Kawazoe, Y; Park, SM; Yamazoe, S; Mizuhata, Y; Inoue, R; Miller, GJ; Hansen, SU; Jayson, GC; Gardiner, JM; Kanaya, T; Tokitoh, N; Ueda, K; Takakura, Y; Kioka, N; Nishikawa, M; Uesugi, M; Small-Molecule-Induced Clustering of Heparan Sulfate Promotes Cell Adhesion; *J. Am. Chem. Soc.* 135, 11032-11-39 (2013) [IF 9.7]

Adhesamine is an organic small molecule that promotes adhesion and growth of cultured human cells by binding selectively to heparan sulfate on the cell surface. Mechanistic analysis showed that multiple adhesamine molecules cooperatively bind to heparan sulfate and induce its assembly, promoting clustering of heparan sulfate-bound syndecan-4 on the cell surface. Animal studies showed that adhesamine improved the viability and attachment of transplanted cells in mice. Further studies could lead to the design of assembly-inducing molecules for use in cell biology and cell therapy.

*** [III-5] Generation of offspring from oocytes derived from in vitro primordial germ cell-like cells in mice**

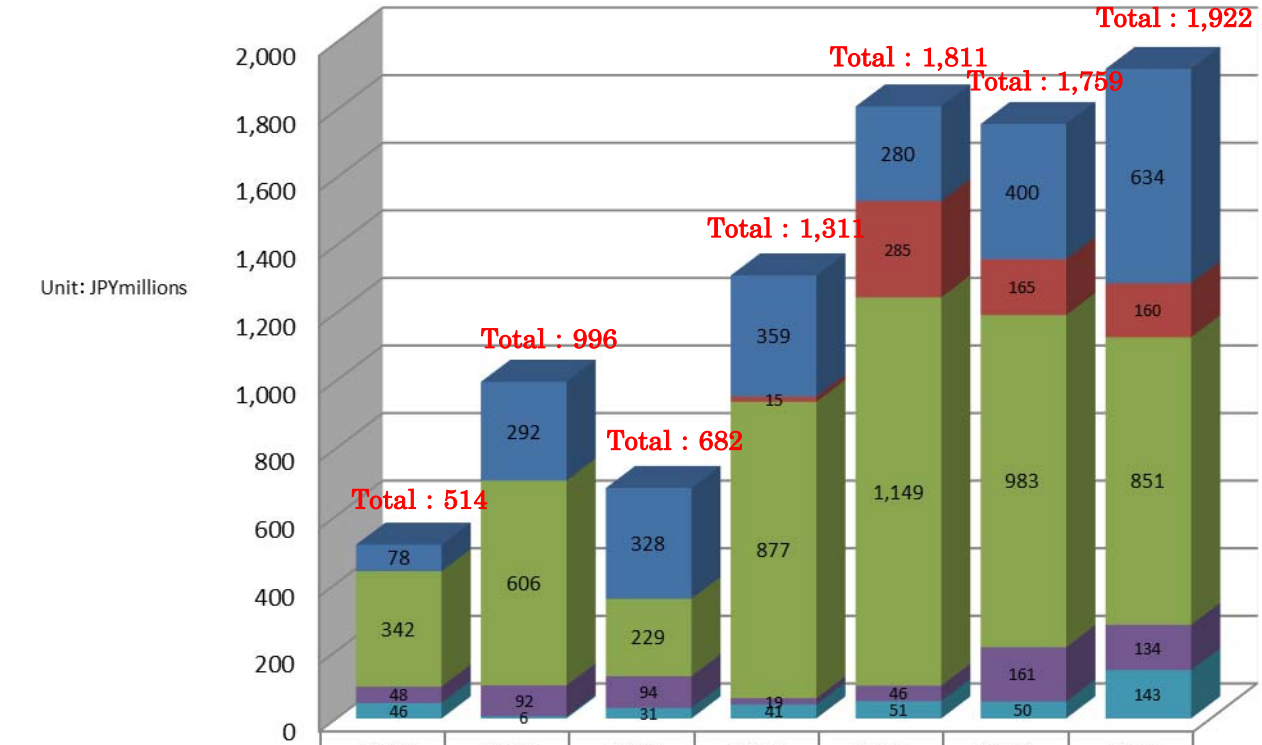
*6.

*7.

2. Annual transition in non-WPI project funding (grants)

*Make a graph of the annual transition in non-WPI project funding (grants).
*Describe external funding warranting special mention.

Figures of external funds acquired in FY2007-2013



	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013
Total	514	996	682	1,311	1,811	1,759	1,922
Grats-in-Aid for Scientific Research	78	292	328	359	280	400	634
Funding Program for Next Generation World-Leading Researchers (NEXT)				15	285	165	160
Sponsored Research Funding (including NEDO)	342	606	229	877	1,149	983	851
Collaborative Research funding	48	92	94	19	46	161	134
Donations	46	6	31	41	51	50	143

[External funding warranting special mention]

1
[Prof Nakatsuji, 2007/10-2010/3]
Ministry of Economy, Trade and Industry's New Energy and Industrial Technology Development Organization (NEDO) programs for Gene Functions R&D (JPY 224 million)

2
[Prof Kitagawa, 2010/3-2013/2]
Ministry of Economy, Trade and Industry's New Energy and Industrial Technology Development Organization (NEDO) programs for Green Sustainable Chemical Process (JPY 617 million)

3
[Prof Takano, 2010/3-2011/3]
Ministry of Economy, Trade and Industry's New Energy and Industrial Technology Development Organization (NEDO) programs for Rare Metal R&D (JPY 65 million)

4
[Prof Ueda, 2010/8-2015/3]
National Agriculture and Food Research Organization (NARO), Bio-oriented Technology Research Advancement Institution's (BRAIN) funding program, Fundamental research for innovation creation (JPY 59 million, not yet fixed due to single year contract)

5
[Prof Nakatsuji, 2011/3-2014/3]
Ministry of Economy, Trade and Industry's New Energy and Industrial Technology Development Organization (NEDO) programs for Industry Application for Human Stem Cell (JPY 956 million)

6
[Prof Koichiro Tanaka, 2012/4-2015/3]
Japan Science and Technology Agency (JST) program of Strategic Basic Research Programs (CREST) (JPY 130 million)
7
[Prof Kitagawa, 2012/10-2016/3]
Japan Science and Technology Agency (JST) program for Advanced Catalytic Transformation program for Carbon utilization (ACT-C) (JPY 147 million, not yet fixed due to single year contract)

8
[Prof Kitagawa, 2013/4-2014/3]
Japan Science and Technology Agency (JST) program for Exploratory Research for Advanced Technology (ERATO) (JPY 65 million)

9
[Prof Kitagawa, 2013/12-2018/3]
Japan Science and Technology Agency (JST) ACCEL program for Molecular Control (JPY 450 million, not yet fixed due to single year contract)

10
[Prof Koji Tanaka, 2012/11-2014/3]
Minister of Economy, Trade and Industry (METI) program for Solar Hydrogen R&D (JPY 174 million)

11
[Prof Takano, 2012/10-2014/3]
Minister of Economy, Trade and Industry (METI) program for Nano-particles R&D (JPY 51 million)

12
[Prof Uesugi, 2011/2-2014/3]
Cabinet Office's Funding Program for Next Generation World-Leading Researchers (NEXT) program for Control and Analysis of Cells by Synthetic Small Molecules (JPY 163 million)

13
[Prof Ueno, 2011/2-2012/3]
Cabinet Office's Funding Program for Next Generation World-Leading Researchers (NEXT) program for Cell Function Control (JPY 82 million)

14
[Prof Kengaku, 2011/2-2014/3]
Cabinet Office's Funding Program for Next Generation World-Leading Researchers (NEXT) program for Mechanisms Underlying the Critical Period Plasticity of Dendrite Arborization and Neural Circuit Formation (JPY 120 million)

15

[Prof Harada, 2011/2-2014/3]
Cabinet Office's Funding Program for Next Generation World-Leading Researchers (NEXT) program for Development of a Novel Single-Molecule Imaging Technique using Fluorescent Diamond Nanoparticles and its Application to Biomolecule Observation (JPY 150 million)

16
[Assoc Profs Sengoku, 2011/2-2014/3]
Cabinet Office's Funding Program for Next Generation World-Leading Researchers (NEXT) program for Integrative Innovation Management Research, Human Resources Development, and Support for Commercialization in the Stem Cell Science and Technology Sphere (JPY 109 million)

17
[Prof Takano, 2008/4-2010/3]
Grants-in-Aid for Scientific Research (S) program for Search of New Material Development and the Chemical / Physical Function (JPY 28 million)

18
[Prof Ueda, 2008/4-2013/3]
Grants-in-Aid for Scientific Research (S) program for Search of Lipid Transportation (JPY 161 million)

19
[Prof Imahori, 2013/4-2018/3]
Grants-in-Aid for Scientific Research (S) program for Utilization of Photoinduced Charge-Separated (JPY 217 million)

20
[Prof Ueda, 2013/4-2018/3]
Grants-in-Aid for Scientific Research (S) program for Elucidation of the ABC Protein (JPY 207 million)

21
[Prof Kitagawa, 2013/4-2018/3]
Grant-in-Aid for Specially Promoted Research program for Chemistry of Hierarchical Coordination Space (JPY 573 million)

3. Major Awards, Invited Lectures, Plenary Addresses (etc.) (within 2 pages)

3-1. Major Awards

* List main internationally-acclaimed awards received announced in order from the most recent.
* For each, write the recipient's name, name of award, and year issued. In case of multiple recipients, underline those affiliated with the center.

