World Premier International Research Center Initiative (WPI)
FY2014 WPI Project Progress Report (Post-Interim Evaluation)

Host Institution	Osaka University	Host Institution Head	Toshio Hirano
Research Center	Immunology Frontier Research Canter	Center Director	Shizuo Akira

Common instructions:
* Unless otherwise specified, prepare this report from the timeline of 31 March 2015.
* So as to base this fiscal year's follow-up review on the document "Post-interim evaluation revised center project," please prepare this report from the perspective of the revised project.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

Summary of State of WPI Center Project Progress (write within two pages)

IFReC was established as a leading Institute in Immunology and Medicine in Osaka University through the support of WPI program. Our institute provides a highly equipped research platform for young next generation researchers and world premier scientists who have contributed greatly in studies of cytokines, molecular mechanisms of innate immunity, cell death, and regulation of immune system. Our mission in WPI is to accelerate immunology research as well as develop fusion studies with other fields, systems reform of the host institute, and globalization of university and our society.

Research of the highest world level: IFReC has continued to publish high quality research activities in highly reputable academic journals during FY2014 in innate immunity, acquired immunity, and the immune regulatory mechanism under the prominent leadership of center director Shizuo Akira, with 195 "WPI papers", whose author(s) can be identified as affiliated with the WPI program. More than 10% of these (20 papers) were published in journals with impact factors higher than 14 such as Science, Cell, Nature, and their journal families. PIs and other researchers were invited to speak at more than one hundred international meetings, including high quality meetings such as the Lerner Lecture (Akira), the Henry Kunkel Lecture (Nagata), and WHO Meeting of Stakeholders for Selected Health R&D (Ken Ishii), indicating that IFReC investigators maintain the highest level of activities. These activities include the fusion of immunology, imaging and/or informatics researches. Another measure to evaluate newly published papers is by internet accesses; this amounted to more than 200 times per month for the prominent papers listed in Section 1, showing significant attention from other scientists around the world. Remarkable research results achieved have been released to the media. Many were widely-publicized to general citizens by newspapers and TV news (Appendix 7). Shimon Sakaguchi gained a lot of media coverage as winner of the Gairdner International Award.

Advancing world premier research organization: IFReC is promoting interdisciplinary research by establishing a **live immune-imaging facility** in the IFReC research building with animal rooms and high-performance imaging devices such as MRI and two-photon microscope, and through **programs to promote fusion research** to encourage IFReC young researchers under the "Research Support Program for Combined Research Fields" and "Dual Mentor Program". **Fusion research units** have been established to foster young, talented researchers to create new fusion fields. **IFReC colloquia** are a series of discussion meetings for IFReC members to assist in the creation of novel concepts through intensive criticisms and discussions. IFReC extended **collaboration with external organizations** such as Quantitative Biology Center (QBiC) of RIKEN and the Center for Information and Neural Networks (CiNet) of the National Institute of Information and Communications Technology (NICT).

Efforts to secure the center's future development over the mid- to long term:

Research plan, research organization and prospects for the fostering and securing of next-generation researchers

IFReC has established the main framework for sustained innovation in science and will continue its activities by maintaining two goals, "IFReC, a cradle of *innovative* immunologists" and "Generation of *innovative*

immunotherapeutics". **IFReC, a cradle of *innovative* immunologists:** At IFReC, senior and young researchers contribute their own specialty to fusion studies. IFReC's interaction with QBiC and CiNet is of great interest and even excitement to IFReC researchers. By collaborating with QBiC, spatio-temporal and collective behavior of immune molecules and cells are observed using cutting-edge imaging methods and the big data obtained are analyzed with computer-aided theories of systems biology for modeling a whole system.
Generation of *innovative* immunotherapeutics: At IFReC, the application of research outcomes to medical/clinical immunology will provide a practical platform to nurture young researchers to be capable of both basic and translational immunology. Listed below are five major projects for such challenges.
① Development of innovative immune-regulating techniques ② Innovative cancer immunotherapy ③ Development of the novel diagnostic and therapeutic strategies for autoimmune diseases ④Promotion of new drug development with innovative PET/MR and PET/CT ⑤Forefront vaccine development

PI composition is maintained at the highest level through retaining world-prominent scientists and recruiting of young and energetic scientists from all over the world. The center director, the vice directors and the administrative office continuously search for investigators and encourage them to study in the center. At the same time, we offer an excellent research environment that attracts prominent scientists to work and develop at IFReC. In 2014, another world-renowned immunologist Shigekazu Nagata joined IFReC, further enhancing the line-up of prominent scientists.

Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure

IFReC has started to secure positions for IFReC members, who, as international scientists, contribute to science and the globalization of Osaka University. IFReC has maintained close cooperation with the Research Institute for Microbial Diseases, Osaka University (RIMD), which will potentially share positions for IFReC's mission. We will also construct an action plan to secure permanent positions for key PI member laboratories before the WPI program ceases.

Measures to sustain the center as a world premier international research center after program funding ends (including measures of support by the host institution)

IFReC was started as a sustainable innovative world premier institute of immunology—a product of the WPI program of Japan. The principal mission is world-leading basic immunology to strongly impact the medical sciences. Osaka University and IFReC are seeking to become a next-generation innovative institute for collaboration with various industries and organizations exceeding the boundaries of the campus.

Leadership for organization in relation with the previous site visit comments:

Director Shizuo Akira performed leadership management in the advancement and recruitment of human resources.

・IFReC recruited new members for new projects in medical and biological sciences and supported their activities using the center director's discretionary funds, which should be increased as the site visit team previously advised.

・Cancer immunotherapy is a big issue for cancer treatment, thus the center director aims to promote the application of various IFReC's seeds data regarding the immune regulatory molecules to the clinical medicine. IFReC joined a consortium for innovative cancer immunotherapy and started collaboration with research groups at the Center of Medical and Translational Research (CoMIT), Osaka University.

・IFReC members are all aware of the importance of standardization of an experimental data management system for creating optimal operating systems for translation and clinical immunology by raising the maturity of experimental protocols and the development of validated databases. This is particularly important for the data validation at the submission to the international journals and also for the patent process.

・IFReC thanks the Kishimoto Foundation that has effectively stimulated and supported the activities of young investigators. The Foundation has supported a PI with an endowed department in IFReC. IFReC will also inspire companies and industries to donate for collaboration.

・Please concisely describe the progress being made by the WPI center project from the viewpoints described below.
・In addressing the below-listed 1-6 criteria, please place emphasis on the following:
(1) Whether research is being carried out at a top world-level (including whether research advances are being made by fusing fields).
(2) Whether a proactive effort continues to be made to establish itself as a "truly" world premier international research center.
(3) Whether a steadfast effort is being made to secure the center's future development over the mid- to long term.
・Please prepare this report within 10 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within two pages)).

1. Conducting research of the highest world level

* Regarding the criteria used when evaluating the world level of center, please note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

In FY2014, IFReC has maintained high level of productivity. There were 195 research papers published (Appendix 1), of which more than 20 papers were published in high-impact journals such as Science, Cell, Nature, and their journal families, demonstrating IFReC's strong commitment to quality science.
Below is a brief description of some research papers selected from the list in Appendix 1. These works reflect the efforts made in basic research, and are thought to be the leading achievements of IFReC in 2014.

a) Nucleic acid sensing by T cells initiates Th2 cell Differentiation

Akira and Saito groups show that unlike in innate cells, T-cell stimulation is induced even by non-CpG DNA and by self-DNA, which is released from dead cells and complexes with antimicrobial peptides or histones. Such nucleic acids (NA) complexes are internalized by T cells and induce costimulatory responses independently of known NA sensors, including TLRs, RIG-I-like receptors (RLRs), inflammasomes and STING-dependent cytosolic DNA sensors. Such NA-mediated costimulation crucially induces Th2 differentiation by suppressing T-bet expression, followed by the induction of GATA-3 and Th2 cytokines. These findings unveil the function of NA sensing by T cells to trigger and amplify allergic inflammation (Nat Commun. 5:3566, 2014).

b) Generation of colonic IgA-secreting cells in the caecal patch

Kurosaki, Masaru Ishii, and Takeda groups analyze the role of the caecal patch using germ-free mice colonized with intestinal bacteria after appendectomy. Appendectomized mice show delayed accumulation of IgA^+ cells in the large intestine, but not the small intestine, after colonization. Decreased colonic IgA^+ cells correlate with altered faecal microbiota composition. Experiments using photoconvertible Kaede-expressing mice or adoptive transfer show that the caecal patch IgA^+ cells migrate to the large and small intestines, whereas Peyer's patch cells are preferentially recruited to the small intestine. IgA^+ cells in the caecal patch express higher levels of CCR10. Dendritic cells in the caecal patch, but not Peyer's patches, induce CCR10 on cocultured B cells. Thus, the caecal patch is a major site for generation of IgA-secreting cells that migrate to the large intestine (Nat Commun. 5:3704, 2014).

c) Selective and strain-specific NFAT4 activation by the *Toxoplasma gondii* polymorphic dense granule protein GRA6

Toxoplasma gondii infection results in co-option and subversion of host cellular signaling pathways. This process involves discharge of T. gondii effector molecules from parasite secretory organelles such as rhoptries and dense granules. Yamamoto group reported that the *T. gondii* polymorphic dense granule protein GRA6 regulates activation of the host transcription factor, the nuclear factor of activated T cells 4

(NFAT4). Their data suggest that GRA6-dependent NFAT4 activation is required for T. gondii manipulation of host immune responses to maximize the parasite virulence in a strain-dependent manner (J Exp Med. 211:2013-32, 2014).

d) Olfactory plays a key role in spatiotemporal pathogenesis of cerebral malaria

Yoshioka, Ken Ishii, and Coban groups showed by ultra-high-field MRI and multiphoton microscopy that the olfactory bulb is physically and functionally damaged (loss of smell) by Plasmodium parasites during ECM. The trabecular small capillaries comprising the olfactory bulb show parasite accumulation and cell occlusion followed by microbleeding, events associated with high fever and cytokine storm. Specifically, the olfactory upregulates chemokine CCL21, and loss or functional blockade of its receptors CCR7 and CXCR3 results in decreased CD8 T cell activation and recruitment, respectively, as well as prolonged survival. Thus, early detection of olfaction loss and blockade of pathological cell recruitment may offer potential therapeutic strategies for ECM (Cell Host & Mirobe. 15:551-63, 2014).

e) Structural basis for simultaneous recognition of an O-glycan and its attached peptide of mucin family by immune receptor PILR-alpha

Arase group shows that sialylated O-linked sugar T antigen (sTn) and its attached peptide region are both required for ligand recognition by PILRα. Furthermore, they determined the crystal structures of PILRα and its complex with a sTn and its attached peptide region. The structures show that PILRα exhibits large conformational change to recognize simultaneously both the sTn O-glycan and the compact peptide structure constrained by proline residues. These findings provide significant insight into the binding motif and molecular mechanism by which O-glycosylated mucin proteins with sTn modifications are recognized in the immune system as well as during viral entry (Proc Natl Acad Sci USA. 111:8877-82, 2014).

f) Laser-targeted photofabrication of gold nanoparticles inside cells

Smith group showed that by infusing gold ion solution, focused laser light-induced photoreduction allows in-situ fabrication of gold nanoparticles at precise locations. The resulting particles are pure gold nanocrystals, distributed throughout the laser focus at sizes ranging from 2 to 20 nm, and remain in place even after removing the gold solution. They demonstrate the spatial control by scanning a laser beam to write characters in gold inside a cell. Plasmonically enhanced molecular signals are then detected from nanoparticles, allowing their use as nano-chemical probes at targeted locations inside the cell, with intracellular molecular feedback. Such light-based control of the intracellular particle generation reaction also offers avenues for in-situ plasmonic device creation in organic targets, and may eventually link optical and electron microscopy (Nat Commun. 5:5144, 2014).

g) Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors

Suzuki group revealed that β2-adrenergic receptors (β2ARs) expressed on lymphocytes regulate their egress from lymph nodes by altering the responsiveness of chemokine receptors CCR7 and CXCR4. In mouse models of inflammation, signals though β2ARs were shown to inhibit trafficking of pathogenic lymphocytes and reduce their numbers recruited into inflamed tissues (J Exp Med. 211:2583-98, 2014).

h) Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation

Kurosaki group found that plasmablasts in the draining lymph nodes (dLNs), but not splenic B lineage cells, predominantly expressed IL-10 during experimental autoimmune encephalomyelitis (EAE). These plasmablasts were generated only during EAE inflammation. Mice lacking plasmablasts by genetic ablation of the transcription factors Blimp1 or IRF4 in B lineage cells developed an exacerbated EAE (Immunity 41:1040-51, 2014).

i) Regulatory T cells control antigen-specific expansion of Tfh cell number and humoral immune responses via the coreceptor CTLA-4

Kurosaki and Sakaguchi groups determined the roles of Treg cells and T follicular regulatory (Tfr) cells in the control of humoral immune responses. Depletion of Treg cells, blocking of CTLA-4 or a Treg cell specific reduction in CTLA-4 expression, resulted in an increase in the formation of antigen-specific Tfh cells, germinal center (GC), and plasma and memory B cells after vaccination. In the absence of Treg cell-expressed CTLA-4, large numbers of Tfr cells were present but were unable to restrain Tfh cell and GC formation. Temporary Treg cell depletion during primary immunization was sufficient to enhance secondary immune responses. Treg cells directly inhibited, via CTLA-4, B cell expression of CD80 and CD86, which was essential for Tfh cell formation. Thus, Treg and Tfr cells control Tfh cell and germinal center development, via CTLA-4-dependent regulation of CD80 and CD86 expression (Immunity 41:1013-25, 2014).

j) Detection of self-reactive CD8+ T cells with an anergic phenotype in healthy individuals

Sakaguchi group found Treg can render self-reactive human CD8+ T cells anergic (i.e., hypoproliferative and cytokine hypoproducing upon antigen restimulation) in vitro, likely by controlling the costimulatory function of antigen-presenting cells. Anergic T cells were naïve in phenotype, lower than activated T cells in T cell receptor affinity for cognate antigen, and expressed several coinhibitory molecules, including cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) (Science 346:1536-40, 2014).

2. Advancing fusion of various research fields

IFReC has been implementing strategic measures to promote fusion research as follow. These measures have successfully led fusion of different research fields in IFReC. The number of "fusion papers" has steadily increased and 53 of 195 papers published in FY2014 include outcomes of fusion research, reaching 27% of total papers. This demonstrates our strategies to create a platform of fusion were effective and fusion research is now a well-established field in IFReC.

Live immune-imaging facility is located inside the IFReC research building and consists of animal rooms and high-performance imaging devices such as MRI and two-photon microscope. There, IFReC researchers can observe immune reactions in the same animals for as long as a few weeks. Having the imaging facility in the vicinity enhances fusion research between immunology and imaging. The number of the fusion researches done using this facility has been increasing.

Programs to promote fusion research have been set up to encourage young IFReC researchers to promote fusion research. Under the "Research Support Program for Combined Research Fields" and the "Dual Mentor Program" a total of 11 projects are underway. The evaluation workshop for the program was held on the 15th of October, 2014 and IFReC PIs evaluated the projects based on the presentations.

Fusion research units have been established to foster young, talented researchers to create new fusion fields. Each unit consists of young researchers of assistant or associate professor level with different research backgrounds and/or experience. Three units have been set up so far.

IFReC colloquia are a series of discussion meetings for IFReC members. In FY2014, six colloquia were held. At each colloquium, three speakers from IFReC laboratories give talks about their latest research progress including fusion research followed by intensive discussion with the audience.

Collaboration with external organizations

In addition to these internal approaches for fusion research, IFReC extended collaboration with external organizations such as Quantitative Biology Center (QBiC) of RIKEN and the Center for Information and Neural Networks (CiNet) of the National Institute of Information and Communications Technology (NICT), both of which are headed by the IFReC deputy director, Toshio Yanagida. Some IFReC researchers are located at

QBiC and advance their research to obtain cutting-edge technologies and new concepts from QBiC researchers. A CiNet researcher, Ben Seymour set up a new laboratory "Brain-immune interaction" at IFReC in April, 2014, opening a new vista in immunology.

3. Globalization of the institution

* Describe what's been accomplished or recognized in the efforts to raise the center's international recognition as a genuine top world-level research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:
  - Efforts being developed based on the analysis of number and state of world-leading, frontline researchers; number and state of visiting researchers; exchanges with overseas entities
  - Proactive efforts to raise the level of the center's international recognition
  - Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

Approach to Global Visualization

Number of overseas researchers The percentage of overseas researchers at all levels was below the WPI target level of 30% during the year (Appendix 3-1), because international researchers, including a PI, left IFReC for promotion in the previous year. IFReC and Osaka University will form future strategies to sustain IFReC after WPI support and to prepare formalities, which will enable the long term employment beyond the current period limitation. IFReC will continue to actively recruit to increase the numbers of international researchers.

International Symposia and Other Meetings IFReC held two annual symposia in FY2014; the International Symposium "Immunology at the Forefront" on February 23-24, 2015, held at Grand Front Osaka; and the 5th Kishimoto Foundation Lecture on 22 September, 2014. IFReC and Bristol-Myers Squibb co-organized "Cancer Immunotherapy Forum" on 21 November 2014 for the acceleration of cancer immunotherapy—one of IFReC's future goals. IFReC jointly organized the first CiNet Conference "New Directions in Pain Neuroscience" on 2-5 December, 2014, which covered the role of the immune system in pain to promote psychoneuroimmunology.

Strategies to Attract and Foster Talented Young Researchers

The 4th Winter School on Advanced Immunology was held in Singapore over 18-23 January, 2015 jointly by IFReC and Singapore Immunology Network (SIgN). 50 young researchers including 3 IFReC researchers were selected out of 180 applicants, and had 16 lectures given by prominent immunologists and opportunities to present their works to their peers. It successfully achieved its educational aims both in fostering young immunologists of the next generation and impressing on them the qualities of IFReC—its high research level and its position as a well-established research center by global standards.

Kishimoto Foundation Fellowship/Scholarship Program Since this program was established in 2009, the fellowship/scholarship has been contributed to increasing the number of overseas researchers in IFReC. In FY2014, nine researchers were employed by the fellowship and one visitor was supported to stay and work at IFReC.

IFReC Young Scientist Support Program for Research IFReC has provided financial support for young researchers to attend conferences or to collaborate with other laboratories abroad since 2013. The program supported seven young researchers (eight cases) in FY2014.

Support for overseas researchers

・Support for overseas researchers is constantly provided as in past years. The orientation for use of facilities commonly available to IFReC and RIMD researchers and required legally for carrying out specific

experiments was again held in English. Staff in the Research Planning and Management Office (RPMO) supported overseas researchers to obtain approval for and to manage experiments with animals, living modified organisms, pathogens etc.

・Overseas researchers, especially PIs, made tremendous efforts to obtain competitive funds including public and private ones. IFReC provides them with support such as grant information, translation of application guidelines and forms into English and of their research plans into Japanese if necessary.

・Applications for Grants-in-Aid for Scientific Research (KAKENHI) are now permitted in English and international researchers have been able to apply without any support, however, this has meant that applications were not checked in-house by a PhD at RPMO and the rate of successful applications has decreased somewhat. In order to recover a high success rate, IFReC is planning to establish a system to check their applications.

・IFReC Liaison Office staff constantly helps overseas researchers to adapt to Japanese culture and life and has organized "Japanese Language Class" and "Japanese Language Café" since FY2012.

4. Implementing organizational reforms

* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.

IFReC has continued various efforts to reinforce its organization, especially aiming to improve the research environment that meets international standards.

・The Research Planning and Management Office (RPMO), which consists of five PhD holders with research experience and bilingual staff, has provided support concerning the acquisition of external research funds not only in application but also after adoption. In order to assist international researchers in the acquisition of MEXT grants-in-aid for scientific research (KAKENHI), IFReC initiated an annual orientation in English in 2011. Osaka University fully recognized its importance and effectiveness and started to host a similar version of the English orientation on a University-scale. Several international researchers at IFReC contributed to the orientation as lecturers to provide practical information for the application and acquisition of KAKENHI.

・IFReC has maintained close cooperation with the Research Institute for Microbial Diseases (RIMD). One of the collaborations is an annual orientation targeted at researchers who are involved in experiments using genetically modified organisms, pathogens and animals. In response to a request from the research ethics committee of Osaka University, IFReC and RIMD conducted a session of researches on human genome analysis to all researchers at Osaka University.

・"The handbook for appropriate use of public research funds" , issued in Japanese by the University, was partially translated into English by bilingual staff at IFReC. It was provided to the whole university via the Office for the Proper Usage of Research Grants and helped raise the awareness of international researchers to prevent misuse of public funds.

IFReC held a seminar for the prevention of research misconduct in order to enhance compliance and understanding among all IFReC staff. In addition, all correspondence from the university relating to misconduct is translated into English by bilingual staff for international members at IFReC.

・In FY2014, we applied the cross-appointment system for an international PI at IFReC, on the basis of an agreement between Osaka University and Kyoto University. This system will serve as a measure to establish a better international research environment and to accelerate interdisciplinary research at IFReC.

5. Efforts to secure the center's future development over the mid- to long term

* Please address the following items, which are essential to mid- to long-term center development:

- Future Prospects with regard to the research plan, research organization and PI composition; prospects for the fostering and securing of next-generation researchers
- Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure
- Measures to sustain the center as a world premier international research center after program funding ends (including measures of support by the host institution)

Research plan, research organization and PI composition; prospects for the fostering and securing of next-generation researchers

IFReC has established the main framework for sustained innovation in science and will continue its activities by maintaining two goals, "IFReC, a cradle of *innovative* immunologists" and "Generation of *innovative* immunotherapeutics".

IFReC, a cradle of *innovative* immunologists: At IFReC, senior and young researchers gather to contribute their own specialty to fusion studies. IFReC's interaction with Quantitative Biology Center (QBiC) of RIKEN and the Center for Information and Neural Networks (CiNet) of the National Institute of Information and Communications Technology (NICT) is of great interest and even excitement to young researchers on all sides. By collaborating with QBiC, spatio-temporal and collective behavior of immune molecules and cells are observed using cutting-edge imaging methods and the big data thus obtained are analyzed with computer-aided theories of systems biology for modeling a whole system. Collaboration with CiNet is a step forward toward psychoneuroimmunology, which is an important research field for elucidating the mechanism underlying certain but yet undetermined crosstalk between the mind (central nervous system [CNS] function) and body, including immune systems. Researchers at IFReC collaborate with specialists of non-invasive functional neuro-imaging at CiNet and clinician/physician scientists at the University Hospital to investigate the maintenance of CNS homeostasis, which is of critical importance to overcome CNS diseases.

Generation of *innovative* immunotherapeutics: At IFReC, the application of research outcomes to medical/clinical immunology will provide a practical platform to nurture young researchers to be capable of both basic and translational immunology. Listed below are five major projects for such challenges.

① Development of innovative immune-regulating techniques ② Innovative cancer immunotherapy ③ Development of the novel diagnostic and therapeutic strategies for autoimmune diseases ④Promotion of new drug development with innovative PET/MR and PET/CT ⑤Forefront vaccine development

PI composition overall is maintained at the highest level through retaining world-prominent scientists and recruiting young and energetic scientists from all over the world by offering an excellent research environment that provides extensive opportunities for work and development at IFReC.

To further enhance activities in science, the center director seeks excellent candidates for PI positions, negotiates with the president of Osaka University and gathers the external collaboration funds for special contracts. Those efforts resulted in the recruitment of Shigekazu Nagata in 2014, further enhancing the scientific prominence of IFReC.

Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure

The president of Osaka University and IFReC are now preparing to secure positions for IFReC members. The host institution fully recognizes the importance of international scientists of IFReC with their excellence in science and effectiveness for globalization of the Osaka University campus. A professor positon was provided by the host institution in FY2014 and two more will be provided in FY2015.

IFReC has maintained close cooperation with the Research Institute for Microbial Diseases, Osaka University

(RIMD). The positions in RIMD are good candidates for cooperation under IFReC's mission. Studying in the IFReC environment will be strongly effective for research activities of the RIMD mission. Moreover, we will also construct the action plan to secure permanent positions for the key PI member laboratories before the WPI program ceases.

