World Premier International Research Center Initiative (WPI)
FY2012 WPI Project Progress Report (Post-Interim Evaluation)

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Common instructions:
* Unless otherwise specified, prepare this report from the timeline of 31 March 2013.
* 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)

Research of the highest world level: IFReC was again very productive in FY2012, publishing 139 "WPI papers", whose author(s) can be identified as affiliated with the WPI program. More than 10 % of these (16 papers) were published in journals of impact factors higher than 14 such as Nature and Immunity. The fact that PIs and other researchers invited as speakers of international meetings outnumbered those in preceding years is a good measure of maintaining such high quality of science at IFReC.

Medical/clinical immunology: The percentage of clinically-oriented papers in the total publication was higher than in preceding years. Furthermore, several groups have started research projects using clinical samples in collaboration with clinicians/physician scientists belonging to the Osaka University Hospital. Worthy of special mention are several clinical trials of immune-therapy, which are either in progress or under review by the Institutional Review Board of the University Hospital and Pharmaceutical and Medical Devices Agency.

To create communication environments for medical immunology between IFReC investigators and clinicians/physician scientists, two platforms have been created. One is the "Osaka University Immunology School" for the interaction between clinical and basic research, which is organized by two PIs of IFReC from the Medical School, Kumanogoh and Takeda, in collaboration with H. Yoshikawa (Professor of orthopedics). It was held twice in FY2012 (July and January). Another is a series of seminars "Immunology Frontier: From Bench to Bed and from Bed to Bench" to discuss medical immunology with wide range of research topics. The initiative for this was taken by Sakaguchi (Deputy Director of IFReC, responsible for future prospect of medical immunology at IFReC). The first seminar was scheduled in May, 2013.

Fusion of various research fields: As judged by the number of papers co-authored by researchers in immunology and imaging and/or informatics groups and those reporting development of new technologies useful in immunological, imaging or informatics research, the challenge of IFReC to advance interdisciplinary research is gradually being met. For its further boosting, two new plans have been set up. One is a complete modification of a part of the 3rd floor of IFReC Research Building to rear as many as 700 mice for continual observation of immune phenomena in live animals with an MRI device and a two-photon microscope under specific pathogen-free conditions, enabling researchers to observe immune phenomena in the same animals over a period of a few weeks. The other is a program of "fusion research units" for young researchers of Assistant or Associate Professor level with different research backgrounds and/or experience. They collaborate to challenge opening up a new vista in immunology with some financial and personnel support directly from IFReC and by sharing research facilities with the parent laboratories (semi-independent). The program is in perfect match with IFReC's philosophy to foster young talented researchers in the next generation. The first unit starting operation in April of 2013 is "Quantitative Immunology Research Unit" consisting of two Assistant Professors, one with research experience in immunology and the other in physics and informatics.

Globalization: While keeping the percentage of overseas researchers at all levels > 30% throughout the year, for which generous support by donations from the Kishimoto Foundation was of great help, the global visibility of IFReC is increasing as indicated by the total number of its visitors from abroad exceeding a hundred (47% from Asia/Oceania, 28% from North America and 25% from Europe) to either give seminars or to make arrangements for research collaborations. In addition, IFReC was approached by the Science and Innovation Section of Embassies and Consulates of Foreign countries in Japan aiming to seek collaboration between IFReC and their private companies, universities and government agencies.

Scientific events at International level: The International Symposium "Dynamism of Immune Reactions & Regulation" was held in May, 2012 with the support of the Kishimoto Foundation and the FIRST Program AKIRA Project. The world's leading scientists discussed current progress in elucidating immune reactions and mechanisms that mediate and regulate immune responses.

IFReC and Singapore Immunology Network (SIgN) jointly organized the second "Winter School on Advanced Immunology", which was held in Singapore from January the 20th to the 25th, 2013. From 256 applications, 54 young participants from 17 different countries were selected, who had the chance to give oral/poster presentations as well as to hear 20 lectures given by prominent immunologists.

Implementation of organizational reforms: While continuing effort to reinforce the organization (promoting staff awareness of elements central to the mission and objectives of IFReC among all members, importance of compliance with the laws and regulations, administration skills, etc.), collaboration with Research Institute of Microbial Diseases (RIMD) was furthered by recruitment of an administrator with PhD and research experience, who was engaged in management of common facilities jointly operated with IFReC and RIMD. This was effective for smoother management of the facilities as well as offering generous support for overseas researchers in preparation of forms required by law or regulations necessary for their researches.