<PIs>

1. Motomu Tanaka, **Philipp Franz von Siebold Award** (2014)
2. Mitinori Saitou, **Japan Academy Medal** (2014) and four others
3. Susumu Kitagawa, **RSC de Gennes Prize** (2013)
4. Norio Nakatsuji, **Fellow of Royal Society of Chemistry** (2013) and one other
5. Mitsuru Hashida, **Life-time Achievement Award (Journal of Drug Targeting)** (2012) and three others
6. Shinya Yamanaka, **Nobel Prize in Physiology or Medicine** (2012) and 39 others
7. John Heuser, **National Academy of Sciences Full Member** (2011) and two others
8. Motonari Uesugi, **German Innovation Award "Gottfried Wagener Prize 2010"** (2011)
9. Akihiro Kusumi, **Science and Technology Film & Video Festival Best Research and Development Video Award** (2011)
10. Susumu Kitagawa, **2010 Thomson Reuters Citation Laureates (2010)** and nine others
11. Kazumitsu Ueda, **Japan Bioscience, Biotechnology and Agrochemistry Society Award** (2010)
12. Hiroshi Imahori, **The 25th Osaka Science Prize (2007)** and one other

<Young scientists>

13. Shuhei Furukawa, **The Chemical Society of Japan Award for young Chemist** (2014)
14. Hiroshi Sato, **PCCP Prize** (2014)
15. Yasuhiro Yamada, **CiRA Award** (2014)
16. Nobuhiro Yanai, **Quadrant Award First Prize** (2013)
17. Hideki Hirori, **The 7th Young Scientist Award of the Physical Society of Japan** (2012)
18. Hiromune Ando, **Japan Society for Bioscience, Biotechnology, and Agrochemistry Award** (2012)
19. Ganesh N. Pandian, **AAAS Days of Molecular Medicine Young Investigator Award** (2011)
20. Yuta Takano, **Best Lecture Award for the Fourth Competition Kanto Division of the Chemical Society of Japan** (2011)
21. Koh Nagara, **ABC2010 Young Investigator Award** (2010)
22. Kazutoshi Takahashi, **Yukawa-Tomonaga Memorial Prize** (2009)
23. Takafumi Ueno, **Young Scientists' Prize for Science and Technology by the Japanese Minister of Education, Culture, Sports, Science and Technology** (2008)

3-2. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

* List up to 20 main presentations in order from most recent.
* For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

<20 main presentations delivered by iCeMS researchers out of 856 in total >

1. Kenichi Suzuki, the Very Fast Steps for Raft Formation and Function, Revealed by Single-MoleculeImaging, **Gordon Research Conference** (January 12, 2014)
2. Norio Nakatsuji, Stem Cell Open Innovation in Japan: Industry-Academia Collaboration on Stem CellLarge-Scale Production and Quality Control, **World Stem Cell Summit 2013** (December 4-6, 2013)
3. Easan Sivaniah, Advanced Polymer Membranes for Gas and Liquid Separations, **Swiss-KyotoSymposium** (November 21-22, 2013)
4. Ryoichiro Kageyama, Dynamic Control of Neural Determination Genes in Multipotency and Fate Choice,**Cold Spring Harbor Asia/ International Society for Stem Cell Research Joint Meeting on Stem Cells in Science and Medicine** (October 14-17, 2013)
5. Yoshie Harada, Development of a New Single-Molecule Imaging Technique Using Fluorescent DiamondNanoparticles, **New Advances in Optical Imaging of Live Cells and Organisms** (August 20-23, 2013)
6. Mitinori Saitou, Mechanism and Reconstitution in Vitro of Germ Cell Specification in Mice, **ISSCR 11thAnnual Meeting** (June 12-15, 2013)
7. Susumu Kitagawa, Welcome to a World of Small Spaces, **Symposium Celebrating 125 Years ofAngewandte Chemie** (March 12, 2013)
8. Motomu Tanaka, Spatio-Temporal Evolution in Diseases and Development, **Self-Organization andEmergent Dynamics in Active Soft Matter** (February 18-20, 2013)
9. Shinya Yamanaka, Induction of Pluripotency by Defined Factors, **Novel Lecture in Physiology orMedicine** (December 7, 2012)
10. Mineko Kengaku, Principles and Mechanisms Governing Dendrite Growth Dynamics in the CerebellarPurkinje Cell, **U.S.-Japan Brain Research Cooperative Program-Growth Cones and Axon Regeneration: Entering the Age of Informatics**, (October 10-12, 2012)
11. Koichiro Tanaka, Nonlinear Carrier Dynamics Induced by Intense Terahertz Wave, **37th InternationalConference on Infrared, Millimeter and Terahertz Waves (IRMMW-THz2012)** (September 23-28, 2012)
12. Kazumitsu Ueda, Mechanism of Cholesterol Efflux by ABCA1, **FASEB Meeting: New Frontiers inTransport ATPases** (June 3-8, 2012)
13. John Heuser, the Central Role of Electron Microscopy in the Birth of Modern Cell Biology, **HewsonSwift Memorial Lecture for the Department of Molecular Genetics and Cell Biology** (May 7, 2012)
14. Kazuto Kato, Conceptual and Practical Considerations for Material and Data Sharing in Stem CellResearch - Lessons from Human Genome Research, **Qatar International Conference on Stem Cell Science and Policy** (February 27-March 1, 2012)
15. Motonari Uesugi, Small Molecule Tools for Cell Therapy, **the 8th AFMC International MedicalChemistry Symposium (AIMECS11)** (November 29-December 2, 2011)
16. Yong Chen, Biomimetic Engineering of in Vitro Cellular Microenvironments, **10th InternationalConference on Nanoimprint and Nanoprint Technology** (October 19-21, 2011)
17. Hiroshi Sugiyama, Chemical Biology that Controls DNA Structure and Function, **CIPSM Fest ofBiological Chemistry** (September 15-16, 2011)
18. Mitsuru Hashida, New Technologies Impacting Drug Discovery, **World Congress of Pharmacy andPharmaceutical Sciences 2011** (September 3-8, 2011)
19. Akihiro Kusumi, Organizing Principle of the Plasma Membrane: Three-Tiered Meso-Scale DomainArchitecture Revealed by Single-Molecule Tracking, **The 8th European Biophysics Congress** (August 23-27, 2011)
20. Hiroshi Imahori, Photoinduced Energy Transfer and Charge Separation in Donor-Acceptor LinkedSystems, **8th International Conference on Excitonic Processes in Condensed Matter** (EXCON'08) (June 22-27, 2008)

4. List of Achievements of Center's outreach activities

* Using the table below, show the achievements of the Center's outreach activities from FY2011 through FY2013 (number of activities, times held).

Activities	FY2011 (number of activities, times held)	FY2012 (number of activities, times held)	FY2013 (number of activities, times held)
PR brochure, pamphlet	5	3	4 (English and Japanese)
Lectures, seminars for general public	30	27	16
Teaching, experiments, training for elementary and secondary school students	22	26	20
Science cafe	6	8	6
Open houses	0	0	0
Participating, exhibiting in events	3	5	11
Press releases	14	13	12
Young Scientists Colloquia and Happy Hour	0	5	5
iCeMS Science 101	0	0	4

Future Plans:
More public-oriented plans are as follows:
1. Raising middle and high school students' scientific literacy
2. Having effective dialogues with communities outside of the institute
3. Engaging scientists in outreach activities

Date	Title	Activity	Target Audience	Objectives
Oct 7 2014	Izumo High School visit	Stem cell board game demonstration, lecture	Izumo High school students of Shimane Pref.	1. Raising students' scientific literacy
Sep 28 2014	Kyoto University Academic Day 2014	Lecture for general public	General public	2. Having effective dialogues 3. Engaging scientists in outreach activities
Nov 29 2014	iCeMS/CiRA Classroom	Hands-on laboratory exercises on stem cells	High school students across Japan	1. Raising students' scientific literacy
Dec 13 2014	WPI Joint Symposium	Stem cell board Game demonstration	High school students in Tokyo area	1. Raising students' scientific literacy
Dec 2015	Science-Art Exhibition	Exhibit artwork created with scientific images provided by iCeMS' researchers	General public	2. Having effective dialogues
Jan 2015	iCeMS Café #17	Science café	General public	2. Having effective dialogues 3. Engaging scientists in outreach activities
March 2015	iCeMS Café #18	Science café	General public	2. Having effective dialogues 3. Engaging scientists in outreach activities

5. List of Media Coverage of Projects carried out between FY 2011 – 2013

(within 2 pages)

** Select main items of press releases, media coverage, and reports in FY 2013 (especially overseas)*

1) Japan

No.	Date	Type media (e.g., newspaper, magazine, television)	Description
1	Apr 18, 2011	TV Tokyo: World Business Satellite [TV]	(Nakatsuji, Yamanaka) The business of iPS cells: Changing the path to new drug development
2	Oct 4, 2011	The Sankei Shimbun [newspaper]	(Hashida) Prof Mitsuru Hashida, Kyoto U Graduate School of Pharmaceutical Sciences, and his drug delivery research
3	Dec 1, 2011	The Nikkan Kogyo Shimbun [newspaper]	(Takano) Kyoto U develops a cheap method to make ferromagnetic iron oxide
4	Nov 28, 2011	NHK [TV]	(Nakatsuji) Researchers identify genetic changes that take place during the culture of ES cells
5	Jan 16, 2012	The Nikkei [newspaper]	(Nakatsuji) Kyoto Univ launches a science journal in collaboration with Royal Society of Chemistry
6	Apr 20, 2012	The Nikkei [newspaper]	(Nakatsuji, Yamanaka) Advancing Alzheimer's drug discovery: Reprocell, Kyoto U use human iPS cells to model the disease
7	Oct 30, 2012	The Nikkei [newspaper]	(Kitagawa, Matsui) Kyoto U makes tiny machine that moves through water with emission force
8	Jan 30, 2013	The Asahi Shimbun [newspaper]	(Yamanaka, Mizumachi) Play iPS cell game board and win Nobel prize
9	Mar 12, 2013	ABC [TV]	(Ueda) First in world to reveal mechanism of high-density lipoprotein production
10	Oct. 28, 2013	The Nikkei Sangyo Shimbun [newspaper]	(Kitagawa) Nitric oxide release triggered by UV rays for potential application to production of iPS cells
11	Nov. 1, 2013	The Nikkan Kogyo Shimbun [newspaper]	Kyoto U discovers gene rhythm determines brain cell fate
12	Jan. 25, 2014	The Nikkei [newspaper]	(Sugiyama) Kyoto U invents small molecule that activates dormant genes
13	Mar. 11, 2014	The Nikkei [newspaper]	(Uesugi, Yamanaka) Chemical compounds that selectively illuminate iPS cells