Measures to sustain the center as a world premier international research center after program funding ends (including measures of support by the host institution)

Preparations are underway for a working group to redesign IFReC as a sustainable innovative world premier institute of immunology as a product of the WPI program of Japan. The principal mission is world-leading basic immunology which provides strong impact on the medical sciences including infectious diseases, autoimmune diseases, allergic diseases, cancer, psycho-neurological diseases and life-style related diseases such as diabetes mellitus, circulatory diseases and respiratory diseases. IFReC will encourage the young scientists and medical doctors to develop their potential for the future creative sciences at the world premier level from Osaka University. Efforts will be focused on the application of the many valuable seeds for medical sciences and clinical application accumulated during the WPI program that are extremely useful for various kinds of industries including pharmacology and medical diagnostics. The working group will set up the future image of IFReC as the leading institute for providing information for such application sciences. The IFReC budget size should be maintained for these three missions in the next stage. IFReC should work to become a new type of collaborative institution in the campus.

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.

Special Achievements on Outreach Activities: Besides the usual outreach activities for the general public and students, IFReC strove to become a more "visible institute" to the host institute and global society through outreach activities.

Immunology Lecture Series for Osaka University members: IFReC started "The Immunology Lecture Series" at the end of FY2013. A junior researcher from IFReC gives a talk about the basics of his/her research including cutting-edge results in an easy-to-understand manner. The lecture is open to all Osaka University members and held in the evening so that participants can attend after their regular work hours. Seven lectures were provided in FY2014, and gathered a total of more than 300 participants.

Online Immunology Course: Osaka University joined edX, one of the major Massive Open Online Course (MOOC) platforms, founded by Massachusetts Institute of Technology (MIT) and Harvard University. IFReC is contributing by providing lectures as the first course of OsakaUx (edX courses by Osaka University). In FY2014, IFReC researchers, as lecturers, started cooperating in preparation for the lectures with the support of IFReC Research Planning and Management Office (RPMO) and the Teaching and Learning Support Center of Osaka University. Over 3,000 people have already enrolled in the course, and it will be distributed in FY2015.

Facebook: In order to be more open to and more easily accessible from the world, IFReC opened its Facebook page (https://www.facebook.com/Osaka.Univ.IFReC) to provide information of various outreach activities of IFReC, research achievements and the awards acquired by IFReC researchers.

Science Café: As the past years, IFReC continued the science café series for general public. A unique attempt achieved in a science café was to invite two guest speakers who were attending the 6th IFReC international symposium from abroad. Arrangement of simultaneous interpretation enhanced and prompted better communication between the speakers and audience. The venue was CAFE Lab., a "real" café in Grand

Front Osaka, which is a brand-new and successful commercial complex in Osaka. The questionnaire survey showed that more than 80 % of participants were satisfied with the event. An unforeseen ripple effect from this was that one of the guests, who was unfamiliar with science café events, discovered the benefits and decided to try adopting such an activity into his home institute.

WPI joint events: Collaboration with other WPI centers was continued and IFReC joined several events at home and abroad such as the 4th annual WPI joint symposium in Tokyo, Super Science High School Student Fair 2014 in Yokohama and Annual Meeting of the American Association for the Advancement of Science (AAAS) in San Jose, U.S.A. In every event, IFReC opened a booth to introduce the institute and its world-leading research activities. The booth appealed to many participants, as immunology is an important topic for many people in the world.

7. Center's response to the results of the FY2014 follow-up (including the results of the site visit)

   * Note how the center has responded to the results of FY2014 follow-up. However, if you have already provided this information, please indicate where in the report.

Recommendations made upon the FY2014 follow-up

Based on its world-leading and highly appreciated scientific achievements in basic immunology, IFReC's new challenge to initiate innovative immunology research for uncured immunological diseases is a logical and reasonable direction for its extension. The center has already accumulated several promising seeds for this new challenge. Through this new endeavor, outstanding basic research on elucidating the dynamism of the immune system, for which IFReC has been most proud, will be further enriched and accelerated, resulting in its continuation as a concrete world-premiere research center.

Center's answer:

IFReC has received strong support for our previous activities and will continue its activities as the world-premier research center by adding two clear goals, "IFReC, a cradle of *innovative* immunologists" and "Generation of *innovative* immunotherapeutics".

IFReC, a cradle of *innovative* immunologists: At IFReC, senior and young researchers contribute their own specialty to fusion studies. A unique and vibrant research environment has been formed with a collection of top-class researchers, excellent facilities and an effective research support system. The researchers fostered here can improve themselves through friendly rivalry and attempt to challenge new fusion research projects in an ever-improving environment which is not found elsewhere—IFReC is a cradle for innovative immunologists in the next generation. In this context, IFReC's interaction with QBiC and CiNet is of great interest and even excitement to young researchers on all sides, and is expected to nourish them with different ideas and methodologies. In the future we can expect greater diversity in technology, research targets, and purpose: therefore, we will continue to innovate science to meet changing needs and adapt to the requirements of society.

Generation of *innovative* immunotherapeutics: IFReC will accelerate the application of research outcomes to medical/clinical immunology through cooperation with the University Hospital. New insight into the immune-regulating mechanism is the foremost achievement attained so far at IFReC under the auspices of the WPI program. The activities will also provide a practical platform to nurture young researchers to be capable of both basic and translational immunology. Listed below are five major projects for undergoing such challenges.

➢ **Development of innovative immune-regulating techniques**

➢ **Innovative cancer immunotherapy**

➢ **Development of the novel diagnostic and therapeutic strategies for autoimmune diseases**
➢ **Promotion of new drug development with innovative PET/MR and PET/CT**
➢ **Forefront vaccine development**

These were described in detail in section 5. We will seek to further promote these challenges.

Advice/Recommendations by the site-visit team

Making of a clear strategy and defining of future perspectives on clinical and translational immunology *Although IFReC's research has been, and should remain focused at the cutting edge of basic and integrative immunology, their results over the past 7 years yielded a number of seeds to be applied to clinical/medical immunology, and these possible subjects are now expanding. It is, therefore, recommended to make a clear strategy and define future perspectives on clinical and translational immunology.*

Center's answer:

In order to promote translational studies toward medical and clinical immunology, in addition to collaborating with PIs in concurrent posts with the University Hospital, IFReC recently joined a consortium for innovative cancer immunotherapy and started collaboration with research groups at the Center of Medical and Translational Research (CoMIT), Osaka University. The former is a collaboration network consisting of researchers from IFReC and the National Institute of Biomedical Innovation (NIBIO) and clinical physicians of Osaka University Hospital and the National Cancer Center East, which aims to develop innovative cancer immunotherapies through accumulation of promising seeds for anticancer drugs and clinical trial data. At CoMIT, dedicated attempts are made to apply outcomes from fundamental research to medical treatment at a much earlier stage than in the current medicine development methods. In accordance with the advice, we are considering the situation practically. We will develop a system to further promote application of basic science data to clinical medicine and translational research studies after the WPI program under the leadership of the president of Osaka University and the center director.

Setting-up of discretionary funds for the Director to continuously advance IFReC as a world premier research institute *To continuously advance IFReC as a world premier research institute, the center, together with the University's direct support, needs to obtain substantial amounts of discretionary funds for the Director --for his/her top-down operation of the center, including the execution of his/her plan for leading IFReC during the next phase of scientific development, as well as the recruitment of female PI's and foreign senior scientists. Such efforts would also contribute to the transformation of Osaka University to become a world premier Research University.*

Center's answer:

The center director's discretionary funds have supported the expenses for laboratory start-up (6 million yen/PI) and upbringing of the young investigators (total 47 cases) as well as the expenses for the introduction of new facilities and equipment (113 cases) since FY2007. In FY2014, IFReC provided 12 million yen in support for two young investigators and 48 million yen for introduction of new facilities and equipment. The financial support of the center's director is highly effective when used at the appropriate time to support young ambitious investigators. Following the advice from the PO and PD, we would like to enrich this type of budget as well as for the recruitment of female PIs and foreign senior scientists in the next budgetary process.

Host institution support includes the Osaka University Institute for Academic Initiatives (IAI), set up in 2011, with the aim to become a world-leading global university that continues to shine into the 22nd century by building a foundation that combines the wisdom and strength of all of its members. Under the strong

leadership of the president, there are moves to cultivate research organizations that will become new WPI-like research centers. Using the IAI framework, the University has provided a tenure position for an international researcher at IFReC in FY2014.

Standardization of an experimental data management system for creating optimal operating systems for translational and clinical immunology *IFReC's should make progress in the standardization of an experimental data management system for creating optimal operating systems for translational and clinical immunology. This would require further maturity of experimental protocols and the development of validated databases. Some kind of quality control in the production and handling of the data is of great importance, especially with regard to the growing efforts in human immunology and clinical research. It would also greatly facilitate relationships with industry.*

Center's answer:

IFReC has recognized the importance of data management and control achieved through the improvement of technical skills and storage for the individual scientists with the responsibility of PIs. This is particularly important for the data validation at the submission to the international journals and for the patent process. All scientists including technicians, laboratory assistants, and PhD students take the course on experimental facilities and the regulation of research. IFReC takes the comment of the site visit team as a critical point for clinical application, and will provide courses for experimental procedures and management of data validation, in compliance with the regulations and guideline of Osaka University.

Appreciation and exploitation of the support of the "Kishimoto Foundation" *The generous support of the "Kishimoto Foundation" might be extended to organizing a "Kishimoto endowed Chair in Immunology" for attracting an outstanding scientist from abroad to join IFReC as a PI in order to continuously advance the center as a competitive, cutting-edge research institute.*

Center's answer:

IFReC highly appreciates the generosity of the Kishimoto Foundation that effectively stimulates and supports the activities of young investigators who have great potential and may achieve challenging projects comparable to the donor's own. The support will continue as long as IFReC stands, as proposed by the foundation. IFReC should certainly organize the effective use of the grant from the Kishimoto Foundation. Kishimoto Foundation already supported a PI with an endowed department in IFReC. IFReC will also inspire the companies and industries to donate laboratory budget for collaboration.

List of Center's Research Results and Main Awards

A. Refereed Papers

List only the Center's papers published in 2014. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.

A. WPI papers
List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state the name of his/her WPI center). (*Not including* papers whose acknowledgements contain the names of persons affiliated with the WPI program.)

B. WPI-related papers
Among papers published in 2014, list those related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (*Including* papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

Note: On 14 December 2011, the Basic Research Promotion Division in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. As some WPI-affiliated authors of papers published up to 2011 may not be aware of this requirement, their papers are treated as "WPI-related papers." From 2012, however, the authors' affiliations must be clearly noted and only category A papers will be listed.

Newly selected centers are to list papers under category C below (in addition to categories A and B above).

(2) Method of listing paper
- List only referred papers. Divide them into categories (e.g., original articles, reviews, proceedings).
- 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. (The names of the center researchers do not need to be underlined.)
- If a paper has many authors (say, more than 20), all of their names do not need to be listed.
- If the papers are written in languages other than English, divide them into language categories when listing them.
- Assign a serial number to each paper to be used to identify it throughout the system.

(3) Submission of electronic data
- In addition to the above, for each paper provide a .cvs file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
- These files do not need to be divided into paper categories.

(4) Use in assessments
- The lists of papers will be used in assessing the state of WPI project's progress in FY 2014.
- They will be used as reference in analyzing the trends and states of research in all the WPI centers, not to evaluate individual researcher performance.
- The special characteristics of each research domain will be considered when conducting assessments.

(5) Additional documents
After all documents, including these paper listings, showing the state of research progress have been submitted, additional documents may be requested.