Efforts to secure the center's future development over the mid- to long-term: Taking the results of the FY2012 site-visit and follow-up, IFReC's future plans were discussed several times, including strategies for further advancement of interdisciplinary research and for development of medical immunology based on fundamental research. Consequently the IFReC Future Planning Committee was set up together with three sub-committees handling the continuance of the center, advancement of interdisciplinary research and the promotion of medical and clinical immunology.

IFReC also started negotiations of its future plan with the Osaka University in FY2012. The first action after the WPI follow-up was the Director's appeal at the president-organized university-wide hearing of deans of graduate schools and directors of institutions in January, 2013, in which IFReC asked that the university's pledge that the continuing existence of IFReC is a prerequisite in future system plans of the Osaka University. This is a good match not only for Osaka University's 2nd Mid-term Goals (FY2010 - FY2015), but also for its new plan of "Institute for Academic Initiatives". Discussion between IFReC and Osaka University had then been repeated on the subject of the continuation of IFReC after the initial period of 10 years of WPI program, resulting in a report of Osaka University submitted to the WPI-working group entitled "*The Dialogues with the Host Institutions and Centers*" (scheduled in June, 2013).

Outreach activities. Together with various outreach activities started in the preceding years such as series of science café and public lectures, IFReC took new approaches in FY2012. "Lectures for career-development for younger generation" were delivered by young researchers to high school and university students for their future career planning. Overseas researchers also gave talks in science classes at neighboring international schools. Collaboration with other WPI centers were continued and IFReC joined several events home and abroad such as WPI joint outreach symposium, Science and Technology Festa in Kyoto and Annual Meeting of the American Association for the Advancement of Science (AAAS) in Boston.

・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 10-20 pages (excluding the attached forms).

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 FY2012, IFReC has maintained a high level of productivity. Even when counted according to the rules imposed from FY2012 onward, 139 research papers were published (Appendix 1A), of which more than 10 % of these (16 papers) were published in journals of impact factors higher than 14, demonstrating IFReC’s strong commitment to quality science. In addition, imaging and informatics groups showed good progress in various aspects of their technologies; some have already been applied to immunological research whereas others are near to being implemented, as judged by many of their published papers.

As for clinically and medically oriented papers, their percentage in the total publication was much higher than in the preceding years. Furthermore, several groups have started research projects using clinical samples in collaboration with clinicians/physician scientists belonging to the Osaka University Hospital. Worthy of special mention are some clinical trials of immune-therapy with the Hospital, which are either in progress or under review of the Institutional Review Board of Osaka university hospital and Pharmaceutical and Medical Devices Agency.

1-1 Fundamental Immunological Research

Below are brief descriptions of selected research papers from the list (Appendix 1A). These works reflect the efforts made in basic research, as well as those of an etiological or clinical nature.

a) A transcription factor that controls bone homeostasis and antibacterial immunity (Akira, Host Defense). Jdp2 is an AP-1 family transcription factor that regulates the epigenetic status of histones. However, the roles of Jdp2 *in vivo* and its pleiotropic functions are largely unknown. This study showed its crucial roles not only in bone metabolism but also in differentiation of neutrophils. The authors also found that ATF3 was an inhibitor of neutrophil differentiation and that Jdp2 directly suppresses its expression via inhibition of histone acetylation. In conclusion, Jdp2 plays pivotal roles in bone homeostasis *in vivo* and host defense by regulating osteoclast and neutrophil differentiation (*Immunity* 37:1024–36, 2012).

b) The role of semaphorin 3A in Osteoprotection (Kumanogoh, Immunopathology). The bony skeleton is maintained by local factors that regulate bone-forming and bone-resorbing osteoclasts, in addition to hormonal activity. This study showed that semaphorin 3A (Sema3A) exerts an osteoprotective effect by both suppressing osteoclastic bone resorption and increasing osteoblastic bone formation. The binding of Sema3A to neuropilin-1 (Nrp1) inhibited receptor activator of nuclear factor-kappa B ligand (RANKL)-induced osteoclast differentiation by inhibiting the immunoreceptor tyrosine-based activation motif and RhoA signaling pathways. Thus, Sema3A is a promising new therapeutic agent in bone and joint diseases (*Nature* 485:69–74, 2012).