2) Overseas

No.	Date	Type media (e.g., newspaper, magazine, television)	Description
1	Aug 27, 2011	International Innovation [magazine]	(Nakatsuji) Development of core technologies for industrial applications of human stem cells
2	Sep 4, 2011	Science Daily [web news]	(Kitagawa) Fast, cheap, and accurate: Detecting CO2 with a fluorescent twist
3	Sep 4, 2011	Phys. Org. [web news]	(Kitagawa) Fast, cheap, and accurate: Detecting CO2 with a fluorescent twist
4	Nov 28, 2011	The Australian [web news]	(Nakatsuji) Stem Cells vulnerable to cancer
5	Nov 28, 2011	The Scientist [web news]	(Nakatsuji) Human ES Cells Evolve in Culture
6	Nov 30, 2011	International Business Times [web news]	(Nakatsuji) New Study Finds DNA That Can Lead to Safer Stem Cell Therapy
7	Dec 20, 2011	Phys. Org. [web news]	(Hirori and Koichiro Tanaka) Terahertz pulse increases electron density 1,000-fold
8	Dec 20, 2011	THz Science and Technology Network [web news]	(Hirori and Koichiro Tanaka) Terahertz pulse increases electron density 1,000-fold
9	Jan 23, 2012	Medical News Today [web news]	(Sugiyama) DNA Motor Programmed To Navigate A Network Of Tracks
10	Jan 24, 2012	KurzweiAI [web news]	(Sugiyama) Motor Made of DNA Runs on Tracks
11	Jan 24, 2012	Bionity.com [web news]	(Sugiyama) Motor Made of DNA Runs on Tracks
12	Jan 24, 2012	Science Daily	(Reboul, Furukawa, and Kitagawa) Faster, cheaper gas and liquid separation using custom designed and built mesoscopic structures
13	Jun 24, 2012	Nanowerk [web news]	(Reboul, Furukawa, and Kitagawa) Faster, cheaper gas and liquid separation using custom designed and built mesoscopic structures
14	Jun 24, 2012	Phys. Org. [web news]	(Reboul, Furukawa, and Kitagawa) Faster, cheaper gas and liquid separation using custom designed and built mesoscopic structures
15	Jun 24, 2013	The Wall Street Journal [web news]	Kyoto University iCeMS to Co-Organize World Stem Cell Summit, San Diego, Ca., Dec.4-6, 2013
16	Aug 4, 2013	33rd Square [web news]	(Saitou) Reproductive Cells on Demand
17	Oct. 25, 2013	33rd Square [web news]	(Kitagawa) Safe and Precise: Light-triggered Delivery System Enables Study of Cells Exposed to NO Gas
18	Oct. 25, 2013	Genetic Engineering & Biotechnology News [web news]	(Sugiyama) Install Epigenetic Switches to Give Silent Genes a Voice

World Premier International Research Center Initiative (WPI)

List of papers of representative of interdisciplinary research activities

** List up to 20 papers that underscoring each interdisciplinary research activity and give brief accounts (within 10 lines).*

** For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. If a paper has many authors, underline those affiliated with the Center.*

** If a paper has many authors (say, more than 10), all of their names do not need to be listed.*

I. Manipulation of Nucleus Information

1. Pandian, GN; Nakano, Y; Sato, S; Morinaga, H; Bando, T; Nagase, H; Sugiyama, H; A synthetic small molecule for rapid induction of multiple pluripotency genes in mouse embryonic fibroblasts; *Sci Rep* 2, 544 (2012)

   As a novel chemical approach to control cell fate via site-specific chromatin modifications, small molecules termed, SAHA-PIPs containing sequence-specific pyrrole-imidazole polyamides (PIPs) and the histone deacetylase inhibitor SAHA, were synthesized. Certain SAHA-PIPs distinctively activate pluripotency genes in mouse fibroblasts by triggering epigenetic marks that are associated with transcriptionally permissive chromatin. Here, we identified that a SAHA-PIP called K capable of triggering unusual transcriptional activation of the PIWI gene that regulates the meiotic process. This first ever report on a germ cell gene switch is a successful representative model that substantiates the scope of iCeMS, which aims to achieve `materials for cell control.` This paper was selected as a `Hot paper` by the editor for the importance of this work in a rapidly evolving field of high current interest. This is an interdisciplinary research of chemistry and cell biology.

2. Pandian, GN.; Taniguchi, J; Junetha, S; Sato, S; Han, L; Saha, A; AnandhaKumar, C; Bando, T; Nagase, H; Vaijayanthi, T; Taylor, R; Sugiyama, H; Distinct DNA-based epigenetic switches trigger transcriptional activation of silent genes in human dermal fibroblasts; *Sci Rep* 4, 3843 (2014)

   Artificial transcriptional activators must encompass both DNA recognition and functional modules to rewire misregulated transcriptional networks. The sugiyama lab has been developing such dual-functional small molecules called SAHA-PIPs as DNA-based epigenetic switches. In this study, we demonstrate through microarray studies and functional analysis about the remarkable ability of thirty-two distinct SAHA-PIPs to trigger the transcriptional activation of exclusive clusters of genes including KSR2, the obesity gene and SEMA6A, the retinal 'ON' circuit factor. Our proof-of-concept study demonstrates the possibility to develop these kind of DNA-based epigenetic switches as `iCeMS developed materials` for controlling the transcription of silent genes associated with cell fate and/or the genes of therapeutic importance. This paper was highlighted in various portals including one in GEN News. This is an interdisciplinary research of chemistry and cell biology.

3. Nakaki, F; Hayashi, K; Ohta, H; Kurimoto, K; Yabuta, Y; Saitou, M; Induction of mouse germ-cell fate by transcription factors in vitro; *Nature* 501, 222-226 (2013)

   This paper reports the identification of transcription factors that are sufficient to induce, upon *in vitro* epiblast-like cells generated from embryonic stem cells, primoridial germ cell-like cells with capacity for spermatogenesis. This is an interdisciplinary research of molecular biology, informatics (biophysics), and reproductive technology.

4. Imayoshi, I; Isomura, A; Harima, Y; Kawaguchi, K; Kori, H; Miyachi, H; Fujiwara, T; Ishidate, F; Kageyama, R; Oscillatory Control of Factors Determining Multipotency and Fate in Mouse Neural Progenitors; *Science* 342, 1203-1208 (2013)

   In this study, time-lapse imaging analysis showed that the expression of multiple fate determination factors oscillates in multipotent neural stem cells, whereas one of them becomes dominant and sustained during cell fate choice. By using an interdisciplinary approach, which can control gene expression with blue light illumination, we successfully showed that oscillatory expression of the proneural factor Ascl1 activates neural stem cell proliferation, whereas sustained expression of Ascl1 induces neuronal fate choice. Thus, a single factor exhibits contradictory functions, promoting stem cell proliferation vs. neuronal differentiation, by changing the oscillatory vs. sustained gene expression. This light technology offers a new way to control cell proliferation and differentiation by changing blue light illumination patterns, showing its applicability to regenerative medicine. This is an interdisciplinary research of Cell Biology and Physics in iCeMS.

II. Manipulation of Membrane Compartments

5. Nagata, KO; Nakada, C; Kasai, RS; Kusumi, A; Ueda, K; ABCA1 dimer-monomer interconversion during HDL generation revealed by single-molecule imaging; *Proc. Natl. Acad. Sci. U. S. A.* 110, 5034-5039 (2013)

   Single molecule analysis using TIRF microscopy in collaboration with the Kusumi group revealed that monomer-dimer interconversion of the ATP binding cassette protein A1 (ABCA1) occurs on the plasma membrane during the generation of high-density lipoprotein (HDL), one of the most critical events for preventing atherosclerosis. ABCA1 temporarily forms a dimer as it accumulates cholesterol in/around the ABCA1 molecule, where two molecules of apoA-I, a lipid acceptor in blood, is recruited and form a pair, presumably during the process of receiving the accumulated cholesterol from ABCA1, and eventually making a nascent HDL. This study will facilitate our understanding of the detailed mechanism of HDL generation and developing a way of preventing atherosclerosis. This is the achievement of the integration of cell biology and physics in iCeMS.

6. Nishimura, H; Ritchie, K; Kasai, RS; Morone, N; Sugimura, H; Tanaka, K; Sase, I; Yoshimura, A; Nakano, Y; Fujiwara, TK; Kusumi, A; Biocompatible fluorescent silicon nanocrystals for single-molecule tracking and fluorescence imaging; *J. Cell Biol.* 202, 967-983 (2013)

   Fluorescence microscopy is used extensively in cell biological and biomedical research, but it is plagued by three major problems with the presently available fluorescent probes: photobleaching, blinking, and large size. In this research, these problems have been essentially resolved by developing biocompatible, red-emitting silicon nanocrystals (SiNCs) with a 4.1-nm hydrodynamic diameter, conjugated to biomolecules precisely at a 1:1 ratio, which neither blinked nor photobleached for at least 5 h. Using the SiNCs, it became possible for the first time to observe the internalization process of receptor molecules at the single-molecule level and to reveal the micron-scale mosaicism in the plasma membrane. This is the achievement of the integration of cell biology and physics in iCeMS.

7. Kasai, RS; Suzuki, KGN; Prossnitz, ER; Koyama-Honda, I; Nakada, C; Fujiwara, TK; Kusumi, A; Full characterization of GPCR monomer-dimer dynamic equilibrium by single molecule imaging; *J. Cell Biol.* 192, 463-480 (2011)

   The G-protein-coupled receptors (GPCRs) represent the largest superfamily in the human genome and more than half of the drug development investments are now spent for drugs that can

modulate the GPCR functions. However, the exact mechanism for its function remains unknown. We found that a GPCR forms transient homodimers, with a lifetime of 90 ms, and succeeded in fully characterizing its monomer-dimer dynamic equilibrium, which is the first time for any membrane molecule. This work is important in GPCR research as well as in the methodology development for determining the dynamic equilibrium in the membrane. This is the achievement of the integration of cell biology and physics in iCeMS.

8. Tanaka, KAK; Suzuki, KGN; Shirai, YM; Shibutani, ST; Miyahara, MSH; Tsuboi, H; Yahara, M; Yoshimura, A; Mayor, S; Fujiwara, TK; Kusumi, A; Membrane molecules mobile even after chemical fixation; *Nat. Methods* 7, 865-866 (2010)

   Chemical crosslinking has been extensively used for immobilizing membrane-associated molecules and cytoskeletal molecules in optical and electron microscopy in virtually all the biomedical fields. We critically reevaluated this method, and reported that under general crosslinking conditions, membrane molecules are hardly immobilized, and described new methods useful for many membrane proteins. This is the achievement of the integration of cell biology and physics in iCeMS.

9. Suzuki, KGN; Kasai, RS; Hirosawa, KM; Nemoto, YL; Ishibashi, M; Miwa, Y; Fujiwara, TK; Kusumi, A; Transient GPI-anchored protein homodimers are units for raft organization and function; *Nat. Chem. Biol.* 8, 774-783 (2012)

   Advanced single-molecule tracking developed in our laboratory revealed that lipid- and protein-based interactions jointly contribute to form the transient homodimer rafts of the glycosylphosphatidylinositol-anchored receptors in the plasma membrane. These homodimer rafts act as the basic units for generating more stable signaling rafts and their functions. Understanding these interactions helps to develop long-evolving and still debated models of raft domains. This is an achievement made possible by the integration of cell biology and physics in iCeMS. This is the achievement of the integration of cell biology and physics in iCeMS.