Order of Listing

A. WPI papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles
5. Articles written in other than English

B. WPI-related papers

1. Original articles
2. Review articles
3. Proceedings
4. Other English articles
5. Articles written in other than English

A. WPI papers

1. Original articles

No	ARTICLE
1	Kitagawa, Yohko; Ohkura, Naganari. Treating type-1 diabetes with an epigenetic drug. Elife 3:e05720, 2014.
2	Maeda, Yuka; Nishikawa, Hiroyoshi; Sugiyama, Daisuke; Ha, Danbee; Hamaguchi, Masahide; Saito, Takuro; Nishioka, Megumi; Wing, James B.; Adeegbe, Dennis; Katayama, Ichiro; Sakaguchi, Shimon. Detection of self-reactive CD8(+) T cells with an anergic phenotype in healthy individuals. Science 346:1536-1540, 2014.
3	Wing, James Badger; Ise, Wataru; Kurosaki, Tomohiro; Sakaguchi, Shimon. Regulatory T Cells Control Antigen-Specific Expansion of Tfh Cell Number and Humoral Immune Responses via the Coreceptor CTLA-4. Immunity 41:1013-1025, 2014.
4	Matsumoto, Masanori; Baba, Akemi; Yokota, Takafumi; Nishikawa, Hiroyoshi; Ohkawa, Yasuyuki; Kayama, Hisako; Kallies, Axel; Nutt, Stephen L.; Sakaguchi, Shimon; Takeda, Kiyoshi; Kurosaki, Tomohiro; Baba, Yoshihiro. Interleukin-10-Producing Plasmablasts Exert Regulatory Function in Autoimmune Inflammation. Immunity 41:1040-1051, 2014.
5	Tanaka, Takashi; Shibazaki, Azusa; Ono, Rumiko; Kaisho, Tsuneyasu. HSP70 mediates degradation of the p65 subunit of nuclear factor kappa B to inhibit inflammatory signaling. Science Signaling 7:119, 2014.
6	Nakai, Akiko; Hayano, Yuki; Furuta, Fumika; Noda, Masaki; Suzuki, Kazuhiro. Control of lymphocyte egress from lymph nodes through beta(2)-adrenergic receptors. Journal of Experimental Medicine 211:2583-2598, 2014.
7	Tanaka, Shinya; Tanaka, Kentaro; Magnusson, Fay; Chung, Yeonseok; Martinez, Gustavo J.; Wang, Yi-Hong; Nurieva, Roza I.; Kurosaki, Tomohiro; Dong, Chen. CCAAT/Enhancer-Binding Protein alpha Negatively Regulates IFN-gamma Expression in T Cells. Journal of Immunology 193:6152-6160, 2014.
8	Vandenbon, Alexis; Teraguchi, Shunsuke; Takeuchi, Osamu; Suzuki, Yutaka; Standley, Daron M.. Dynamics of enhancers in myeloid antigen presenting cells upon LPS stimulation. Bmc Genomics 15:S4, 2014.
9	Hitomi, Yutaka; Aoki, Kazuki; Miyachi, Ryosuke; Ohyama, Junya; Kodera, Masahito; Tanaka, Tsunehiro; Sugihara, Fuminori. Gold Nanoparticles Coated with Manganese-Porphyrin That Effectively Shorten the Longitudinal Relaxation Time of Water Molecules Depending on the Particle Size. Chemistry Letters 43:1901-1903, 2014.
10	Hendron, Eunan; Wang, Xizhuo; Zhou, Yandong; Cai, Xiangyu; Goto, Jun-Ichi; Mikoshiba, Katsuhiko; Baba, Yoshihiro; Kurosaki, Tomohiro; Wang, Youjun; Gill, Donald L.. Potent functional uncoupling between STIM1 and Orai1 by dimeric 2-aminodiphenyl borinate analogs. Cell Calcium 56:482-492, 2014.
11	Morishima, Atsuyoshi; Hirano, Toru; Nishikawa, Hiroyoshi; Nakai, Kei; Sakaguchi, Shimon; Kumanogoh, Atsushi. Comprehensive exploration of autoantibody in Behcet's disease: A novel autoantibody to claudin-1, an essential protein for tight junctions, is identified. Joint Bone Spine 81:546-548, 2014.
12	Yamazaki, Sayuri; Nishioka, Akiko; Kasuya, Saori; Ohkura, Naganari; Hemmi, Hiroaki; Kaisho, Tsuneyasu; Taguchi, Osamu; Sakaguchi, Shimon; Morita, Akimichi. Homeostasis of Thymus-Derived Foxp3(+) Regulatory T Cells Is Controlled by Ultraviolet B Exposure in the Skin. Journal of Immunology 193:5488-5497, 2014.

13	Schubert, Desiree; Bode, Claudia; Kenefeck, Rupert; Hou, Tie Zheng; Wing, James B.; Kennedy, Alan; Bulashevska, Alla; Petersen, Britt-Sabina; Schaeffer, Alejandro A.; Gruening, Bjoern A.; Unger, Susanne; Frede, Natalie; Baumann, Ulrich; Witte, Torsten; Schmidt, Reinhold E.; Dueckers, Gregor; Niehues, Tim; Seneviratne, Suranjith; Kanariou, Maria; Speckmann, Carsten; Ehl, Stephan; Rensing-Ehl, Anne; Warnatz, Klaus; Rakhmanov, Mirzokhid; Thimme, Robert; Hasselblatt, Peter; Emmerich, Florian; Cathomen, Toni; Backofen, Rolf; Fisch, Paul; Seidl, Maximilian; May, Annette; Schmitt-Graeff, Annette; Ikemizu, Shinji; Salzer, Ulrich; Franke, Andre; Sakaguchi, Shimon; Walker, Lucy S. K.; Sansom, David M.; Grimbacher, Bodo. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nature Medicine 20:1410-1416, 2014.
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16	Tokunaga, Masahiro; Kokubu, Chikara; Maeda, Yusuke; Sese, Jun; Horie, Kyoji; Sugimoto, Nakaba; Kinoshita, Taroh; Yusa, Kosuke; Takeda, Junji. Simulation and estimation of gene number in a biological pathway using almost complete saturation mutagenesis screening of haploid mouse cells. Bmc Genomics 15:1016, 2014.
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19	Yamashita, Kazuo; Ikeda, Kazuyoshi; Amada, Karlou; Liang, Shide; Tsuchiya, Yuko; Nakamura, Haruki; Shirai, Hiroki; Standley, Daron M.. Kotai Antibody Builder: automated high-resolution structural modeling of antibodies. Bioinformatics 30:3279-3280, 2014.
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29	Franchi, Luigi; Eigenbrod, Tatjana; Munoz-Planillo, Raul; Ozkurede, Ulas; Kim, Yun-Gi; Chakrabarti, Arindam; Gale, Michael, Jr.; Silverman, Robert H.; Colonna, Marco; Akira, Shizuo; Nunez, Gabriel. Cytosolic Double-Stranded RNA Activates the NLRP3 Inflammasome via MAVS-Induced Membrane Permeabilization and K+ Efflux. Journal of Immunology 193:4214-4222, 2014.
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31	Saito, Takuro; Wada, Hisashi; Yamasaki, Makoto; Miyata, Hiroshi; Nishikawa, Hiroyoshi; Sato, Eiichi; Kageyama, Shinichi; Shiku, Hiroshi; Mori, Masaki; Doki, Yuichiro. High expression of MAGE-A4 and MHC class I antigens in tumor cells and induction of MAGE-A4 immune responses are prognostic markers of CHP-MAGE-A4 cancer vaccine. Vaccine 32:5901-5907, 2014.
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37	Piao, Zhenyu; Akeda, Yukihiro; Takeuchi, Dan; Ishii, Ken J.; Ubukata, Kimiko; Briles, David E.; Tomono, Kazunori; Oishi, Kazunori. Protective properties of a fusion pneumococcal surface protein A (PspA) vaccine against pneumococcal challenge by five different PspA clades in mice. Vaccine 32:5607-5613, 2014.
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39	Ma, Ji Su; Sasai, Miwa; Ohshima, Jun; Lee, Youngae; Bando, Hironori; Takeda, Kiyoshi; Yamamoto, Masahiro. Selective and strain-specific NFAT4 activation by the Toxoplasma gondii polymorphic dense granule protein GRA6. Journal of Experimental Medicine 211:2013-2032, 2014.

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171	Kinoshita, Taroh. Biosynthesis and deficiencies of glycosylphosphatidylinositol. Proceedings Of The Japan Academy Series B-Physical And Biological Sciences 90:130-143, 2014.
172	Nishikawa, Hiroyoshi; Sakaguchi, Shimon. Regulatory T cells in cancer immunotherapy. Current Opinion in Immunology 27:1-7, 2014.
173	Simmons, Szandor; Ishii, Masaru. Sphingosine-1-Phosphate: a Master Regulator of Lymphocyte Egress and Immunity. Archivum Immunologiae Et Therapiae Experimentalis 62:103-115, 2014.
174	Karagiannis, Peter; Ishii, Yoshiharu; Yanagida, Toshio. Molecular Machines Like Myosin Use Randomness to Behave Predictably. Chemical Reviews 114:3318-3334, 2014.
175	Tanaka, Toshio; Narazaki, Masashi; Ogata, Atsushi; Kishimoto, Tadamitsu. A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade strategy. Seminars in Immunology 26:88-96, 2014.
176	Wing, James B.; Sakaguchi, Shimon. Foxp3 T-reg cells in humoral immunity. International Immunology 26:61-69, 2014.

177	Ogura, Hideki; Atsumi, Toru; Bando, Hidenori; Sabharwal, Lavannya; Yamada, Moe; Jiang, Jing-Jing; Nakamura, Akihiro; Arima, Yasunobu; Kamimura, Daisuke; Murakami, Masaaki. The Reverse-Direction Method Links Mass Experimental Data to Human Diseases. Archivum Immunologiae Et Therapiae Experimentalis 62:41-45, 2014.
178	Nyati, Kishan Kumar; Prasad, Kashi Nath. Role of Cytokines and Toll-Like Receptors in the Immunopathogenesis of Guillain-Barre Syndrome. Mediators Of Inflammation :758639, 2014.
179	Morimoto, Yasuo; Izumi, Hiroto; Kuroda, Etsushi. Significance of Persistent Inflammation in Respiratory Disorders Induced by Nanoparticles. Journal of Immunology Research :962871, 2014.
180	Yoshida, Yuji; Tanaka, Toshio. Interleukin 6 and Rheumatoid Arthritis. Biomed Research International :698313, 2014.
181	Atsumi, Toru; Singh, Rajeev; Sabharwal, Lavannya; Bando, Hidenori; Meng, Jie; Arima, Yasunobu; Yamada, Moe; Harada, Masaya; Jiang, Jing-Jing; Kamimura, Daisuke; Ogura, Hideki; Hirano, Toshio; Murakami, Masaaki. Inflammation Amplifier, a New Paradigm in Cancer Biology. Cancer Research 74:8-14, 2014.

3. Proceedings

No	ARTICLE
182	Goritzka, M.; Durant, L.; Pereira, C.; Makris, S.; Kausar, F.; Kumagai, Y.; Akira, S.; Johansson, C.. Alveolar macrophage-derived type I IFNs orchestrate immune responses to RSV through recruitment of antiviral monocytes. Immunology 143:104-104, 2014.
183	Fujita, Morihisa; Lee, Gun-Hee; Murakami, Yoshiko; Kanzawa, Noriyuki; Maeda, Yusuke; Kinoshita, Taroh. Shedding of GPI-anchored proteins by a novel GPI cleaving enzyme. Glycobiology 24:1102-1103, 2014.
184	Hirata, Tetsuya; Fujita, Morihisa; Nakamura, Shota; Gotoh, Kazuyoshi; Motooka, Daisuke; Murakami, Yoshiko; Maeda, Yusuke; Kinoshita, Taroh. Endosomes-to-TGN retrograde transport mediated by GARP is required for post-Golgi anterograde transport and glycosylation. Glycobiology 24:1188-1189, 2014.
185	Akira, Shizuo. Regnase-1, a ribonuclease involved in the inflammatory and immune responses. Cytokine 70:21-21, 2014.
186	Lee, Soyoung; Ripley, Barry; Chinen, Ichino; Millrine, David; Kishimoto, Tadamitsu. Aryl hydrocarbon receptor negatively regulates type I interferon production and the development of murine lupus. Cytokine 70:54-54, 2014.
187	Mori, Yuki; Yoshioka, Yoshichika. Non-invasive single cell-tracking in mouse brain by using time-lapse MRI. Journal of Neuroimmunology 275:23-23, 2014.
188	Schulz, E.; Klampfl, P.; Holzapfel, S.; Janeke, A. R.; Ulz, P.; Renner, W.; Kashofer, K.; Najima, S.; Leitner, A.; Zebisch, A.; Woelfler, A.; Hofer, S.; Gerger, A.; Lax, S.; Beham-Schmid, C.; Steinke, V; Geigl, J. B.; Hoefler, G.; Speicher, M. R.; Boland, C. R.; Kumanogoh, A.; Sill, H.. Germline variants in the semaphorin SEMA4A confer susceptibility to familial colorectal cancer type X. Oncology Research And Treatment 37:105-105, 2014.
189	Ohtsuka, Masato; Miura, Hiromi; Kimura, Minoru; Isotani, Ayako; Ikawa, Masahito; Sato, Masahiro; Gurumurthy, Channabasavaiah. Concurrent production of multiple targeted transgenic mouse lines with C57BL/6N genetic background by improved PITT. Transgenic Research 23:855-856, 2014.
190	Haseda, F.; Imagawa, A.; Nishikawa, H.; Mitsui, S.; Tsutsumi, C.; Fujisawa, R.; Sano, H.; Murase-Mishiba, Y.; Terasaki, J.; Sakaguchi, S.; Hanafusa, T.. A novel autoantibody detected in patients with fulminant type 1 diabetes. Diabetologia 57:S185-S185, 2014.
191	Briquez, P.; Tortelli, F.; Martino, M.; Pisano, M.; Hubbell, J.. Extracellular matrix molecules regulate growth factor and cytokine delivery through their heparin-binding domains and promote wound healing. Journal of Tissue Engineering And Regenerative Medicine 8:189-189, 2014.
192	Henmi, Masahisa; Tachibana, Masashi; Tsuzuki, Sayaka; Shoji, Masaki; Sakurai, Fuminori; Kobiyama, Koji; Ishii, Ken J.; Akira, Shizuo; Mizuguchi, Hiroyuki. Type I IFN Signaling Induced By Systemically Administrated Adenovirus Vector Promotes the Antigen-Specific Mucosal Immunity. Molecular Therapy 22:S272-S272, 2014.