c) A critical role of GBP family genes in host defense against *Toxoplasma gondii* (Yamamoto, Immunoparasitology & Takeda, Mucosal Immunology). Stimulation of innate immune cells by IFN-γ up-regulates ~2000 effector genes such as immunity-related GTPases including p65 guanylate-binding

protein (GBP) family genes. This study showed that a cluster of GBP genes was required for host cellular immunity against the intracellular parasite *Toxoplasma gondii*. The authors generated mice deficient for all six GBP genes located on chromosome 3 (Gbpchr3) by targeted chromosome engineering. Mice lacking Gbpchr3 were highly susceptible to *T. gondii* infection, resulting in increased parasite burden in immune organs. The results suggest that Gbpchr3 play a pivotal role in anti-*T. gondii* host defense by controlling IFN-γ-mediated Irgb6-dependent cellular innate immunity (*Immunity* 37:302–13, 2012).

d) TCR stimulation-induced epigenetic changes and Foxp3 expression for Treg development (Sakaguchi, Experimental Immunology). The transcription factor Foxp3 is essential for the development of regulatory T (Treg) cells, yet its expression is insufficient for establishing the Treg cell lineage. This study showed that Treg cell development is achieved by the combination of two independent processes, i.e., the expression of Foxp3 and the establishment of Treg cell-specific CpG hypomethylation pattern. Both events were induced by T cell receptor stimulation. This model explains how Treg cell fate and plasticity is controlled and can be exploited to generate functionally stable Treg cells (*Immunity* 37:785–799, 2012).

e) The role of the Bach2 transcription factor in unique traits of IgG1 type memory B cells (Kurosaki, Lymphocyte Differentiation). In regard to explaining the robust antibody responses of IgG1 type memory B cells, two-non-mutually exclusive models (BCR-intrinsic and BCR-extrinsic) have been long debated. By establishing a novel mouse model in which antigen-non-experienced B cells express an IgG type BCR, the BCR-intrinsic model alone has now turned out not to be sufficient to explain the unique properties of IgG1 type memory B cells. Instead, authors' data suggest that repression of the transcription factor Bach2 (as one of the BCR-extrinsic changes) in IgG1 memory B cells is involved in manifesting the heightened differentiation activity (*Immunity* in press).

f) Regulation of Neutrophil infiltration during inflammation by PILR-α (Arase, Immunochemistry). Acute inflammatory responses are important in host defense, whereas dysregulated inflammation results in life-threatening complications. This study showed that paired immunoglobulin-like type 2 receptor alpha (PILRα) negatively regulated neutrophil infiltration during inflammation. Pilrα-/- mice had increased neutrophil recruitment to inflammatory sites and were highly susceptible to endotoxin shock. The data demonstrate that neutrophil recruitment in inflammatory responses is regulated by PILRα *via* modulation of integrin activation (*Nat. Immunol.* 14:34–40, 2013).

g) Arid5a controls IL-6 mRNA stability, which contributes to elevation of IL-6 level *in vivo* (Kishimoto, Immune Regulation). Posttranscriptional regulation of IL-6 has been largely uncharacterized, with the exception of the ribonuclease Regnase-1, which prevents autoimmunity by destabilizing IL-6 mRNA. Here, we identified AT-rich interactive domain-containing protein 5A (Arid5a) as a unique RNA binding protein, which stabilizes IL-6 but not TNF-α mRNA through binding to the 3′ untranslated region of IL-6 mRNA. Arid5a was enhanced in macrophages in response to LPS, IL-1β, and IL-6. Arid5a deficiency inhibited elevation of IL-6 serum level in LPS-treated mice and suppressed IL-6 levels and the development of T_H17 cells in experimental autoimmune encephalomyelitis. Importantly, Arid5a inhibited the destabilizing effect of Regnase-1 on IL-6 mRNA. These results indicate that Arid5a plays an important role in promotion of inflammatory processes and autoimmune diseases（*Proc. Natl. Acad. Sci.* 110: 9409-14, 2013）.