10. Diring, S; Wang, DO; Kim, C; Kondo, M; Chen, Y; Kitagawa, S; Kamei, K; Furukawa, S; Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform; *Nat. Commun.* 4, 2684 (2013)

    Nitric oxide (NO) is, a crucial signaling molecule with highly site-specific and concentration-dependent activities. The Kitagawa group synthesized spatiotemporally controllable NO releasing platforms based on photoactive porous coordination polymers (PCPs) and demonstrated that the organization of poorly reactive motives into PCP structures affords increased photoreactivity. In collaboration with the Chen and Wang groups, we embedded photoactive PCP crystals in a biocompatible polymer matrix and achieved precise control of NO delivery at a cellular level by two-photon laser activation. The biological relevance of the exogenous NO produced by the PCPs is demonstrated by an intracellular calcium change, mediated by a NO-responsive plasma membrane channel protein. This is truly an interdisciplinary study of state-of-the-art materials chemistry with bioengineering and cell biology.

11. Reboul, J; Furukawa, S; Horike, N; Tsotsalas, M; Hirai, K; Uehara, H; Kondo, M; Louvain, N; Sakata, O; Kitagawa, S; Mesoscopic architectures of porous coordination polymers fabricated by pseudomorphic replication; *Nat. Mater.* 11, 717-723 (2012)

Size and shape control of crystalline PCP is necessary for the application to Cells. This paper describes a method for the formation of mesoscopic architectures made of PCPs with designed morphology in both two and three dimensions. Inspired by pseudomorphic mineral replacement events, this method relies on the replacement of a sacrificial metal oxide priory shaped via a sol-gel procedure by an analogous PCP architecture. In particular, the replication of macroporous alumina aerogels resulted in a PCP architecture with hierarchical porosity that enhanced the material's selectivity and mass transfer for water/ethanol separation. This new synthetic method will allow for the fabrication of hollow structures, which compartmentalize the space similarly to cells and implement the sequential selection-condensation protocols, thus the creation of cell-inspired materials. This resulted from intensive discussions between chemists and cell biologists.

12. Murakami, T; Nakatsuji, H; Inada, M; Matoba, Y; Umeyama, T; Tsujimoto, M; Isoda, S; Hashida, M; Imahori, H; Photodynamic and Photothermal Effects of Semiconducting and Metallic-Enriched Single-Walled Carbon Nanotubes; *J. Am. Chem. Soc.* 134, 17862-17865 (2012)

Photodynamic effect (PDE) and Photothermal effect (PTE) of SWNTs have been evaluated extensively by using semiconducting- and metallic-enriched SWNTs for the first time. Semiconducting-enriched SWNTs caused photo killing of cancer cells through singlet oxygen generation, providing fundamental insights for developing SWNT-based cancer therapies. The iCeMS internal collaboration between material fabrications (the Murakami and Imahori, groups) and drug-delivery research (the Hashida group) realized this new research direction of cell-material integrations. This is the achievement of the integration of chemistry and cell biology.

13. Koshiyama, T; Shirai, M; Hikage, T; Tabe, H; Tanaka, K; Kitagawa, S; Ueno, T; Post-Crystal Engineering of Zinc-Substituted Myoglobin to Construct a Long-Lived Photoinduced Charge-Separation System; *Angew. Chem.-Int. Edit.* 50, 4849-4852 (2011)

An artificial photoinduced electron-transfer system has been constructed by accumulating redox cofactors in a protein crystal. Inspired by natural photosynthesis, the Kitagawa and Ueno groups utilized as host matrices myoglobin crystals with inner voids, into which two distinct ruthenium redox complexes, each for oxidation or reduction process, can be incorporated in an organized fashion. With the K. Tanaka group, the interdisciplinary research team identified that both redox cofactors have low reorganization energies, as observed similarly to native photosynthesis, which leads to the drastic increase of a half-life time of a charge-separated state with a half-life 2800 times longer than that in organic solution. The interdisciplinary research between protein chemistry and photophysics generates a new design concept of an artificial photosynthetic system based on cell-inspired materials. This is the achievement of the integration of chemistry and cell biology.

14. Igarashi, R; Yoshinari, Y; Yokota, H; Sugi, T; Sugihara, F; Ikeda, K; Sumiya, H; Tsuji, S; Mori, I; Tochio, H; Harada, Y; Shirakawa, M; Real-Time Background-Free Selective Imaging of Fluorescent Nanodiamonds in Vivo; *Nano Lett.* 12, 5726-5732 (2012)

By combining single molecule fluorescence measurement and optically detected magnetic resonance, the iCeMS interdisciplinary research team has successfully established a powerful method not only for eliminating extrinsic signals completely in fluorescence measurement for higher organisms, but also for realizing real-time observation of fluorescent nanodiamonds. This is the fruitful result of excellent cooperation between physicists skilled at operating instrumentation and biologists paying close attention to sample preparations.

15. Sakata, Y; Furukawa, S; Kondo, M; Hirai, K; Horike, N; Takashima, Y; Uehara, H; Louvain, N; Meilikhov, M; Tsuruoka, T; Isoda, S; Kosaka, W; Sakata, O; Kitagawa, S; Shape-Memory Nanopores Induced in Coordination Frameworks by Crystal Downsizing; *Science* 339, 193-196 (2013)

A physical form of inorganic materials is known to affect the material property; for instance, metallic gold shows a catalytic property only when being downsized into a few nanometer size. The iCeMS researchers demonstrated, for the first time, that inorganic-organic hybrid materials also provide a novel property simply by downsizing the materials into the mesoscale. The Kitagawa group targeted flexible PCPs that change their structure in response to molecular incorporation and showed that the crystal downsizing regulates the structural flexibility and induces a shape-memory effect in the coordination frameworks only at the mesoscale (a few tens of nanometers). Experimental physicists in iCeMS were heavily involved in supporting this new discovery by providing a phase transition theory and a wide range of characterization techniques. This resulted from intensive discussions between chemists and physicists.

16. Numata, T; Murakami, T; Kawashima, F; Morone, N; Heuser, JE; Takano, Y; Ohkubo, K; Fukuzumi, S; Mori, Y; Imahori, H; Utilization of Photoinduced Charge-Separated State of Donor-Acceptor-Linked Molecules for Regulation of Cell Membrane Potential and Ion Transport; *J. Am. Chem. Soc.* 134, 6092-6095 (2012)

The iCeMS interdisciplinary research team has successfully controlled the membrane potential and ion transport across the cell membrane by synthetic ferrocene–porphyrin–fullerene triad molecules. The Imahori group synthesized molecules with a very long photoinduced charge separated state and the Murakami group delivered this molecules into the plasma membrane of PC12 cells by high density lipo protein (HDL). By collaborating with cell biologists in iCeMS, the research team for the first time achieved the generation of photoinduced ion flux through the cell membrane using the synthetic donor acceptor molecules with photoinduced charge-separated state. This new approach suggested by iCeMS researchers gives an impact on the society of optogenetics, which regulates a variety of cell functions, in particular neuronal functions, by light irradiation. This is the fruitful outcome of excellent cooperation of chemists, physicists, and cell biologists in iCeMS.

III. Manipulation of Cell Communication

17. Hirata, N; Nakagawa, M; Fujibayashi, Y; Yamauchi, K; Murata, A; Minami, I; Tomioka, M; Kondo, T; Kuo T; Endo, H; Inoue, H; Sato, S; Ando, S; Kawazoe, Y; Aiba, K; Nagata, K; Kawase, E; Chang, Y; Suemori, H; Eto, K; Nakauchi, H; Yamanaka, S; Nakatsuji, N; Ueda, K; Uesugi, M; A chemical probe that labels human pluripotent stem cells; *Cell Reports* 6, 1165-1174 (2014)

This institute-initiated project combined expertise from four groups in iCeMS (Uesugi, Ueda, Nakatsuji, and Yamanaka) and two groups in CiRA (Eto and Inoue) to develop a chemical tool useful for stem cell biology. Screening of fluorescent chemical libraries with human induced pluripotent stem cells (iPSCs) identified a fluorescent molecule (Kyoto probe 1 [KP-1]) that selectively labels human pluripotent stem cells. Multidisciplinary mechanistic analyses indicated that the selectivity results primarily from a distinct expression pattern of ABC transporters in human pluripotent stem cells and from the transporter selectivity of KP-1. KP-1 may widely be used as a tool in the field of stem cell biology. This is the achievement of the integration of chemistry and cell biology.

18. Minami, I; Yamada, K; Otsuji, TG; Yamamoto, T; Shen, Y; Otsuka, S; Kadota, S; Morone, N; Barve, M; Asai, Y; Tenkova-Heuser, T; Heuser, JE; Uesugi, M; Aiba, K; Nakatsuji, N; A Small

Molecule that Promotes Cardiac Differentiation of Human Pluripotent Stem Cells under Defined, Cytokine- and Xeno-free Conditions; *Cell Reports* 2, 1448-1460 (2012)

A multidisciplinary collaboration among Nakatsuji, Uesugi, and Heuser groups discovered, through chemical library screening and organic synthesis, a small molecule that boosts cardiomyogenesis. The discovery of the molecule named KY02111 led to a novel, defined method to induce differentiation of functional ventricular and pace maker cardiomyocytes at high efficiency from human pluripotent stem cells including ES and iPS cell lines. This cytokine- and xenon-free method is currently considered as the most suitable technology for production of human cardiomyocytes for clinical application. This is the achievement of the integration of chemistry and cell biology.

19. Takemoto, N; Suehara, T; Frisco, HL; Sato, S; Sezaki, T; Kusamori, K; Kawazoe, Y; Park, SM; Yamazoe, S; Mizuhata, Y; Inoue, R; Miller, GJ; Hansen, SU; Jayson, GC; Gardiner, JM; Kanaya, T; Tokitoh, N; Ueda, K; Takakura, Y; Kioka, N; Nishikawa, M; Uesugi, M; Small-Molecule-Induced Clustering of Heparan Sulfate Promotes Cell Adhesion; *J. Am. Chem. Soc.* 135, 11032-11039 (2013)

Adhesamine is an organic small molecule that the Uesugi group previously discovered to promote adhesion and growth of cultured human cells by binding selectively to heparan sulfate on the cell surface. A multidisciplinary collaboration among Uesugi, Ueda, and others revealed its mesoscopic mechanism of action. Chemical and cell biological analysis showed that multiple adhesamine molecules cooperatively bind to heparan sulfate and induce its assembly, promoting clustering of heparan sulfate-bound syndecan-4 on the cell surface. Animal studies showed that adhesamine improved the viability and attachment of transplanted cells in mice. Further studies could lead to the design of assembly-inducing molecules for use in cell biology and cell therapy. This is the achievement of the integration of chemistry and cell biology.