193	Hartmann, J.; Karl, R. M.; Alexander, R. P. D.; Adelsberger, H.; Brill, M. S.; Ruehlmann, C.; Ansel, A.; Sakimura, K.; Baba, Y.; Kurosaki, T.; Misgeld, T.; Konnerth, A.. STIM1 regulates neuronal Ca(2+)stores, mGluR1 signaling in cerebellar Purkinje cells and motor coordination. Acta Physiologica 210:68-68, 2014.
194	Morikawa, Takamitsu J.; Machiyama, Hiroaki; Okamoto, Kazuko; Yoshizawa, Keiko; Fujita, Hideaki; Ichimura, Taro; Imada, Katsumi; Nagai, Takaharu; Yanagida, Toshio; Watanabe, Tomonobu M.. Evaluating Intracellular Crowded with a Glycine-Inserted Mutant Fluorescent Protein. Biophysical Journal 106:19A-19A, 2014.
195	Kakizuka, Taishi; Ichimura, Taro; Fujita, Hideaki; Watanabe, Tomonobu M.. Simultaneous Tracking of Multiple Myosins in Sub-Diffraction Scale Based on Spectral Division. Biophysical Journal 106:570A-570A, 2014.

B. WPI-related papers; NONE

B. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY2014 in order from most recent.
- For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

No.	Lecturer/presenter names and details
1	Taroh Kinoshita/Gordon Research Conference on Glycobiology, "Shedding of Cripto-1 by PGAP6, a membrane-bound, GPI-specific phospholipase A2", Italy, March 4, 2015.
2	Kiyoshi Takeda/2nd Hengstberger Symposium on Microbial sensors in the B lymphocyte response "Regulation of antibody responses in the appendix", Heidelberg, Germany, January 7, 2015.
3	Hisashi Arase/France-Japan Immunology Meeting 2014, "Cellular misfolded proteins complexed with MHC class II molecules are targets for autoantibodies in autoimmune diseases Cassis", France, October 23, 2014.
4	Tomohiro Kurosaki/ The 2nd Symposium of International Immunological Memory and Vaccine Forum, "Mechanisms underlying rapid memory IgG responses", USA, August 26, 2014.
5	Takashi Saito/ FASEB Science Research Conference, "Direct sensing of nucleotides by T cells induces Th2 differentiation", Snowmass, USA, June 30, 2014.
6	Shizuo Akira/The 1st KI-OU Joint Symposium, "Regnase-1, an endoribonuclease regulating", Sweden, June 10, 2014.
7	Ken Ishii/WHO Meetings of Stakeholders for Selected Health R&D Demonstration Project, "Experience of clinical development of CpG ODN in vaccine", Geneva, Switzerland, May 7, 2014.
8	Cevayir Coban/The 2nd International Molecular Immunology & Immunogenetics Congress, "Host-Pathogen Interactions in the Context of Malaria", Antalya, Turkey, April 27, 2014.
9	Shizuo Akira/Distinguished Ludwig Lecture Series, "Regnase-1, a ribonuclease involved in the immune regulation", Switzerland, April 24, 2014.
10	Shigekazu Nagata/The Henry Kunkel Lecture 2014, "Human Immunology in Health and Disease", New York, April 3, 2014.

C. Major Awards

- List up to 10 main awards received during FY2014 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.

No.	Recipient names and details
1	Shimon Sakaguchi; The Gairdner International Prize 2015 "for his discovery of regulatory T cells, characterization of their role in immunity and application to the treatment of autoimmune diseases and cancer"
2	Shizuo Akira; The Member of the Japan Academy
3	Toshio Yanagida; Honorary Member of the Physical Society of Japan
4	Takashi Satoh; Young Investigator Award 2014, Japanese Society for Immunology
5	Masaru Ishii; JSPS Award 2014, The Japan Society for the Promotion of Science
6	Ken Ishii; Osaka Science Prize 2014, Osaka city & Osaka prefecture
7	Kazutaka Kato; Young Scientist Initiative Award 2014, Society of Evolutional Studies, Japan
8	Shizuo Akira, Ken Ishii, Masahiro Yamamoto; Thomson Reuters "Highly Cited Researchers"
9	Kenta Maruyama; Takenaka Award 2014, Astellas Foundation for Research on Metabolic Disorders
10	Ben Seymour; NICT Award of Excellence 2014, National Institute of Information and Communications Technology

FY 2014 List of Principal Investigators

NOTE:
・Underline names of principal investigators who belong to an overseas research institution.
・In case of researchers not listed in the latest report, attach "Biographical Sketch of a New Principal Investigator".

<Results at the end of FY2014>

Principal Investigators Total:

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 Shizuo Akira* (62)	Director and Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	90%	10%	0%	0%	01/10/2007	Usually stays at IFReC	
Tadamitsu Kishimoto* (75)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	70%	0%	30%	0%	01/11/2007	Usually stays at IFReC	
Hitoshi Kikutani* (64)	Professor, Research Institute for Microbial Diseases, Osaka University	MD, PhD (Immunology)	70%	10%	20%	0%	01/10/2007	Usually stays at IFReC	
Taroh Kinoshita* (63)	Professor and Deputy Director, WPI Immunology Frontier Research Center, Osaka University	PhD (Immunology, Biochemistry)	66%	4%	0%	30%	01/10/2007	Usually stays at IFReC	

Atsushi Kumanogoh* (48)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	50%	0%	0%	50%	01/10/2007	Usually stays at IFReC	
Kiyoshi Takeda* (48)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	70%	0%	0%	30%	01/11/2007	Usually stays at IFReC	
Hisashi Arase* (49)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	95%	0%	0%	5%	01/10/2007	Usually stays at IFReC	
Shimon Sakaguchi* (64)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	50%	10%	17%	23%	01/12/2007	Usually stays at IFReC	
Takashi Saito* (64)	Group Director, RIKEN, Research Center for Integrative Medical Sciences	PhD (Immunology)	20%	0%	70%	10%	03/12/2007	Usually stays at RIKEN IMS satellite	
Tomohiro Kurosaki* (59)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology and molecular biology)	80%	10%	10%	0%	03/12/2007	Usually stays at IFReC	
Fritz Melchers* (78)	Max Planck Fellow	PhD (Immunology)	10%	0%	10%	80%	01/10/2007	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	

Toshio Yanagida* (68)	Professor, Graduate School of Frontier Biosciences, Osaka University	PhD (Molecular imaging)	25%	0%	65%	10%	01/11/2007	Usually stays at IFReC	
Yoshichika Yoshioka* (61)	Professor, WPI Immunology Frontier Research Center, Osaka University	DSc (Biophysics)	100%	0%	0%	0%	01/02/2008	Usually stays at IFReC	
Yutaka Hata* (53)	Professor, Graduate School of Engineering, University of Hyogo	PhD (Computer Engineering)	20%	0%	30%	50%	10/12/2007	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	
Daron M. Standley (47)	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Chemistry)	100%	0%	0%	0%	01/10/2008	Usually stays at IFReC	
Jun Hatazawa* (61)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Nuclear Medicine)	5%	5%	45%	45%	16/01/2009	Usually stays at IFReC	
Masaru Ishii (41)	Professor, Graduate School of Frontier Biosciences, Osaka University	MD, PhD (Bioimaging)	30%	0%	70%	0%	01/12/2008	Usually stays at IFReC	
Kazuya Kikuchi (49)	Professor, Graduate School of Engineering, Osaka University	PhD (Chemical Biology)	28%	2%	50%	20%	01/08/2009	Usually stays at IFReC	

Cevayir Coban (42)	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Clinical Microbiiology)	100%	0%	0%	0%	01/04/2008	Usually stays at IFReC	
Nicholas Isaac Smith (40)	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Engineering / Applied Physics)	100%	0%	0%	0%	01/06/2009	Usually stays at IFReC	
Ken Ishii* (46)	Project Leader, National Institute of Biomedical Innovation (NIBIO)	MD, PhD (Immunology, Vaccine Science)	5%	5%	85%	5%	01/11/2007	He visits his laboratory at IFReC once a week.	
Tsuneyasu Kaisho* (55)	Professor, WPI Immunology Frontier Research Center	MD, PhD (Immunology)	100%	0%	0%	0%	01/03/2011	Usually stays at IFReC	
Kazuhiro Suzuki (39)	Associate Professor, WPI Immunology Frontier Research Center	MD, PhD (Immune cell dynamics	100%	0%	0%	0%	01/04/2011	Usually stays at IFReC	
Rikinari Hanayama (40)	Associate Professor, WPI Immunology Frontier Research Center	MD, PhD (Cell Biology)	100%	0%	0%	0%	01/10/2011	Usually stays at IFReC	
Masahiro Yamamoto (36)	Professor, Research Institute for Microbial Diseases, Osaka University	PhD (Immunology)	90%	10%	0%	0%	01/04/2012	Usually stays at IFReC	

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	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Nagata Shigekazu* (65)	Professor, Department of Medical Chemistry Graduate School of Medicine, Kyoto University	PhD (Science)	5%	10%	55%	30%	01/04/2014	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	Prof. Patric Willamson (USA) spent two months sabbatical (June-August)
Seymour Benjamin John (42)	NICT Invited Executive Researcher and Wellcome Trust Intermediate Clinical Fellow (Cambridge University)	PhD (Neurological Science)	20%	5%	65%	10%	01/04/2014	He visits his laboratory at IFReC once a week.	

Biographical Sketch of a New Principal Investigator

Name (Age)	Ben Seymour (42)
Affiliation (Position title, department, organization)	Specially Appointed Professor (IFReC), Principle Investigator (NICT, CiNet) Wellcome Clinical Fellow, Cambridge University
Academic degree, specialty	MRCP (Medicine), PhD (Neuroscience)

Research and education history

Ben Seymour is a neurologist and neuroscientist working jointly in the Computational and Biological Learning Lab in Cambridge University, and the Center for Information and Neural Networks (CiNet) and IFReC in Osaka, Japan. He trained in neurology in London and Cambridge, and in imaging neuroscience at the Wellcome Trust Centre for Neuroimaging at UCL, where he developed his research in computational and systems neuroscience.

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.)*

Ben Seymour is a computational neuroscientist studying the nature of pain. He has mapped out the basic architecture of the pain system in the brain, using a combination of neuroimaging techniques, primarily in humans.