h) Dynamic visualization of osteoclast function (Masaru Ishii, Cellular Dynamics). How the bone resorptive functions of osteoclasts are controlled *in vivo* remains poorly characterized. The authors visualized fluorescently labeled mature osteoclasts in intact mouse bone tissues using intravital multiphoton microscopy. Within this mature population, they observed cells with distinct motility behaviors and function, with the relative proportion of static - bone resorptive (R) to moving - nonresorptive (N) varying in

accordance with the pathophysiological conditions of the bone. The findings provide new insights into the activities of mature osteoclasts *in situ* and identify actions of RANKL-expressing Th17 cells in inflammatory bone destruction (*J. Clin. Invest.* 123:866–873, 2013).

i) A point mutation in Semaphorin 4A that causes retinal degenerative diseases (Kumanogoh, Immunopathology). In humans, mutations in Semaphorin 4A (Sema4A) are thought to contribute to retinal degenerative diseases. The authors generate a series of knock-in mouse lines with corresponding mutations in the Sema4A gene and find that Sema4A F350C causes retinal degeneration phenotypes. The F350C mutation results in abnormal localization of the Sema4A protein, leading to impaired endosomal sorting of molecules indispensable for photoreceptor survival. Their findings not only indicate the importance of the Sema4A protein conformation in human and mouse retina homeostasis but also identify a novel therapeutic target for retinal degenerative diseases (*Nat. Commun*. 4:1406, 2013).

j) A role for Lipocalin 2 against malaria infection (Coban, Malaria Immunology). Although Plasmodium parasites require host iron for replication, how host iron homeostasis and responses to these fluxes affect Plasmodium infection are incompletely understood. The authors determined that Lipocalin 2, a host protein that sequesters iron, is abundantly secreted during human (*P. vivax*) and mouse (*P. yoelii* NL) blood-stage malaria infections and is essential to control *P. yoelii* NL parasitemia, anemia, and host survival. They further demonstrate that a chronic iron imbalance due to a Lipocalin 2 deficiency results in impaired adaptive immune responses against Plasmodium. Thus, Lcn2 exerts antiparasitic effects by maintaining iron homeostasis and promoting innate and adaptive immune responses (*Cell Host & Microbe* 12:705-16, 2012).

k) Inhibition of TCR signaling by programmed cell death 1 (Saito, Cell Signaling). Single cell imaging elucidated a molecular mechanism of Programmed cell death 1 (PD-1)-mediated suppression of T cell activation. PD-1 becomes clustered with T cell receptors (TCRs) upon binding to its ligand PD-L1 and is transiently associated with the phosphatase SHP2. In addition to PD-1 clustering, PD-1-TCR colocalization within microclusters is required for efficient PD-1-mediated suppression. Therefore, PD-1 microcluster formation is important for regulation of T cell activation (*J. Exp. Med.* 209:1201-7, 2012).

l) Discovery and characterization of new transcripts from RNA-seq data in mouse CD^{4+} T cells (Miranda-Saavedra, Bioinformatics and Genomics). By combining bioinformatics with experimental research on the same level, studies were made to understand the regulation of the interleukin 10-mediated anti-inflammatory response. It was shown that the essential transcription factor STAT3 controls specific genes that are involved in shutting down inflammation, and that STAT3 regulates its own self-regulatory signaling pathway by means of both positive and negative feedback loops (*Blood* 119:e110-9**,** 2012; *Nucleic Acids Res*. 41:2155-70, 2013).

1-2 Innovating Technology for Immunological Research

In FY2012, imaging groups of IFReC showed considerable progress in developing new technologies useful for immunological research, some of which have proved to be powerful techniques for clinical diagnosis.

a) Development of high-speed super-resolution microscopy (Yanagida, Single molecule imaging). Super-resolution microscopy is of interest in many biological research fields as a powerful tool to observe nano-structure by overcoming the diffraction limit of light. However, its temporal resolution of current technology is too low to observe fast biological phenomena of nano-scale. The group have developed a novel super-resolution system with MEMS mirror array and attained the spatial-temporal resolution of 120 nm/2 ms. Using this system, the authors successfully observed the structural changes of small autophagosomes (≤ 300 nm) during their drifty movement in a living cell (*PLoS One* 7:e44028, 2012).