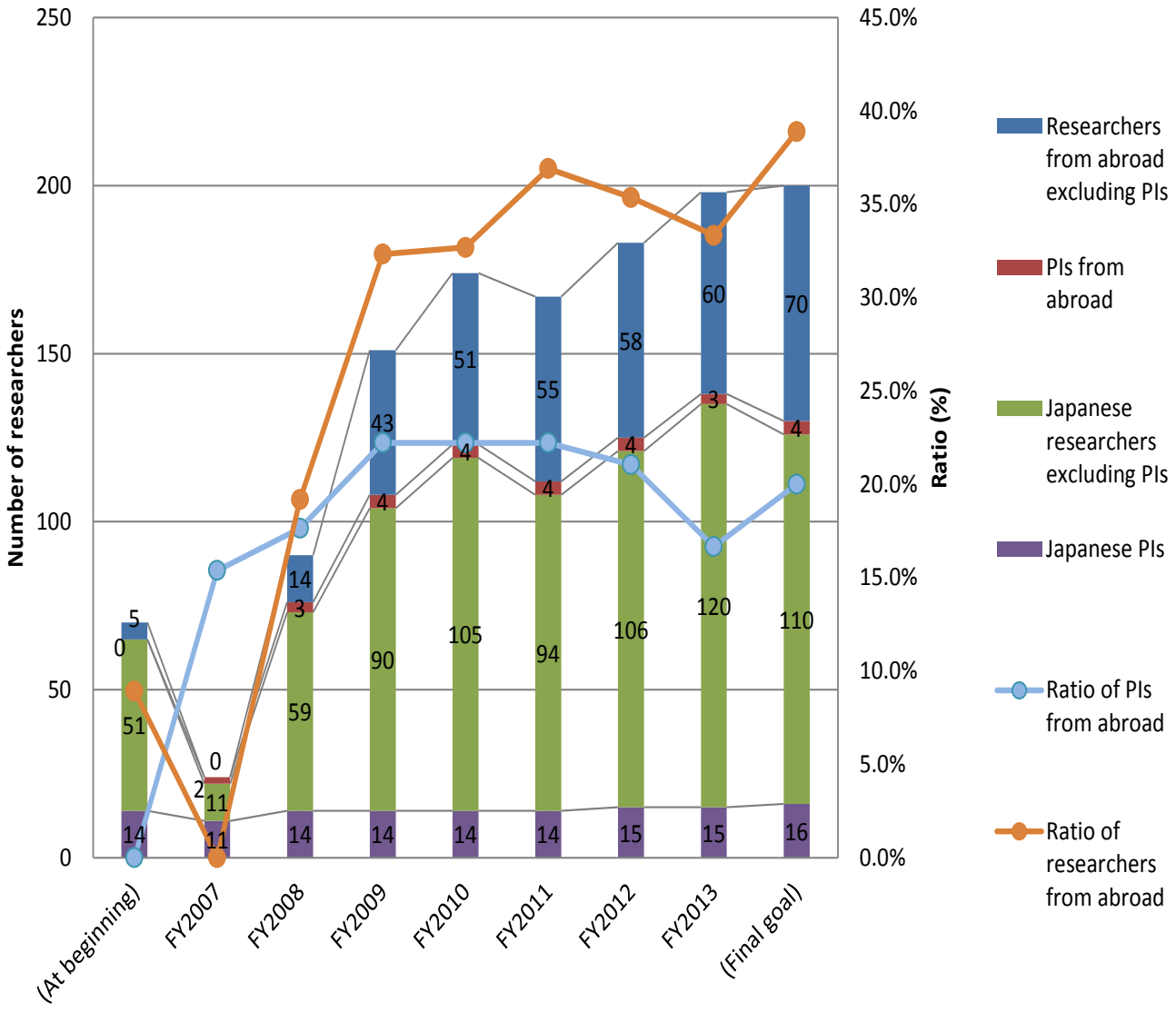
20. Wickham, SFJ; Bath, J; Katsuda, Y; Endo, M; Hidaka, K; Sugiyama, H; Turberfield, AJ; A DNA-based molecular motor that can navigate a network of tracks; *Nat. Nanotechnol.* 7, 169-173 (2012)

DNA is a material that conveys information. Clever use of its properties leads to the design of intelligent materials. The Sugiyama group and others designed a branched motor-track on a DNA origami scaffold and controlled the movement of a DNA motor with programmable instructions. To control motor strand movement, a branched track was constructed on the DNA origami scaffold, and three branching points and four final destinations were created. Block strands introduced at both sides of the branching points controlled the direction of the DNA motor. The DNA passed the two branching points, meaning that the two releasing strands can determine the pathway and destinations in a programmed fashion. The DNA motor was found at the predefined destinations by following the programmed instructions. This system could be further used for programmed drug delivery into cells. This is the achievement of the integration of chemistry and cell biology.

World Premier International Research Center Initiative (WPI)

1. Number of overseas researchers and annual transition

*Make a graph of the transition in the number of overseas researchers since the application.



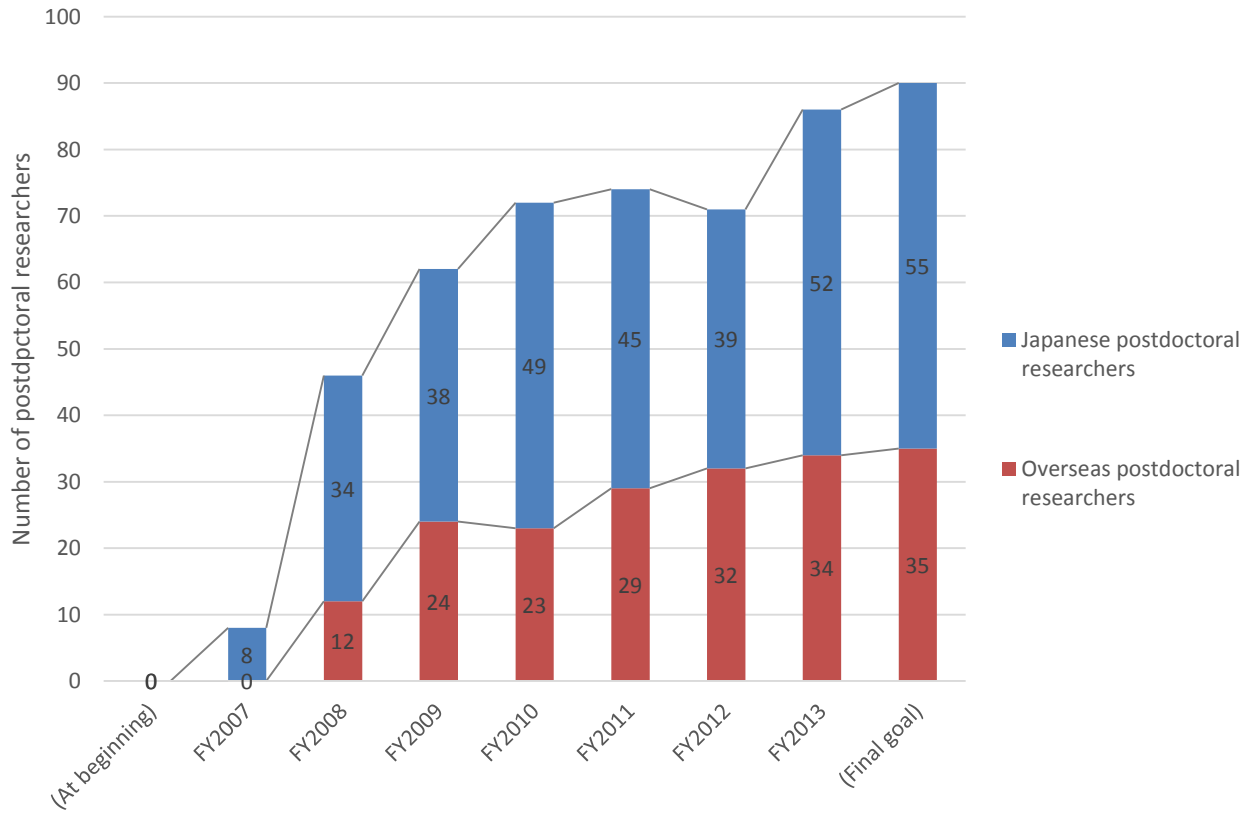
2. Postdoctoral positions through open international solicitations

* In the column of number of applications and number of selection, put the number and percentage of overseas researchers in the < > brackets.

FY	number of applications	number of selection
FY2007	51 < 20, 39.2%>	8 < 0, 0%>
FY2008	62 < 14, 22.6%>	33 < 6, 18.2%>
FY2009	183 < 144, 78.7%>	52 < 13, 25.0%>
FY2010	190 < 180, 94.7%>	35 < 10, 28.6%>
FY2011	402 < 393, 97.8%>	23 < 11, 47.9%>
FY2012	337 < 329, 97.7%>	29 < 10, 34.4%>
FY2013	161 < 159, 98.8%>	31 < 17, 54.8%>

3. Number of overseas postdoctoral researchers and annual transition

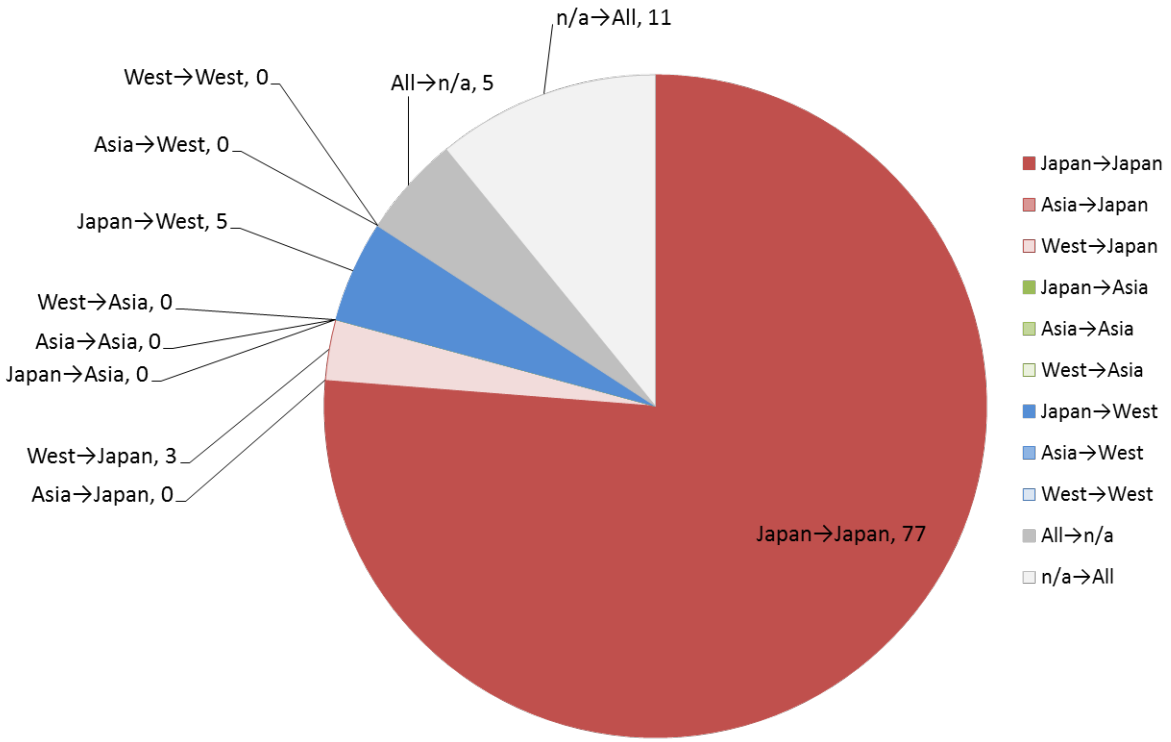
*Make a graph of the transition in the number of overseas postdoctoral researchers since the application.