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.*

2015 NICT Award for Excellence.
2015 Guest Professor, Graduate School of Frontier Biosciences, Osaka University
2014 Japanese Society for the Study of Pain International Conference Keynote Lecture
2013 European Federation of IASP Chapter International Conference Plenary Address
2012 Wellcome Trust Clinical Fellowship
2010 Queen Square Prize for Neurology
2008 Fellowship of the Royal Society of Arts

Editorial Board: Scientific Reports, Neuroimage, F1000 Research, Frontiers in Neuroscience.

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

2014 -2017 JSPS Strategic International Research Exchange, Co-PI.
2014 -2017 Ministry of Health, Labor and Welfare, Co-investigator
2014 UK Consulate: International Conference Grant (PI)
2014 -2017 NICT International Cooperation Award (PI)
2014- 2017 W. D. Armstrong Award for PhD Studentship (PI)
2014- 2015 Great British Sasakawa Foundation (PI)
2013 -2018 MEXT 'Nou-Pro' Consortium member
2013 -2017 Wellcome Trust Clinical Fellowship (PI)
2011 -2015 Wellcome Trust Henry Wellcome Fellowship (Collaborator)

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

Empathy for pain involves the affective but not sensory components of pain
T Singer, B Seymour, J O'Doherty, H Kaube, RJ Dolan, CD Frith
Science 303 (5661), 1157-1162
Cites 2479

Empathic neural responses are modulated by the perceived fairness of others
T Singer, B Seymour, JP O'Doherty, KE Stephan, RJ Dolan, CD Frith
Nature 439 (7075), 466-469
Cites 1104

Cortical substrates for exploratory decisions in humans
ND Daw, JP O'Doherty, P Dayan, B Seymour, RJ Dolan
Nature 441 (7095), 876-879
Cites 911

Frames, biases, and rational decision-making in the human brain
B De Martino, D Kumaran, B Seymour, RJ Dolan
Science 313 (5787), 684-687
Cites 840

Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans
M Pessiglione, B Seymour, G Flandin, RJ Dolan, CD Frith
Nature 442 (7106), 1042-1045
Cites 684

Temporal difference models describe higher-order learning in humans
B Seymour, JP O'Doherty, P Dayan, M Koltzenburg, AK Jones, RJ Dolan, ...
Nature 429 (6992), 664-667
Cites 402

When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans
D Mobbs, P Petrovic, JL Marchant, D Hassabis, N Weiskopf, B Seymour, ...
Science 317 (5841), 1079-1083
Cites 336

Differential encoding of losses and gains in the human striatum
B Seymour, N Daw, P Dayan, T Singer, R Dolan
The Journal of Neuroscience 27 (18), 4826-4831
Cites 266

Opponent appetitive-aversive neural processes underlie predictive learning of pain relief
B Seymour, JP O'doherty, M Koltzenburg, K Wiech, R Frackowiak, ...
Nature neuroscience 8 (9), 1234-1240
Cites 225

The neurobiology of punishment
B Seymour, T Singer, R Dolan
Nature Reviews Neuroscience 8 (4), 300-311
Cites 177

Emotion, decision making, and the amygdala
B Seymour, R Dolan
Neuron 58 (5), 662-671
Cites 148

A key role for similarity in vicarious reward
D Mobbs, R Yu, M Meyer, L Passamonti, B Seymour, AJ Calder, ...
Science 324 (5929), 900-900
Cites 130

Primary antibody deficiency and diagnostic delay
B Seymour, J Miles, M Haeney
Journal of clinical pathology 58 (5), 546-547
Cites 94

Anchors, scales and the relative coding of value in the brain
B Seymour, SM McClure
Current opinion in neurobiology 18 (2), 173-178
Cites 80

Serotonin selectively modulates reward value in human decision-making
B Seymour, ND Daw, JP Roiser, P Dayan, R Dolan
The Journal of Neuroscience 32 (17), 5833-5842
Cites 56

Pain: a distributed brain information network?
H Mano, B Seymour
Cites PLoS biology 13 (1), e1002037

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

Biographical Sketch of a New Principal Investigator

Name (Age)	Nagata, Shigekazu (65)
Affiliation (Position title, department, organization)	Professor, Department of Medical Chemistry, Graduate School of Medicine, Kyoto University Osaka University Guest Professor
Academic degree, specialty	Ph.D (Science), Biochemistry and Molecular Biology

Research and education history

Apr. 1977-Oct. 1977	Research Associate at the Department of Chemistry, Institute of Medical Science, University of Tokyo
Nov. 1977-Dec. 1981	Post-Doctoral Fellow at the Institute of Molecular Biology I, University of Zürich
Jan. 1982-Mar. 1987	Assistant Professor at the Institute of Medical Science, University of Tokyo
Apr. 1987-Mar. 1998	Head, Department of Molecular Biology, Osaka Bioscience Institute
Jul. 1995-Mar. 2002	Professor, Department of Genetics, Osaka University Medical School
Apr. 2002-Mar. 2007	Professor, Integrated Biology Laboratories, Graduate School of Frontier Bioscience, Osaka University
Apr. 2007-Mar.2015	Professor, Department of Medical Chemistry, Graduate School of Medicine, 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.)*

After obtaining a Ph.D. in 1977 from University of Tokyo, Dr. Nagata did his post-doctoral training in University of Zürich, where he identified human interferon-α cDNA. In 1982, he returned as an assistant professor to University of Tokyo, and identified cDNA for granulocyte colony-stimulating factor (G-CSF). Interferon and G-CSF are now produced in a large scale using the cDNAs that were identified by Dr. Nagata, and widely used for patients of hepatitis and cancer, respectively. In 1987, Dr. Nagata became a Department Head in Osaka Bioscience Institute, and started a project on apoptosis. He identified the Fas and Fas ligand system that induce apoptosis, and elucidated its signal transduction. In 1995, Dr. Nagata moved as a professor to Osaka University Medical School, where his group elucidated the molecular mechanism of the engulfment of apoptotic cells by macrophages, and its physiological and pathological roles. He then became a professor in the Graduate School of Medicine, Kyoto University in 2007, and remained there until March, 2015. In Kyoto University, his group identified molecules (scramblase and flippase) that regulate the distribution of phospholipids at plasma membranes. Dr. Nagata was frequently invited to give Keynote Address or Plenary Lectures in various conferences such as Gordon Conference, Keystone Meetings, and Cold Spring Harbor Meeting. Dr. Nagata was an editorial member for Science, Immunity, Cancer Cell, and others. Awards include Emil von Behring Prize, Robert Koch Award, Prix Lacassagne, Debrecen Award, and Keio Medical Science Prize. He was recognized as a Person of Cultural Merit from the Japanese Government, and has been an associate of Japan Academy since 2010.

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.*

a) Guest speaker, chair, director, or honorary member of a major international academic society in the subject field

May 1994	Keynote Address, 5th International Conference on Tumor Necrosis Factor and Related Cytokines, Monterey, California, USA
Oct. 1994	Keynote Address, ASMBM Fall Symposium "Genetic and Biochemical Approaches for Studying Cell Death", Lake Tahoe, California, USA
Oct. 1996	Co-Organizers, Programmed Cell Death, AACR Special Conference on Cancer Research, Lake George, New York, USA
Sep. 1997	Keynote Address, The Second Cold Spring Harbor Meeting on Programmed Cell Death, Cold Spring Harbor, New York, USA
Nov. 1999	Keynote Address, Euroconference on Apoptosis, Ein Gedi, Israel
Jan. 2000	Keynote Address, Keystone Symposia on "Cellular Immunity and Immunotherapy of Cancer", Santa Fe, New Mexico, USA
Feb. 2003	Keynote Address, Keystone Symposia on Molecular Mechanism of Apoptosis, BANFF, Canada
Feb. 2004	Keynote Address, Keystone Symposium on Apoptosis in Development, Keystone, Colorado, USA
Jan. 2005	Keynote Address, AACR Special Conference on Regulation of Cell Death in Oncogenesis, Wikoloa Village, Hawaii, USA
Jun. 2005	Keynote Address, Gordon Research Conference on Apoptotic Cell Recognition & Clearance, New London, Connecticut, USA
Mar. 2006	Keynote Address, The 6th Hunter Cellular Biology Meeting, Hunter Valley NSW, Australia
Oct. 2009	Organizer, The 2009 Cold Spring Harbor meeting on "Cell Death", The Cold Spring Harbor Laboratory, New York, USA
May 2011	Organizer, The 13th International Conference on Tumor Necrosis Factor, Awaji, Japan

b) Holder of a prestigious lectureship

Aug. 1997	Chester Beatty Lecture, 17th International Congress of Biochemistry and Molecular Biology, San Francisco, USA
Sep. 1997	Seventy-eighth Mellon Lecture, University of Pittsburgh Medical Center, Pennsylvania, USA
May 2008	The Marian Elliott Koshland Memorial Lecture, Chicago University, Chicago, U.S.A.
Dec. 2010	2010 Charles Janeway Lecture, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia
May 2012	Edwin J. Cohn Lecture, The Harvard Medical School, Boston, USA
Apr. 2014	The Henry Kunkel Lecture 2014 at The Rockefeller University, New York, USA

c) Member of a scholarly academy and honorary doctor in a major country

Apr. 2012	Honorary Doctor from University of Zurich, Switzerland

d) Recipient of an international award(s)

Nov. 1994	Emil von Boehring Prize (Marburg Univ., Germany)
Oct. 1995	Robert Koch Award (Koch Foundation, Germany)
Jan. 1997	Prix Laccasagne (French National Cancer League, France)
Dec. 2012	Debrecen Award for Molecular Medicine, Debrecen University (Hungary)
Jul. 2013	The Keio Medical Science Prize (Keio University, Tokyo)

e) Editor of an influential journal etc.

1994-present	Cell Death & Differentiation
1998-present	Immunity
2000-2003	Science
2001-present	Cancer Cell

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

Grants-in-Aid for Scientific Research
Specially Promoted Research (22000013) 2010-2014
"Molecular mechanism of engulfment and degradation of dead cells in macrophages"
JP¥ 318,700,000（2010:JP¥ 64,900,000 / 2011:JP¥ 64,100,000 / 2012:JP¥ 64,100,000 / 2013:JP¥ 64,100,000 / 2014:JP¥ 61,500,000）

Japan Science Technology Agency-CREST

「Etiological basics of and techniques for treatment of allergic and autoimmune diseases」(Research Supervisor: Kazuo Sugamura)
"Disease caused by defects in engulfment and degradation of apoptotic cells"(08062225) 2008-2012
JP¥ 280,000,000（2008:JP¥ 20,000,000 / 2009:JP¥ 64,000,000 / 2010: JP¥ 67,800,000 / 2011:JP¥ 66,000,000 / 2012:JP¥ 62,200,000）

「Structural Life Science and Advanced Core Technologies for Innovative Life Science Research」(Research Supervisor: Keiji Tanaka)
"Asymmetrical distribution of phospholipids and its breakdown"(14530266) 2014-2020
2017: JP¥ 53,500,000

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

Nagata, S. (1997). Apoptosis by death factor. **Cell** *88*, 355-365. (times cited: **3870**)

Nagata, S., and Golstein, P. (1995). The Fas death factor. **Science** *267*, 1449-1456. (times cited: **3691)**

Itoh, N., Yonehara, S., Ishii, A., Yonehara, M., Mizushima, S., Sameshima, M., Hase, A., Seto, Y., and Nagata, S. (1991). The polypeptide encoded by the cDNA for human cell surface antigen Fas can mediate apoptosis. **Cell** *66*, 233-243. (times cited **2560)**

Enari, M., Sakahira, H., Yokoyama, H., Okawa, K., Iwamatsu, A., and Nagata, S. (1998). A caspase-activated DNase that degrades DNA during apoptosis and its inhibitor ICAD. **Nature** *391*, 43-50. (times cited **2384)**

Suda, T., Takahashi, T., Golstein, P., and Nagata, S. (1993). Molecular cloning and expression of the Fas ligand: a novel member of the tumor necrosis factor family. **Cell** *75*, 1169-1178. (times cited **2292)**

Watanabe-Fukunaga, R., Brannan, C.I., Copeland, N.G., Jenkins, N.A., and Nagata, S. (1992). Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. **Nature** *356*, 314-317. (times cited **2285)**

Ogasawara, J., Watanabe-Fukunaga, R., Adachi, M., Matsuzawa, A., Kasugai, T., Kitamura, Y., Itoh, N., Suda, T., and Nagata, S. (1993). Lethal effect of the anti-Fas antibody in mice. **Nature** *364*, 806-809. (times cited **1672)**

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

Records of FY2014 Center Activities

1. Researchers and center staffs, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Enter the total number of people in the columns below. In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [ ] brackets.
- In the "Administrative staffs" column, put the number and percentage of bilingual staffs in the ( ) brackets.
- In the "Final Goal" column, enter the currently projected goal at [OO month, OO year (next year of the end of WPI grant)].