b) Advanced technologies in MRI (Yoshioka, Biofunctional Imaging). To overcome the limitation of sensitivity of MRI, the group developed new highly sensitive MRI coils (domestic patent No.2011-122326;

international patent No.PCT/JP2012/63325) and new MRI contrast probes for visualizing the dynamics of the immune system. Using these new technologies, the dynamics of migration and localization of labeled immune cells were visualized in the mouse lymph nodes *in vivo* at normal and pathological conditions (manuscript in preparation). In addition, MRI contrast and labeling efficiency of macrophages was successfully optimized, enabling the visualization of the recruitment of peripheral endogenous immune cells into the central nervous system *in vivo* at a single-cell level (manuscript in preparation). The group collaborated with immunology groups to investigate the early event of mouse model of several diseases. By high-resolution MRI, the inflammation-mediated alterations were found to change the homeostasis in the CNS, which were previously invisible (submitted). Thus, in combination with the method of *in vivo* cellular tracking and the continuous monitoring of pathological development, the new technologies would be useful for noninvasive immunological analysis to know the temporal mechanisms of how and when immune cells affect disease progression and remission.

c) Novel fluorescent imaging technology for obtaining data in immune cell dynamics（Masaru Ishii, Cellular Dynamics). The group succeeded in visualizing the dynamic behaviors of certain functional molecules *in vivo*, as well as those of cells. For example, they originally generated a reporter mice, whose V-type H^+-ATPase (proton pump), an essential machinery for bone resorption as well as digestive activity of phagocytes, are fluorescently labeled with GFP. By exploiting the reporter mice, they succeeded in tracking time-dependent displacement of bone-destroying cells, as well as the changes in subcellular distribution of the proton pump molecule during the action (*J. Clin. Invest*., 123: 866–873, 2013). Complex image information containing the changes in cell shapes and molecular distribution could be well analyzed by an originally developed image analysis software, which identified at least two functionally distinct states of cells/molecules. This advanced imaging analysis made it possible to grasp the real mode of function of different immune and inflammatory cells and the complicated regulation by cell-cell interaction and environmental niches *in vivo*.

d) Raman label-free imaging (Smith, Biophotonics). Evaluation of T cell type and activation status was determined by label-free analysis (manuscripts in preparation). Additional findings with Raman investigation of malaria were that changes in macrophage response to malarial hemozoin were evident and Raman could also be used for early detection of malaria disease (*Analyst* 138: 3927-33, 2013). Immunological effects of nanoparticle-assisted Raman were investigated with the conclusion that nano-antenna to boost Raman signal can be used without provoking or inhibiting the macrophage immunological response (*Part. Part. Sys. Charact*, 30:427-433, 2013). A multimodal label-free setup was constructed to allow quantitative phase measurement for rapid visualization of cell dynamics during the slower Raman imaging acquisition (manuscript in preparation), while enhanced data mining techniques now developed are allowing us to more quantitatively determine how an ensemble of cellular spectra is distributed spatially (*J. Biophotonics*, in press).

e) Integrated PET/MRI imaging (Hatazawa, Nuclear Medicine). To visualize metabolic responses in inflammation, cancer, and immune-related disorders by using specific tracers, attempts were made to develop a new methodology for *in vivo* PET imaging, evaluation of patients receiving therapy with new metabolic based criteria, and new imaging modalities. Successful examples include *in vivo* imaging of activated microglia and macrophage with translocator protein radioligands (*J. Nucl. Med.* 53: 872-80, 2012). Evaluation of response to neoadjuvant chemotherapy for esophageal cancer patients by new PET-based criteria, and SPECT imaging of activated dendritic cells after intratumoral administration for esophageal cancer. In the central nervous system, astrocytic energy metabolism by means of ^{11}C acetate and PET was studied in multiple sclerosis, an inflammatory autoimmune disease of the CNS (in preparation).

f) Development of protein labeling techniques (Kikuchi, Chemical Imaging Techniques). A fluorogenic probe was developed for labeling photoactive yellow protein (PYP) tag. PYP is a small protein (14 kDa) derived from purple bacteria. The labeling kinetics was significantly improved by these probes. Also developed was a novel ^{19}F MRI probe. Novel silica nanocapsules (NCs) including high concentration of perfluorocarbons to increase the sensitivity was developed. Detection of tumors *via* enhanced permeation and retention effect was also successful using PEGylated NCs (*Angew. Chem. Int. Ed.*, 51: 5611-14, 2012).