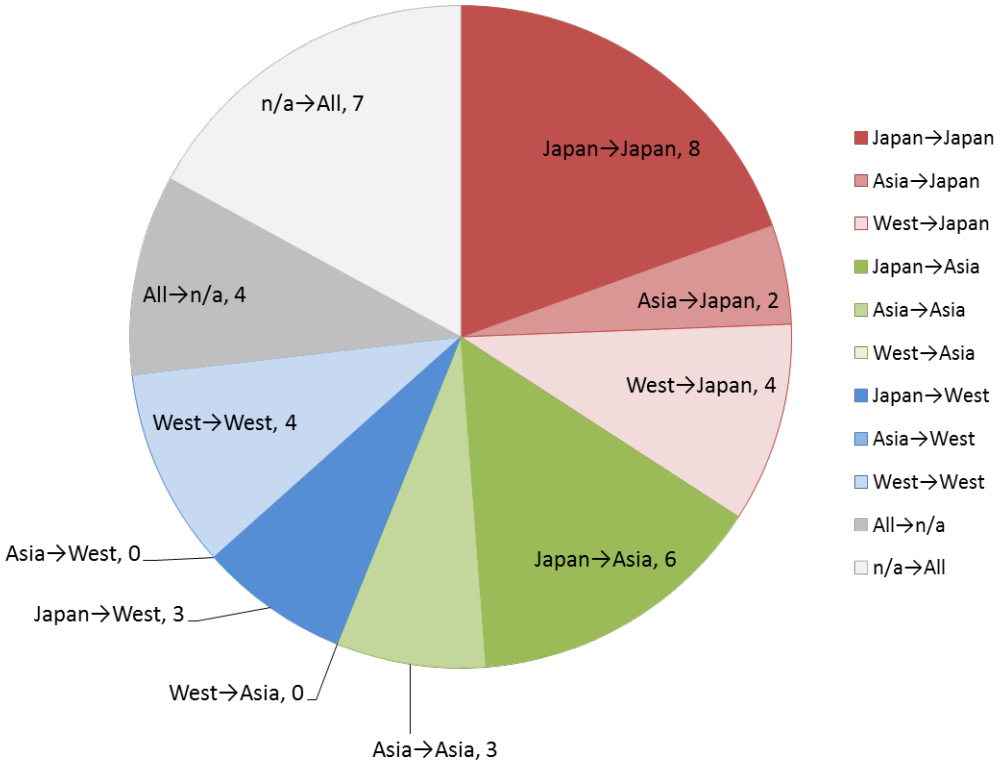
4. Status of postdoc employment at institutions of postdoctoral researchers

- ○○→△△ indicates that a posdoc has come to the WPI Center from an institute in ○○ and moved to one in △△.
- n/a indicates unknown or resignation for personal reason.

Japanese Postdocs



Overseas Postdocs



5. List of the cooperative research agreements outside Japan

1. Counterpart of an Agreement: California NanoSystems Institute, UCLA
   Name of an Agreement:
   MEMORANDUM OF UNDERSTANDING
   THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, ON BEHALF OF ITS LOS ANGELES CAMPUS, USA, AND ON BEHALF OF THE CALIFORNIA NANOSYSTEMS INSTITUTE (CNSI) AND THE INSTITUTE FOR INTEGRATED CELL-MATERIAL SCIENCES (iCeMS), KYOTO UNIVERSITY
   Dates of an Agreement: 15 March, 2010
   Summary of an Agreement:
   Exchange of researchers and administrative staff, research collaboration, joint symposium, exchange of information

2. Counterpart of an Agreement: National Centre for Biological Science, Tata Institute of Fundamental Research (NCBS)
   Name of an Agreement:
   Memorandum of Understanding National Centre for Biological Sciences Tata Institute of Fundamental Research, Bangalore and the Institute for Integrated Cell-Material Sciences (iCeMS) Kyoto University
   Dates of an Agreement: 28 April, 2010
   Summary of an Agreement:
   Exchange of researchers, administrative staff

3. Counterpart of an Agreement: Medical Bioconvergence Research Center, Seoul National University
   Name of an Agreement: General Memorandum for Academic Cooperation and Exchange between Medical Bioconvergence Research Center, Seoul National University, Korea and Institute for Integrated Cell- Material Sciences, Kyoto University, Japan
   Dates of an Agreement: 29 March, 2011
   Summary of an Agreement:
   Exchange of researchers, administrative staff and students

4. Counterpart of an Agreement: Center for Regenerative Medicine, University of Edinburgh
   Name of an Agreement: Memorandum of Understanding between the University Court of the University of Edinburgh (MRC- Centre for Regenerative Medicine) and the Institute for Integrated Cell- Material Sciences (iCeMS), Kyoto University
   Dates of an Agreement: 30 March, 2011
   Summary of an Agreement:
   Exchange of researchers, administrative staff and students

5. Counterpart of an Agreement: Moscow Institute of Physics and Technology (MIPT)
   Name of an Agreement:
   General Memorandum for Academic Cooperation and Exchange between Moscow Institute of Physics and Technology, Russia, and the Institute for Integrated Cell- Material Sciences, Kyoto University, Japan
   Dates of an Agreement: 31 March, 2011
   Summary of an Agreement:
   Exchange of researchers, administrative staff and students

6. Counterpart of an Agreement: Jawaharal Nehru Center for Advanced Scientific Research
   Name of an Agreement:
   Memorandum of Understanding on Academic Exchanges between Jawaharal Nehru Center for Advanced Scientific Research (JNCASR), India, and the Institute for Integrated Cell- Material Sciences (iCeMS), Kyoto University, Japan
   Dates of an Agreement: 18 April, 2011
   Summary of an Agreement: Exchange of researchers

7. Counterpart of an Agreement: Division of Advanced Materials Science, Pohang University of Science and Technology
   Name of an Agreement:
   General Memorandum for Academic Cooperation and Exchange between Division of Advanced Materials Science, Pohang University of Science and Technology, Korea, and Institute for Integrated Cell-Material Sciences, Kyoto University, Japan
   Dates of an Agreement: 16 November, 2011
   Summary of an Agreement:
   Exchange of researchers, administrative staff and students

8. Counterpart of an Agreement: Center for Regenerative Medicine, National Institute of Health
   Name of an Agreement:
   General Memorandum for Academic Cooperation and Exchange between the NIH Center for Regenerative Medicine, National Institutes of Health, USA and the Institute for Inetgrated Cell-Material Sciences, Kyoto University, Japan
   Dates of an Agreement: 21 November, 2011
   Summary of an Agreement:
   Exchange of researchers, administrative staff and students, research collaboration, joint symposium, exchange of information

9. Counterpart of an Agreement: Center for Life Science, Peking Unieristy
   Name of an Agreement:
   GENERAL MEMORANDUM FOR ACADEMIC COOPERATION AND EXCHANGE BETWEEN THE CENTER FOR LIFE SCIENCES, CHINA AND THE INSTITUTE FOR INTEGRATED CELL-MATERIAL SCIENCES, KYOTO UNIVERSITY, JAPAN
   Dates of an Agreement: 20 April, 2012
   Summary of an Agreement:
   Exchange of researchers, administrative staff and students, research collaboration, joint symposium, exchange of information

10. Counterpart of an Agreement: Welcome Trust Centre for Stem Cell Research, University of Cambridge
    Name of an Agreement:
    (University Level Agreement) GENERAL MEMORANDUM FOR ACADEMIC COOPERATION AND EXCHANGE BETWEEN THE UNIVERSITY OF CAMBRIDGE (THE UNITED KINGDOM) AND KYOTO UNIVERSITY (JAPAN)
    Dates of an Agreement: 5 August, 1997
    Summary of an Agreement:
    Exchange of researchers, administrative staff and students, research collaboration, joint symposium, exchange of information

11. Counterpart of an Agreement: Heidelberg University

Name of an Agreement:
(University Level Agreement) RAHMENVEREINBARUNG UBER WISSENSCHAFTLICHE ZUSAMMENARBEIT UND DEN AUSTAUSCH zwishen der RUPRECHT-KARLS-UNIVERSITAT HEIDELBERG (Bundesrepublik Deutschland) und der UNIVERSITAT KYOTO (Japan)
Dates of an Agreement: 11 October 1990
Summary of an Agreement:
Exchange of researchers and students, research collaboration, joint symposium, exchange of information

12. Counterpart of an Agreement: Max Planck Institute of Molecular Cell Biology and Genetics
Name of an Agreement: (Official MOU has not concluded yet)
Dates of an Agreement:
Summary of an Agreement:
Exchange of researchers and students, research collaboration, exchange of information

13. Counterpart of an Agreement: Center for Basic and Applied Membrane Sciences, Purdue University
Name of an Agreement: (Official MOU has not concluded yet)
Dates of an Agreement:
Summary of an Agreement:
Exchange of researchers and students, research collaboration, exchange of information

14. Counterpart of an Agreement: Stem Cells Australia, the University of Melbourne
Name of an Agreement:
(University Level Agreement) MEMORANDUM OF UNDERSTANDING AS BETWEEN KYOTO UNIVERSITY, JAPAN AND THE UNIVERSITY OF MELBOURNE, AUSTRALIA
Dates of an Agreement: 14 September, 2009
Summary of an Agreement:
Exchange of researchers and students, research collaboration, exchange of information

15. Counterpart of an Agreement: Institute for Stem Cell Biology and Regenerative Medicine (inStem)
Name of an Agreement: (Official MOU has not concluded yet)
Dates of an Agreement:
Summary of an Agreement:
Exchange of researchers and students, research collaboration, exchange of information

6. Holding international research meetings

* Give up to twenty examples of the most representative ones of international research conferences or symposiums held between FY2007-2013 using the table below.