	Goal set in the "Post-interim evaluation revised center project"	Results at end of FY 2014	Final goal (Date: April, 2017)
Researchers	180 <61, 34%> [38, 21%]	179 <42, 23%> [35,20%]	180 <60, 34%> [38, 21%]
Principal investigators	30 <8, 27%> [3, 10%]	27 <5, 19%> [1,4%]	30 <8, 27%> [3, 10%]
Other researchers	150 <53, 35%> [35, 23%]	152 <37, 24%> [34, 22%]	150 <53, 35%> [35, 23%]
Research support staffs	50	74	50
Administrative staffs	30	32 (19, 59%)	30 (20, 67%)
Total	260	285	260

Other matters of special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working to mobilize/circulate the world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
RIKEN Center for Integrative Medical Sciences	Takashi Saito	
Kyoto University, Institute for Frontier Medical Sciences		

The National Institute of Biomedical Innovation	Ken J. Ishii	

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
Division of Life Science & Division of Integrative Bioscience and Biotechnology, Pohang University of Science and Technology (POSTECH)		Korea
Indian institute of Science Education and Research (IISER), Bhopal		India
Seoul St. Mary's Hospital, The Catholic University of Korea Convergent Research Consortium for Immunologic Disease (CRCID)		Korea
Maurice Wilkins Center, The University of Auckland		New Zealand

2. Securing competitive research funding

- Competitive and other research funding secured in FY2014:

Total: 1,312 million yen (indirect cost is not included.)

- Describe external funding warranting special mention. Include the name and total amount of each grant.

Agency	Program	Grantee	Amount (million JPY)	Term
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (Specially Promoted Research)	Nagata	318	2010-2014
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kurosaki	195	2014-2018
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kikuchi	219	2013-2014
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Saitoh	218	2012-2016
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Hatazawa	157	2012-2016
JST	Strategic Basic Research Programs (CREST)	Arase	230	2009-2014
JST	Strategic Basic Research Programs (CREST)	Kurosaki	160	2009-2014
JST	Strategic Basic Research Programs (CREST)	Sakaguchi	370	2012-2016
JST	Strategic Basic Research Programs (CREST)	Takeda	341	2010-2016
JST	Strategic Basic Research Programs (CREST)	Ishii M.	240	2011-2015
JST	Strategic Basic Research Programs (CREST)	Kumanogoh	246	2012-2017
JST	Strategic Basic Research Programs (CREST)	Nagata	255	2014-2018

MEXT	Platform for Drug Discovery, Informatics, and Structural Life Science	Standley	98	2012-2016
MEXT	Project for Development of Innovative Research on Cancer Therapeutics	Ishii M.	44	2011-2015
MEXT	Project for Development on Innovative Research on Cancer Therapeutics	Sakaguchi	110	2014-2015
MHLW	Grants-in-Aid for Scientific Research	Ishii K.	888	2012-2016
MHLW	Grants-in-Aid for Scientific Research	Standley	46	2012-2016
MHLW	Contracted Scientific Research	Sakaguchi	110	2014-2016
JST	Strategic Basic Research Programs (PRESTO)	Hanayama	52	2012-2014
HFSP	Carrier Development Award	Hanayama	30	2011-2014
Private	Daiichi Sankyo Healthcare Co.,Ltd.	Ishii K.	80	2011-2014
Overseas	National Institute of Health (USA)	Akira	215	2012-2017

MHLW: Ministry of Health, Labor and Welfare, JST: Japan Science and Technology Agency
JSPS: Japan Society for the Promotion of Science (Unit: million yen)
HFSP: Human Frontier Science Program

3. International research conferences or symposiums held to bring world's leading researchers together

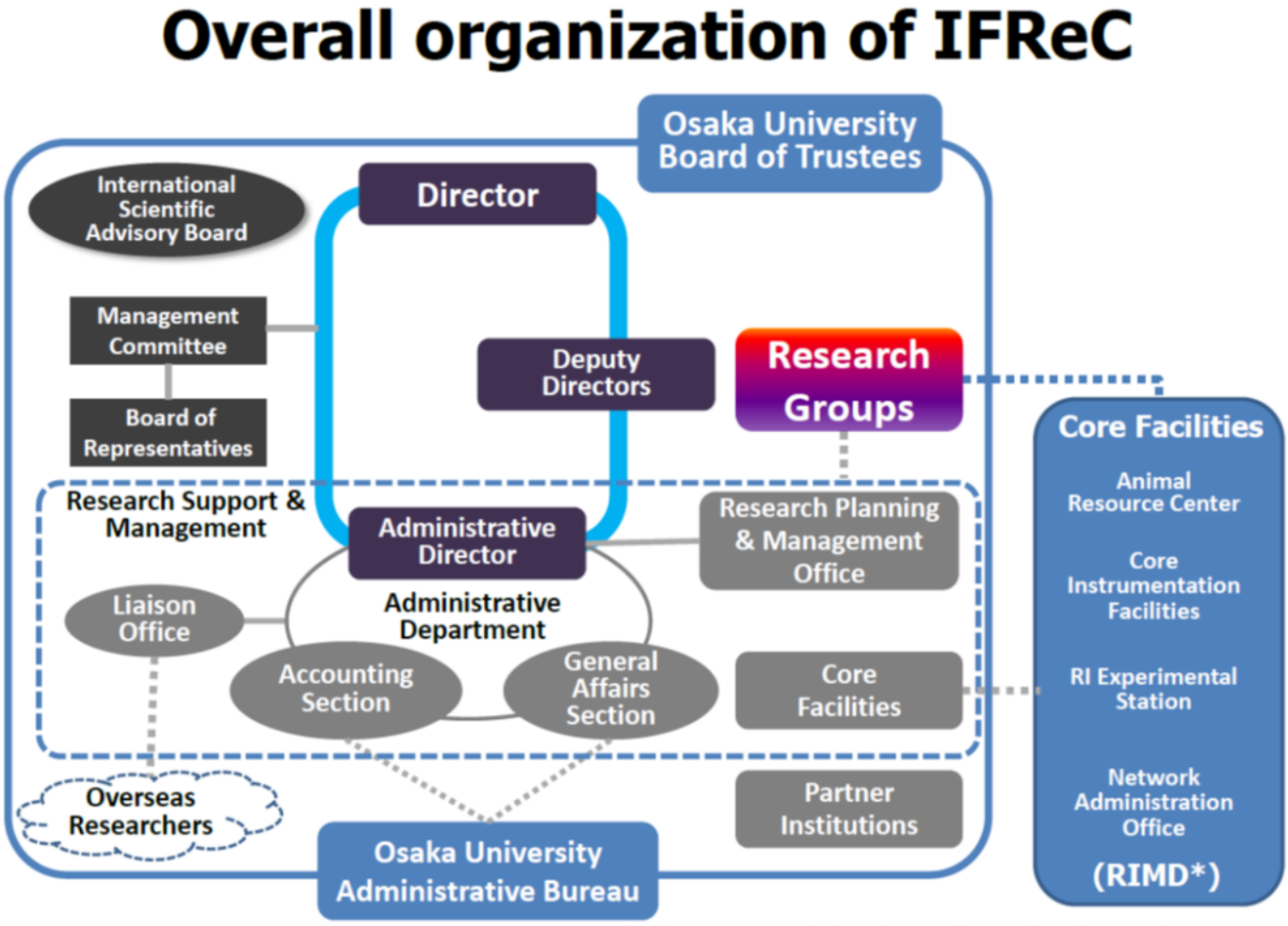
- Indicate the number of international research conferences or symposiums held in FY2014 and give up to three examples of the most representative ones using the table below.

FY 2014: Three meetings

Major examples (meeting title and place held)	Number of participants
"Immunology at the Forefront", the 6th IFReC International Symposium DATE: February 23-24, 2015 VENUE: KNOWLEDGE THEATER, Grand Front Osaka, Japan	From domestic institutions: 130 From overseas institutions: 30
"Cancer Immunotherapy Forum" presented by IFReC and Bristol-Myers DATE: November 21, 2014 VENUE: Rihga Royal Hotel Osaka	From domestic institutions: 120 From overseas institutions: 30
CiNet Conference "New Directions in Pain Neuroscience", jointly organized by CiNet and IFReC DATE: December 2-5, 2014 VENUE: Center for Information and Neural Networks (CiNet), Osaka	From domestic institutions: 138 From overseas institutions: 26

4. Center's management system

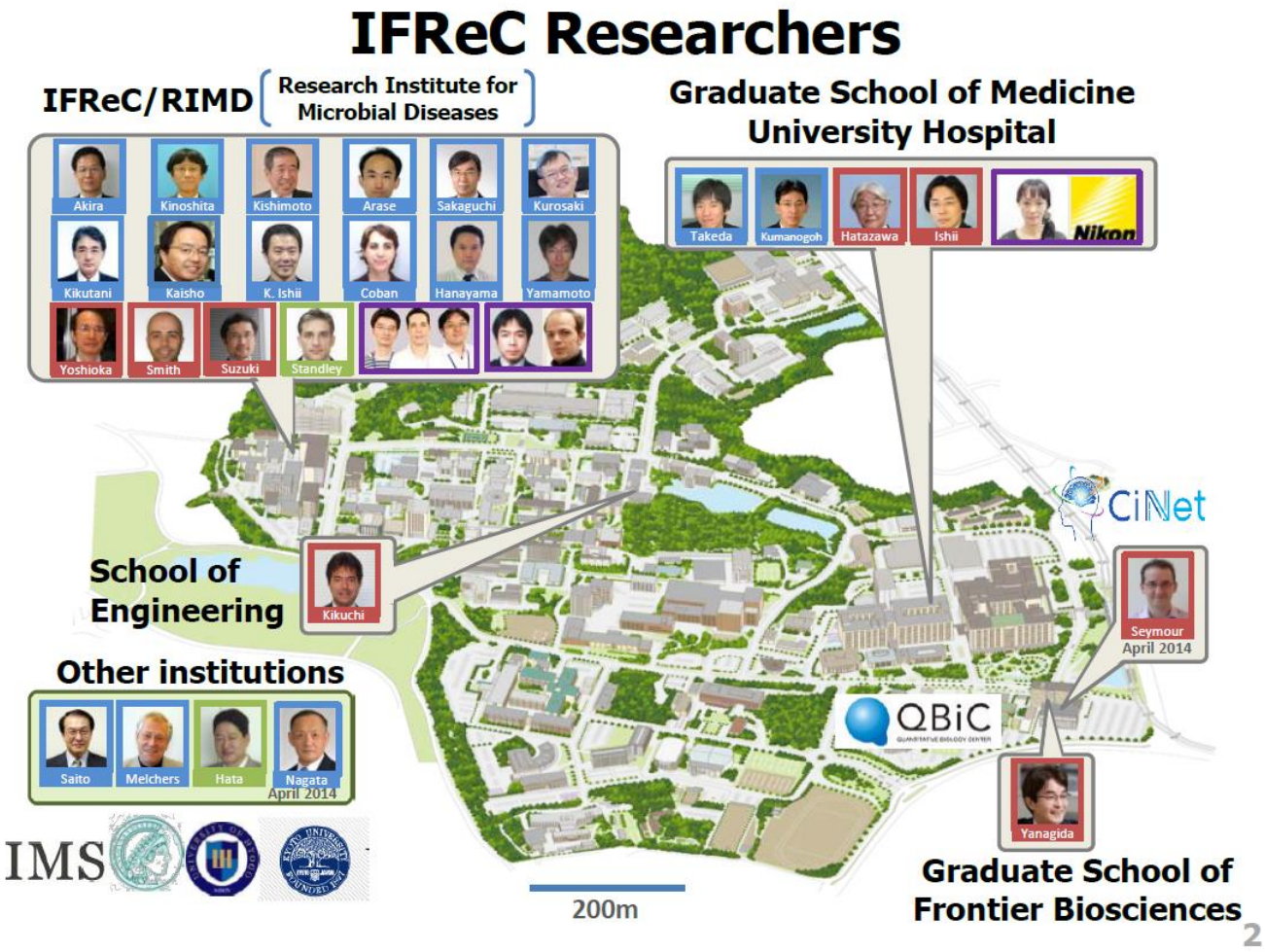
- Please diagram management system in an easily understood manner.
- If any changes have been made in the management system from that in the"Post-interim evaluation revised center project," please describe them. Please describe any changes made in the administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research)