g) 3D reconstruction of lymphoid organs (Suzuki, Immune Response Dynamics). To overcome the limitation in depth penetration of two-photon microscopy, a method to render lymphoid organs optically clear was developed, which allowed visualization of lymphoid organs from top to bottom. Based on the acquired data, the 3D reconstruction of the whole lymph nodes was performed to visualize cell localization all over the lymph node from various angles (manuscript in preparation). In combination with selective and efficient fluorescent reporters, this technique would be useful to define the localization of rare cell populations such as memory lymphocytes that could be overlooked in sectioned organs.

h) Development of software tools (Standley, Systems Immunology). Our joint team with Astellas Pharma was judged to produce the most accurate models in the *Second Antibody Modeling Assessment,* organized by Pfizer and Johnson & Johnson. For this contest, we generated models using our 3D modeling software Spanner (*Immunome Research* 7:1-8, 2011) and evaluated the models using our atomic force-field OSCAR (*J. Chem. Theory Comput.* 8:1820-27, 2012). We also developed a new method for predicting combinatorial regulation of transcription, identified a set of genes regulated by C/EBPalpha and NF-kappaB in dendritic cells, and experimentally verified our predictions (*BMC Genomics* 13 Suppl 7: S11, 2012). In addition, we introduced a novel method for the prediction of regulatory DNA motifs (*BMC Bioinformatics* 14, 26, 2013) as well as an efficient way of computing structure-informed sequence alignments (*Mol. Biol. Evol.* 30: 772-80, 2013).

i) Bioinformatics methods with experimental research (Miranda-Saavedra, Bioinformatics and Genomics). A novel computational tool was developed for the reconstruction of transcriptional regulatory modules by combining next-generation sequencing data with bioinformatic predictions and data integration (*Nucleic Acids Res*. 41:2155-70, 2013; Diez et al., in press). Using these unique tools, followed by experimental validation, it has been demonstrated that STAT3´s self-regulatory loop can be exploited therapeutically for enhancing the anti-inflammatory response (and thus dampen inflammation). Furthermore a systems biology approach was taken to analyze this pathway on its multiple levels of regulation, an important one being chromatin epigenetics. In this context the best-performing bioinformatic method for predicting enhancers from epigenetic signatures has been published (*Nucleic Acids Res.* 40:e77, 2012), which will help us decipher the temporal resolution of inflammation by IL-10.

1-3 Development toward translational studies in medical/clinical immunology

In FY2012, translational studies at IFReC into medical/clinical immunology were clearly accelerated. Persons of particular note are Sakaguchi (Deputy Director of IFReC in charge of promotion of medical/clinical immunology under the Future Planning Committee of IFReC set up in FY2012) and Kumanogoh (the chair of the Department of Respiratory Diseases, Allergy and Rheumatic Diseases, Osaka University Hospital). Several groups took the first step toward such direction, using clinical samples supplied from the Osaka University Hospital. Furthermore, several clinical trials of immune-therapy are planned or actually in progress in collaboration between the Hospital clinicians and IFReC researchers. In addition, effective platforms for communication between IFReC investigators and clinician/physician scientists have been gradually arranged (see 2-3 for details).

a) An investigator-driven Phase-I clinical trial for a Treg-targeted immunotherapy of cancer (Sakaguchi, Experimental Immunology). We previously showed that human $FOXP3^{+}CD4^{+}$ T cells were composed of three subsets; $CD45RA^{+}FOXP3^{lo}$ naïve Tregs (Fr. I), $CD45RA^{-}FOXP3^{hi}$ effector Tregs (Fr. II), and $CD45RA^{-}FOXP3^{lo}$ non-Tregs (Fr. III). With this classification, we showed that tumor-infiltrating T cells in a variety of cancers contained a higher frequency of effector Tregs compared with peripheral blood, and that naïve Tregs were barely detected in tumor tissues. These effector Tregs dominantly expressed CCR4 and were depleted by anti-CCR4 mAb treatment *in vitro*. Based on these data, we have started this year an investigator-driven Pharmaceutical and Medical Devices Agency (PMDA)-approved Phase-I clinical trial of Treg-targeted therapy of solid tumors (including lung and prostate cancers) with anti-CCR4 mAb.