Date	Meeting title and Place held	Number of participants
February 20-22, 2008	1st iCeMS International Symposium /The 11th Membrane Research Forum Held at: Hotel Fujita Kyoto	136
June 22-27, 2008	2nd iCeMS International Symposium/The 8th International Conference on Excitonic Processes in Condensed Matter Held at: The Clock Tower, Kyoto University	191
January 27-29, 2009	3rd iCeMS International Symposium: Symposium on the MESO CONTROL of the cells, by the cells, for the cells -- featuring transportsomes Held at: Hotel Fujita Kyoto	173
May 27-29, 2009	4th iCeMS International Symposium: “Integrated Physical/Chemical Biologyof the Cell: from Genes to Membrane Systems” Held at: Hotel Fujita Kyoto	205
July 27-28, 2009	5th iCeMS International Symposium: Meso-Control of Functional Architectures “Biomaterials at the Interface of Chemistry, Physics, and Biology” Held at: The Clock Tower, Kyoto University	146
January 27-29, 2010	6th iCeMS International Symposium/ The Thirteenth Membrane Research Forum Held at: Hotel Fujita Kyoto	210
June 14, 2010	Kitagawa-iCeMS/ERATO (JST)–Yaghi CNSI Joint Symposium: Framework materials in the future: PCPs meet COFs & MOF Held at: UCLA, California	62
June 24, 2010	7th International Symposium: Emerging Approaches and Applications in Developmental Biology: Taking the Next Step Held at: The Clock Tower, Kyoto University	146
November 9-11, 2010	8th iCeMS International Symposium: Meso-Control of Functional Architectures Held at: Shiran Kaikan, Kyoto University	250
December 2-3, 2010	9th iCeMS International Symposium: Mesoscale Control and Engineering of Self-Organized and Excitable Systems in Biology and Chemistry Held at: iCeMS, Kyoto University	85
December 17, 2010	NCBS-inStem/iCeMS joint symposium Held at: iCeMS, Kyoto University	40
July 21-23, 2011	10th iCeMS International Symposium: “Crossing Boundaries: Stem Cells, Materials and Mesoscopic Sciences” Held at: Heidelberg University, Germany	296
July 25, 2011	MRC-CRM and iCeMS Joint Symposium: “Next Generation Stem Cells: Tools and Technologies Symposium” Held at: Edinburgh University, UK	150

December 6, 2011	11th iCeMS International Symposium: “Chemical Control of Cells” Held at: Shiran Kaikan, Kyoto University	152
April 20-22, 2012	iCeMS-CLS Joint Symposium: Crossing Boundaries: Stem Cells, Materials, Mesoscopic Sciences and Beyond Held at: Peking University, China	236
November 8-9, 2012	12th iCeMS International Symposium/6th Annual Symposium on Nanobiotechnology “Kyoto Cell-Material Integration” Held at: Shiran Kaikan, Kyoto University	142
March 7-8, 2013	UK-Japan Workshop on Stem Cells "Building a Better Environment for Application" Held at: iCeMS, Kyoto University	49
March 18–19, 2013	13th iCeMS International Symposium/RSC-iCeMS Joint International Symposium “Cell-Material Integration and Biomaterials Science” Held at: Shiran Kaikan, Kyoto University	157
June 6-9, 2013	14th iCeMS International Symposium/CNRS-4WPI: 10th Japan-France Workshop on Nanomaterials Held at: iCeMS, Kyoto University	81
October 10-11, 2013	15th iCeMS International Symposium: UK-Japan Workshop on “Organic-Inorganic Framework Materials” Held at: iCeMS, Kyoto University	82

World Premier International Research Center Initiative (WPI)

1. Host institution's commitment

1-1. Contributions from host institution

(1) Fund, Personnel

(2007-2014)

<Fund> **(million yen)**

Fiscal Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
Personnel	76	230	255	217	213	209	238	221	1,659
- Faculty members (including researchers)	52	164	148	152	142	139	158	138	1,093
Full-time	52	121	113	144	116	113	137	118	914
Concurrent	0	43	35	8	26	26	21	20	179
- Postdocs	0	0	0	0	0	0	0	0	0
- RA etc.	0	0	0	0	0	0	0	0	0
- Research support staffs	0	2	16	6	6	5	3	0	38
- Administrative staffs	24	64	91	59	65	65	77	83	528
Project activities	41	317	790	296	60	39	97	141	1,781
Travel	0	1	11	30	22	15	11	11	101
Equipment	65	370	1,525	68	8	21	86	85	2,228
Research projects	45	34	88	188	39	44	39	48	525
Total	227	952	2,669	799	342	328	471	506	6,294

<Personnel> **(person)**

Fiscal Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**Total**
Personnel	16	27	34	24	25	26	25	24	201
- Faculty members (including researchers)	8	18	17	12	13	15	16	16	115
Full-time	7	9	11	11	11	11	11	10	81
Concurrent	1	9	6	1	2	4	5	6	34
- Postdocs	0	0	0	0	0	0	0	0	0
- RA etc.	0	0	0	0	0	0	0	0	0
- Research support staffs	0	1	10	3	3	3	1	0	21
- Administrative staffs	8<8>	8<8>	7<7>	9<9>	9<9>	8<8>	8<8>	8<8>	65 <65>

* Regarding "Fund" entry, describe with reference to the items in the Progress Report(実績報告書,Jisseki-hokoku-sho)based on Article 12 of the Grant Guidelines(交付要綱,Kofu-yoko).
* Don't include competitive funding obtained by researchers (used as research project funding)
* Under "Personnel", enter the number of full-time administrative staff within the parenthesis.

(2) Provision of land and/or building(s), lab space, etc.

1) Kyoto University provides a high-quality research environment with a total area of about 11,000 m^2 including exclusive-use facilities with fully equipped infrastructure.
2) Kyoto University built a new, iCeMS dedicated use research building with 3,000m^2 in 2010.

1-2. System under which the center's director is able to make substantive personnel and budget allocation decisions

(a) Strong directorship authorized

Except university overall management matters and appointment of the iCeMS Director, all of the top-down decision making is carried out by the Director.

The iCeMS director, for example, has authority over personnel affairs and salaries for program-specific research center faculty and researchers, as well as award amounts for an "iCeMS Incentive" program and the structure of the institute's internal organization.

The host institution, meanwhile, is responsible for the appointment of the iCeMS Director, the role of the institute within the university, the overall hiring structure for program-specific faculty and researchers, and the rules governing the awarding of incentives.

(b) Dense communication channel

A close relationship exists between the iCeMS and Kyoto University, with the center director frequently discussing important matters with the university president and the executive vice president for research.

(c) Membership of deans meeting

The director is a regular member of the university's Deans and Directors Meeting, the highest deliberative board of Kyoto University. This membership helps to raise the iCeMS' profile.

(d) Indirect costs

As a necessary financial measure for the center's operation, the university fully provides indirect costs associated with competitive grants to iCeMS.

(e) Personnel support

The university provides five positions and expenses for principal investigator-class personnel. For the administration, the university provides eight full-time administrative staff and necessary personnel expenses in order to establish an independent administrative organization.

(f) Financial support

Financial support by action plan until FY2013 (Total: JPY 709 million)

1-3. Support for the center director in coordinating with other departments at host institution when recruiting researchers, while giving reasonable regard to the educational and research activities of those departments

(a) Support for researcher transfers to iCeMS

Six iCeMS PIs have been affiliated with departments where they had held positions prior to joining the institute. This dual affiliation system has allowed these PIs to continue taking part in a portion of these departments' research and graduate education programs, as well as allowing graduate students in these departments to participate in research taking place at the institute. In the case of moving faculty posts (primary affiliation) to iCeMS, some compensation money is specially allocated to the original departments.

(b) Support for faculty staff to participate in other departments

There are faculty members who are employed specifically by WPI iCeMS and not affiliated with other departments. One of their biggest problems is not being able to supervise graduate course students and participate in education. If approved by the departments, these faculty members will be allowed to do so as adjunct professors while concurrently doing research in iCeMS. This dual affiliation system contributes towards promoting collaborative, multidisciplinary research with other departments as well. Two PIs (Profs Kengaku and Harada) and one PI (Prof Motomu Tanaka) have dual affiliations with Graduate School of

Biostudies and Graduate School of Science, respectively.

1-4. Revamping host institution's internal systems to allow introducing of new management methods (e.g., English-language environment, merit-based pay, cross appointment, top-down decision making unfettered by conventional modes of operation)

(a) Establishing Kyoto University International Strategy (Approved on September 2013)

As globalization continues to advance at a rapid pace, Kyoto University has launched The **2x by 2020 Initiative** as its new international strategy to promote the further development of the university as a world-class institution of higher learning, and consolidate our global position as a World Premier University (WPU). 2x by 2020 is the slogan of the new International Strategy by which Kyoto University aims to double its international indices in research, education and international service by the year 2020.

(b) Kyoto University Global Academy (Approved on September 2013)

Global Academy is designed as one of the Kyoto University International Strategies to be a suite of innovative education and research programs and initiatives that seek to instill international competence in our students from the undergraduate level and expand our international cooperative research undertakings.

Kyoto University Global Academy covers a wide area from education to research, ranging from "Institute for Liberal Arts and Sciences" to foster practical international communication skills of young students to "International Center for Emerging Sciences" under which the present iCeMS will be designed to be one of its main institutes.

(c) Establishment of new educational organizations (started in April, 2013)

With the aim to cultivate global leaders and strengthen the university's level of education, the Graduate School of Advanced Integrated Studies in Human Survivability (Shishu-Kan) and the Institute for Liberal Arts and Studies were established in April, 2013.

In the Institute for Liberal Arts and Studies, more than one hundred of overseas faculty are employed as tenured staff to teach classes in English. These overseas faculty have dual-appointments with other graduate schools and research institutes where they are partially engaged in research. 10 bilingual administration staff are already allocated to graduate schools and institutes.

