

# 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 Center	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<sup>+</sup> cells in the large intestine, but not the small intestine, after colonization. Decreased colonic IgA<sup>+</sup> cells correlate with altered faecal microbiota composition. Experiments using photoconvertible Kaede-expressing mice or adoptive transfer show that the caecal patch IgA<sup>+</sup> cells migrate to the large and small intestines, whereas Peyer’s patch cells are preferentially recruited to the small intestine. IgA<sup>+</sup> 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 & Microbe. 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 PILR $\alpha$ . Furthermore, they determined the crystal structures of PILR $\alpha$  and its complex with a sTn and its attached peptide region. The structures show that PILR $\alpha$  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 $\beta$ 2-adrenergic receptors**

Suzuki group revealed that  $\beta$ 2-adrenergic receptors ( $\beta$ 2ARs) 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 through  $\beta$ 2ARs 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 15<sup>th</sup> 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** ④ **Promotion of new drug development with innovative PET/MR and PET/CT** ⑤ **Forefront 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 position 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 22<sup>nd</sup> 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.