In addition, we plan to initiate a new immunotherapy of adult T-cell leukemia/lymphoma (ATLL), in which leukemic cells are CD4+ and the majority, if not all, of them express FOXP3, CD25, CTLA-4, and CCR4, thus resembling Tregs. Our group showed that ATLL expressed Cancer/Testis antigens at high levels; for example, NY-ESO-1 (61.4%), MAGE-A3 (31.6%), and MAGE-A4 (61.4%). These CT antigens were recognized by the immune system, and CT-antigen-specific T cell and B cell responses could be elicited (*Blood* 119:3097-104, 2012). An investigator-driven Phase-I/II clinical trial of a combination immunotherapy with NY-ESO-1 (one of the most immunogenic CT antigens) protein vaccine and anti-CCR4 mAb for Treg depletion is currently under evaluation by PMDA. This is the first cancer vaccine trial in the world combined with Treg-targeted therapy.

b) An investigator-driven Phase-I clinical trial for a novel-adjuvanted vaccine to prevent malaria infection (Ken Ishii, Vaccine Science; Kumanogoh, Immunopathology). We were successful in developing a nucleic-acid-based adjuvant; humanized K-type CpG-ODN for a travelers' malaria vaccine targeting a blood stage parasite antigen (*Human Vacc*. 9: 283-90, 2013). Preclinical studies assessing safety and efficacy have been completed with GMP grade humanized CpG ODN and we conducted multiple pre-clinical studies to ensure safety and efficacy. As a result, we obtained approval from the Institutional Review Board (IRB) of Osaka University Hospital and PMDA to initiate investigator driven GCP Phase-I clinical trial during 2013 in Osaka University Hospital.

c) Development of semaphorin-targeted immune therapy (Kumanogoh Immunopathology). The group collaborated with Chugai Pharmaceutical to develop semaphorin-targeted immune therapy by generating humanized antibodies against semaphorins and their receptors. Also his clinical group has started clinical collaborations with IFReC PIs, Sakaguchi (ATL anti-tumor immunity), Arase (Autoimmune diseases), Kurosaki (SLE), and Kikutani (SLE) as well as Ken Ishii (see above). In addition, the group proceeds clinical trials of anti-IL-6R antibody (tocilizumab) for its wider use in collaboration with Kishimoto and Chugai Pharmaceutical. Clinical studies of tocilizumab that have been performed for the past six years have suggested that therapies targeting IL-6 receptor would be widely applicable to the treatment of various intractable immune-mediated diseases. Thus, investigator-initiated clinical trials of tocilizumab are in progress for systemic sclerosis and Takayasu arteritis and are planned for polymyositis, polymyalgia rheumatica and amyloid A amyloidosis.

d) Control of inflammation via PILRα (Arase, Immunochemistry). Paired immunoglobulin-like type 2 receptor alpha (PILRα), an inhibitory receptor containing immunoreceptor tyrosine-based inhibitory motifs (ITIMs), negatively regulated neutrophil infiltration during inflammation. We have previously shown PILRα is involved in herpes simplex virus infection (*Cell* 132: 935-944, 2008). This study using PILR-deficient mice showed that neutrophil recruitment in inflammatory responses is regulated by PILRα *via* modulation of integrin activation (*Nat. Immunol.* 14:34-40, 2013).

e) Identification of B cell receptor (BCR) repertoire for pathogenic autoantibodies in rheumatoid arthritis (RA) (Kurosaki, Lymphocyte Differentiation). The importance of pathogenic B cells and subsequent autoantibodies in initiation and maintenance of human autoimmune diseases such as

rheumatoid arthritis (RA) has become increasingly accepted. Thus, identifying pathogenic B cell receptor (BCR) repertoire is one of the critical steps to understand the patho-physiology of these diseases. In collaboration with Kumanogoh, we are establishing single-cell-basis BCR repertoire analysis and applying this new method to B cells and plasmablasts in human RA patients.

f) Generation and characterization of recombinant antibodies from patients with autoimmune diseases and chronic viral infection (Kikutani, Molecular Immunology). Chronic viral infections are often associated with production of autoantibodies and development of autoimmunity. The group has shown that self-reactive and polyreactive antibody-producing B cells are positively selected in germinal centers during Murine gammaherpesvirus 68 (MHV68) infection, a mouse model of EB virus (EBV) infection. A fraction of EBV-reactive antibodies derived from healthy donors and SLE patients are also polyreactive or self-reactive. To determine an involvement of self-reactivity and polyreactivity of virus-reactive antibodies in pathogenesis of autoimmune diseases, the group is generating and characterizing recombinant antibodies from self-reactive and EBV-reactive memory B cells and plasma cells of patients with autoimmune diseases such as SLE or EBV infection in collaboration with clinical groups of Osaka University Hospital and National Center for Child Health and Development.