(d) Establishment of a new system for faculty management (approved on February, 2014)

All faculty members have traditionally had primary affiliations with a single educational or research organization, such as a graduate school or research institute. However, the inflexibility of this system has been the cause of delays, hampering efforts to establish new educational and research organizations or rebuild existing ones.

In order to overcome these difficulties, a new Faculty Management Organization is being implemented to act as the primary affiliation for all university teaching and research staff, from which they will be appointed as necessary to one or more department, research center, etc. All faculty will be expected to participate fully in undergraduate teaching. Peer evaluation and other personnel matters (including those related to organizational reforms) will be decided by designated committees within the new system.

This new faculty system will enable the post-WPI institute to dynamically bring top-level researchers together from across the university for the purposes of pursuing collaborative work and to discover new fields of endeavor.

(e) Reappointment of tenured positions (approved on July 2013)

150 reappointed tenured positions are to be established at the president's discretion over the course of 8 years starting in 2014, to be assigned strategically according to the achievements and future potential of applicable university organizations. After WPI finishes, iCeMS is requested to acquire some of these positions competitively.

(f) Establishing cross appointment scheme and merit-based salary system (approved on March 2014)

Researchers can be employed by multiple organizations including Kyoto University, other universities and companies. In this scheme collaboration between the Kyoto University and industries will be further promoted. Merit-based annual salary-system will be partially introduced.

Abolishment of retirement age has been conducted in other institutes such as CiRA and Graduate School of Shishu-Kan and will be expanded to other organizations.

(g) Change of Kyoto University presidential selection scheme (approved on May 2014)

Until now The Kyoto University President is selected via voting by about 3,000 faculty members. Intensive discussions have been done on the presidential election scheme so far. This time the traditional scheme has been slightly modified by the presidential selection committee and its drastic change is left for further discussion.

1-5. Accommodation of center's requirements for infrastructural support

Utilities and other infrastructure support provided by host institution.
*(*In addition to listed in the item 1. Contributions from host institution)*

1-6. Support for other types of assistance

(a) Featuring in University publications

Frequent introduction of iCeMS research activities through Kyoto University PR magazines. Given the iCeMS' mandate to fulfill a role as an international research hub, the university supports the institute's international publicity and linkage efforts via measures including the issuance of publications such as pamphlets and press releases.

(b) Exemption from administrative committees

There are a variety of administrative committees with the university in which researchers should participate. iCeMS members are exempted from participating in these routine committees to reduce their administrative burden and allow them to devote time to their research. iCeMS Director has a duty to attend to the university's Deans and Directors Meeting, being exempted from other administrative duties.

2. Transition in the number of female researchers

Enter the number and percentage of female researchers in the top of each space from 2010 to 2013 and the total number of all the researchers in the bottom.

(Person)

	FY2010	FY2011	FY2012	FY2013	Final goal
Researchers	45, 25.9%	48, 28.7%	41, 22.4%	51, 25.9%	52, 26.0%
	174	167	183	197	200
Principal investigators	2, 11.1%	2, 11.1%	2, 10.5%	2, 11.1%	2, 10.0%
	18	18	19	18	20
Other researchers	43, 27.6%	46, 30.9%	39, 23.8%	49, 27.4%	50, 27.8%
	156	149	164	179	180

3. "Mid-term objectives" and "Mid-term plan" mentioned at 5-4-2

(a) iCeMS positioning during the Kyoto University second mid-term goal period

Kyoto University has positioned iCeMS clearly as one of most important enterprises in the second mid-term goal period. The following is some description on iCeMS in the proposal of the second mid-term goal period.

Overview of Medium-Term Goals and Plans

Corporation Identification Number:52 Name of University: Kyoto University

Medium-Term Goals	Medium-Term Plans
◆ The Time Frame and Education and Research Organization to acheive the Medium-Term Goals	
1. The Time Frame for the Medium-Term Goals	
The time frame is from April 1, 2010 to March 31, 2016.	
2. Goals Related to Research	2. Measures for Achieving the Goals Related to Research
(1) Goals Related to Research Standards and Results	(1) Measures for Achieving the Goals Related to Research Standards and Results
・ We will prioritize fundamental research as the wellspring of academic pursuits and contribute to harmonious coexistence within the human and ecological community on this planet through the construction of academic systems and the creation of an academic culture.	・ We will maintain and develop an environment for fundamental and advanced research and set up our own strategic research support system aimed at promoting new developments and greater depth in all fields of research, including the humanities, social sciences, and natural sciences. ・ We aim to increase the depth and breadth of research throughout the university, and we will support a wide range of research activities, including interdisciplinary research and pioneering initiatives in new fields. We will administer the university in a flexible manner, taking a university-wide view of matters.
・ We will promote cutting-edge, creative, and cross-disciplinary research, increasing our standing as a world-renowned international research site.	・ We will promote cutting-edge cooperative research both in Japan and overseas by supporting specialized and cross-disciplinary research activities at joint usage/research centers, research bases formed by cooperation among industry, government, and academia, and other research facilities. ・ We will expand Japan-based research on iPS cells, and will strive to establish international standards in this area with the aim of making the promise of regenerative medicine a reality as soon as possible. ・ We will expand our role as an international research center by supporting advanced research activities that are being conducted at such world-class institutions as the Institute for Integrated Cell-Material Sciences (iCeMS), the Center for iPS Cell Research and Application (CiRA), as well as by supporting programs selected for the Global COE Program that aim "to establish education and research centers that are at the apex of global excellence to elevate the international competitiveness of Japanese universities," and "Super Special Consortia" to advance the development of the latest innovations in medical care.

Fig A5-1.
iCeMS positioning during the Kyoto University second mid-term goal period

(b) Establishing the International Center for Emerging Science

Kyoto University announced in September 2013 the plan to establish the **International Center for Emerging Science** as one of its International Strategies. Discussions on the basic framework of the new institute commenced in April 2014 and were summarized as an interim report in July 2014. The final report will be formally approved at Dean and Directors Meeting no later than the end of FY 2014. Implementation details on the new center will be settled before FY2016 when the third mid-term goal period starts.

The management principles of the International Center for Emerging Sciences will be as follows:

- Serve as a global center of excellence where world-renowned scholars can join for collaborative research
- Act as a global hub to promote world-class research and investigate proto-sciences
- Provide an environment where select, talented Kyoto University scientists can devote time to their research interests and where young, promising researchers are nurtured
- Exist under the university president's leadership in order to act as a sustainable testbed for implementing university reforms and to apply them university-wide

If the 5-year extension is awarded, iCeMS in its current state will continue to be the main institute of the new center. However, if not granted or after the 5-year extension finishes in FY2021, iCeMS will be retained as scale-down version of its present state. For more details, refer to Progress Plan Application and its Appendix 3.

Fig A5-2. Brief Introduction of International Center for Emerging Sciences in the **2x by 2020** Brochure

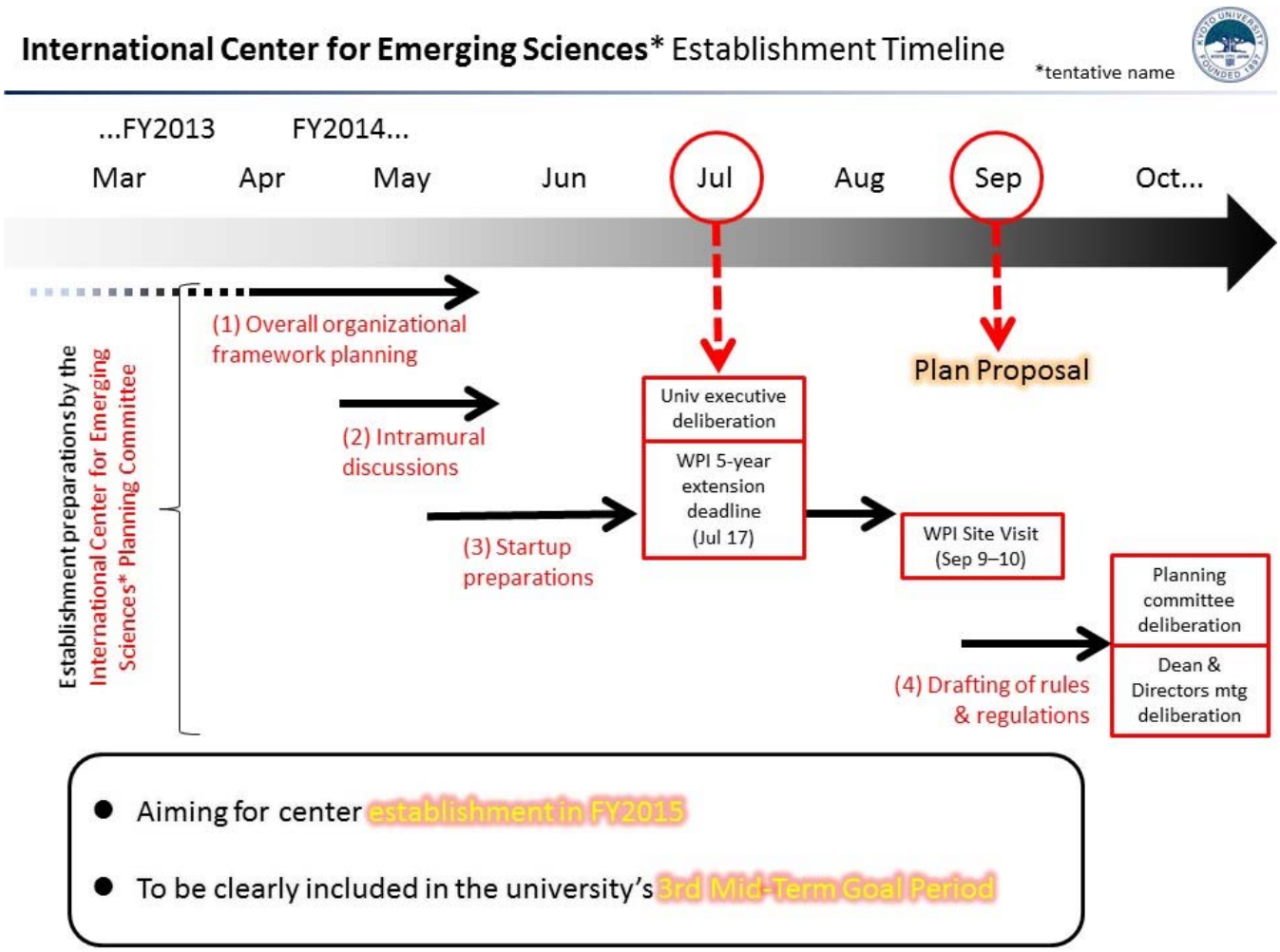


Fig A5-3.
Time-line to establish International Center for Emerging Sciences