∗ Research Institute for Microbial Diseases, Osaka University

5. Campus Map

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



6. FY2014 Project Expenditures (the exchange rate used: 1USD= 120 JPY)

i) Overall project funding

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	25.8
	Principal investigators (no. of persons):21	132.5
	Other researchers (no. of persons):153	494.2
	Research support staffs (no. of persons):58	185.0
	Administrative staffs (no. of persons):14	90.8
	Total	928.3
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0.0
	Cost of dispatching scientists (no. of persons):10	20.0
	Research startup cost (no. of persons):1	4.2
	Cost of satellite organizations (no. of satellite organizations):0	0.0
	Cost of international symposiums (no. of symposiums):1	10.0
	Rental fees for facilities	8.3
	Cost of consumables	1.7
	Cost of utilities	59.2
	Other costs	463.3
	Total	566.7
Travel	Domestic travel costs	0.8
	Overseas travel costs	5.8
	Travel and accommodations cost for invited scientists (no. of domestic scientists): (no. of overseas scientists):5	1.7
	Travel cost for scientists on secondment (no. of domestic scientists):2 (no. of overseas scientists):	0.8
	Total	9.1
Equipment	Depreciation of buildings	218.3
	Depreciation of equipment	583.3
	Total	801.6
Other research projects	Projects supported by other government subsidies, etc.	30.0
	Commissioned research projects, etc.	595.0
	Grants-in-Aid for Scientific Research, etc.	255.8
	Total	880.8
Total		3186.5

Ten thousand dollars

WPI grant	1090.78
Costs of establishing and maintaining facilities	0
Establishing new facilities (Number of facilities: , m²) Costs paid:	
Repairing facilities (Number of facilities: , m²) Costs paid:	
Others	
Cost of equipment procured	42.5
Name of equipment: High resolution 3D/4D imaging analysis software Number of units: 1 Costs paid:	2.5
Name of equipment: Individually Ventilated Cage System Number of units: 1 Costs paid:	26.7
Name of equipment: Rack for breeding of animal Number of units: 1 Costs paid:	6.7
Name of equipment: XY Motorized Stages for Microscopes Number of units: 1 Costs paid:	0.8
Name of equipment: System Microscope, etc. Number of units: 1 Costs paid:	0.8
Name of equipment: Three-axis Water Hydraulic Micromanipulator Number of units: 1 Costs paid:	0.8
Others	4.2

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (no. of persons):1	
	Other researchers (no. of persons):8	
	Research support staffs (no. of persons):2	
	Administrative staffs (no. of persons):0	
	Total	12.5
Project activities		0.0
Travel		0.0
Equipment		0.0
Other research projects		55.8
Total		68.3

Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY2014 that were coauthored between the center's researcher(s) in domestic institution(s) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2015 and not described in Appendix 1.

Overseas Satellite 1 (Total: OO papers)

No.	Author names and details
1-	NONE
1-	
1-	

Overseas Satellite 2 (Total: OO papers)

No.	Author names and details
2-	NONE
2-	
2-	

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY2014. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2014					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2014					

Overseas Satellite 2:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2014					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2014					

FY 2014 Visit Records of World Top-caliber Researchers from Abroad

Researchers Total: 13

Name (Age)	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
Sylviane Muller	Professor, CNRS, Institute of Molecular and cellular Biology Strasbourg University, France	Ph.D. Immunology	Silver Medal of CNRS (2010)	April 10, 2014	participation in the seminar
Paul Horton	Professor, Computational Biology Research Center, AIST	Ph.D. Immunology	Best poster award at the 2011 Cold Spring Harbor Conference	June 23, 2014	participation in the seminar
Yair Reisner	Professor, Weizmann Institute of Science, Israel	Ph.D. Immunology	Samuel and Paula Elkales Prize for Scientific Excellence in Medicine (2012)	September 12, 2014	participation in the seminar
Gaetan Burgio	Senior Research Fellow , John Curtin School of Medical Research, Australian National University	Ph.D. Immunology	Science 338(6112):1348-51 , 2012.	November 6, 2014	participation in the seminar
Alan F. Cowman	Professor, Department of Medical Biology Faculty of Medicine, Dentistry and Health Sciences The University of Melbourne	Ph.D. Microbiology	2013 Victoria Prize for Science & Innovation	September 22, 2014	participation in the lecture
David Tarlinton	Honorary Professor, Department of Medical Biology Faculty of Medicine, Dentistry and Health Sciences The University of Melbourne	Ph.D. Immunology	Eureka Prize for Scientific Research (2014)	September 22, 2014	participation in the lecture
Magnus Rattray	Professor, University of Manchester, UK	Ph.D. System Biology	PLoS Comput Biol, 10(5), e1003598.	February 23-24, 2015	participation in the symposium

Gabriel D. Victora	Fellow, Whitehead Institute for Biomedical Research, USA	Ph.D. Immunology	Harold M. Weintraub Award (2011) NIH Director's Early Independence Award (2012)	February 23-24, 2015	participation in the symposium
Paola Di Meglio	Principal Investigator, MRC National Institute for Medical Research, UK	Ph.D. Immunology	Wyeth Advances in Psoriasis Research Grant award (2008)	February 23-24, 2015	participation in the symposium
Markus Feuerer	Principal Investigator, German Cancer Research Center	Ph.D. Immunology	Immunity 41:343-5, 2014. Nat Immunol. 14:821-30,2013.	February 23-24, 2015	participation in the symposium
Daniel Gray	Principal Investigator, The Walter and Eliza Hall Institute of Medical Research, Australia	Ph.D. Immunology	Nature Rev Immunol. 14: 154–65, 2014.	February 23-24, 2015	participation in the symposium
Joseph C. Sun	Principal Investigator, Memorial Sloan Kettering Cancer Center, USA	Ph.D. Immunology	Geoffrey Beene Junior Faculty Chair (2014) AAI Pfizer-Showell Early Career Investigator Award (2012) Cancer Research Institute Investigator Award (2011)	February 23-24, 2015	participation in the symposium
Yeonseok Chung	Professor, Seoul National University, Korea	Ph.D. Immunology	Pioneer award for the outstanding achievement in research, Korean-American Bio-Medical Scientists Symposium (2006) Seymour and Vivian Milstein Young Investigator Award (2010) Early career junior faculty travel award, AAI (2013)	February 23-24, 2015	participation in the symposium

State of Outreach Activities

- Using the table below, show the achievements of the Center's outreach activities in FY2014(number of activities, times held).
- Describe those activities that have yielded novel results or that warrant special mention in the "Special Achievements" space below.
- In appendix 7, list and describe media coverage (e.g., articles published, programs aired) in FY2014 resulting from press releases and reporting.

Activities	FY2014(number of activities, times held)
PR brochure, pamphlet	4
Lectures, seminars for general public	8
Teaching, experiments, training for elementary and secondary school students	0
Science cafe	2
Open houses	2
Participating, exhibiting in events	3
Press releases	17

Special Achievements

Besides the usual outreach activities for the general public and students, IFReC strove to become a more "visible institute" to the host institute and global society through outreach activities.

[Immunology Lecture Series for Osaka University members]
IFReC started "The Immunology Lecture Series" at the end of FY2013. A junior researcher from IFReC gives a talk about the basics of his/her research including cutting-edge results in an easy-to-understand manner. The lecture is open to all Osaka University members and held in the evening so that participants can attend after their regular work hours. Seven lectures were provided in FY2014, and gathered a total of more than 300 participants.

[Online Immunology Course]
Osaka University joined edX, one of the major Massive Open Online Course (MOOC) platforms, founded by Massachusetts Institute of Technology (MIT) and Harvard University. IFReC is contributing by providing lectures as the first course of OsakaUx (edX courses by Osaka University).
In FY2014, IFReC researchers, as lecturers, started cooperating in preparation for the lectures with the support of IFReC RPMO and the Teaching and Learning Support Center of Osaka University. Over 3000 people have already enrolled in the course, and it will be distributed in FY2015.

[Facebook]
In order to be more open to and more easily accessible from the world, IFReC opened its Facebook page (https://www.facebook.com/Osaka.Univ.IFReC) to provide information mainly on the various outreach activities of IFReC, and research achievements and awards acquired by IFReC researchers.

[Novel Trial of Science Café]
A unique attempt achieved in a science café was to invite two guest speakers of the 6th IFReC international symposium to speak at the cafe. An unforeseen ripple effect from this was that one of the guests, who was unfamiliar with science café events, discovered the benefits and decided to try adopting such an activity into his home institute.

FY 2014 List of Project's Media Coverage

- Select main items of coverage, and list them within these 2 pages.

No.	Date	Type media (e.g., newspaper, television)	Description
1	Apr. 11, 2014	Nikkei Newspaper	Cecal patch has an important role (Dr. Takeda)
2	May 15, 2014	Asahi Newspaper	Early detection of cerebral malaria (Dr. Coban)
3	June 19, 2014 June 26, 2014	Asahi Newspaper	Series: Open a Gate -Parasites are guardian? (Dr. Yamamoto) -Animals performing photosynthesis? (Dr. Yamamoto)
4	June 26, 2014	Nikkei Newspaper	The day my life was changed (Dr. Yanagida)
5	Aug. 3, 2014	Mainichi Newspaper	Summer School in Koyasan (Dr. Kishimoto)
6	Sep. 8, 2014	Asahi Newspaper	Gifts for a life -Part 1 (Dr. Kishimoto)
7	Sep. 9, 2014	Asahi Newspaper	Gifts for a life -Part 2 (Dr. Kishimoto)
8	Sep. 10, 2014	Asahi Newspaper	Gifts for a life -Part 3 (Dr. Kishimoto)
9	Sep. 13, 2014	Asahi Newspaper Mainichi Newspaper TV news	Receiving Osaka Science Prize (Dr. Ken Ishii)
10	Sep. 23, 2014	Nikkei Newspaper	Cancer therapy by immune regulation (Dr. Hiroyoshi Nishikawa)
11	Oct. 9, 2014	Mainichi Newspaper	Progressive technology for Nobel Prize in Chemistry (Dr. Yanagida)

12	Oct. 17, 2014	Nikkei Newspaper	Discovering a protein related to Rheumatism (Dr. Sakaguchi)
13	Nov. 25, 2014	Sankei Newspaper	Fluctuation is the fundamental of molecules, and of even human –Part 1 (Dr. Yanagida)
14	Nov. 26, 2014	Sankei Newspaper	Fluctuation is the fundamental of molecules, and of even human –Part 2 (Dr. Yanagida)
15	Nov. 27, 2014	Sankei Newspaper	Fluctuation is the fundamental of molecules, and of even human –Part 3 (Dr. Yanagida)
16	Nov. 28, 2014	Sankei Newspaper	Fluctuation is the fundamental of molecules, and of even human –Part 4 (Dr. Yanagida)
17	Dec. 13, 2014	Nikkei Newspaper Asahi Newspaper Mainichi Newspaper Yomiuri Newspaper	New member of the Japan Academy (Director Akira)
18	Jan. 18, 2015	Yomiuri Newspaper	Restore the damaged credibility in science researches (Dr. Kishimoto)
19	Feb. 18, 2015	Nikkei Newspaper	A protein regulating chronic allergic responses (Dr. Takeda)
20	Feb. 24, 2015	Nikkei Newspaper Asahi Newspaper Mainichi Newspaper Yomiuri Newspaper TV news	Regulating osteoclast differentiation by a black tea component (Dr. Keizo Nishikawa & Dr. Masaru Ishii)
21	Mar. 26, 2015	Nikkei Newspaper Asahi Newspaper Mainichi Newspaper Yomiuri Newspaper Sankei News paper TV news	Receiving Canada Gairdner International Award (Dr. Sakaguchi)