g) Neuroinflammation: a major factor of expanding brain infarction studied with PET/CT, PET/MRI, and translocator protein probes in rats (Hatazawa, Nuclear Medicine). Using a newly synthesized probe, ^{11}C-DPA731, which binds translocator protein 18kDa(TSPO) and is a marker of neuro-inflammation, and PET/CT and MRI imaging system, we first evaluated cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) in a rat experimental model of brain ischemia as performed in clinical studies in males. By changing the duration of middle cerebral artery occlusion and monitoring CBF and $CMRO_2$, mild, moderate, and severe brain injuries were produced. ^{11}C-DPA731 accumulation was specifically found in moderately injured brain (*J. Nucl. Med.* 54: 283-90, 2013). ^{11}C-DPA731 accumulation was located not homogenously in entire brain infarct demonstrated by the MRI T2 weighted images, but was located along the border zone between infarcted and normal brain tissue. Immunohistochemical staining (GFP and CD11b) of autopsied brain confirmed that ^{11}C-DPA731 accumulation corresponded with activated microglia and astrocytes. We have already conducted ^{11}C-PBR28 (alternative TSPO probe) PET in normal volunteers. We plan to study patients with brain infarction and neurodegenerative diseases including Alzheimer's disease and Parkinson disease.

h) Genetic and biochemical basis of inherited GPI-anchor deficiencies (Kinoshita, Immunoglycobiology). Many cell surface proteins are anchored to the plasma membrane by glycosylphosphatidylinositol (GPI). We cloned more than 20 genes involved in biogenesis of GPI-anchored proteins and previously demonstrated that somatic mutation of *PIGA* gene in the hematopoietic stem cell causes paroxysmal nocturnal hemoglobinuria, an acquired GPI deficiency. The group recently identified the first and the second types of inherited GPI deficiency caused by hypomorphic mutations in *PIGM* and *PIGV* genes, respectively. This year, our group reported the third type of inherited GPI deficiency caused by mutations in *PIGO* gene (*Am. J. Hum. Genet.* 91:146-51, 2012). The patients suffered from intellectual disability with seizures and hyperphosphatasia. Release of anchor-less alkalinephosphatase, a situation of hyperphosphatasia, causes reduction of membrane-bound enzyme, which in turn causes reduction of intraneuronal pyridoxal and GABA. Based on this, seizure of one of the patients was successfully treated with pyridoxine, indicating that hyperphosphatasia was causally related to seizures (*Neurology*, in press).

1-4 Quantitative Evaluation of Science Level

a) Publication. In FY2012 IFReC published 139 "WPI papers" whose author(s) can be identified as affiliated with the WPI program (Appendix 1A). Among these, as many as 16 papers were published in

journals of impact factors higher than 14, indicating that the research at IFReC is of an internationally high quality.

b) Invitation to international symposia and major awards. Many PIs of IFReC have been invited as lecturers of international meetings; those noteworthy are listed in Appendix 1B. In FY2012, the total number of lectures at international conferences was larger than that of the last fiscal year. Among many awards given to IFReC researchers (Appendix 1C), the most prestigious was election of Sakaguchi as a Foreign Associate of the National Academy of Sciences (NAS). Together with Kishimoto (1991) and Akira (2009), IFReC has now three NAS members.

1-5 Research Facilities and Instrumental Installation

a) Live Immuno-Imaging Facility. The whole experimental area of the third floor of the IFReC Research Building was remodeled into a live immuno-imaging facility. It provides specific pathogen-free environment, consisting of animal rooms to rear 700 mice and rooms for an 11.7T MRI and a two-photon microscope, enabling researchers to observe immune phenomena in the same animals over a period of a few weeks.

b) PC servers. Installation of new PC servers and an upgrade of all the servers have been carried out to support the increasing activities among bioinformatics and imaging groups.

c) Imaging center. The Leica Interdisciplinary Collaboration Hub for Techno-development (LICHT) on bioimaging was established with the cooperation of Leica microsystems in July, 2012. It is equipped with a multi-photon microscope of high performance and it is expected that the collaboration between Leica and IFReC researchers can lead to development of a high level imaging system and thus in turn cutting-edge achievement in this research field.

1-6 Securing Research Funds

In FY2012, the sum total of research funds raised by IFReC investigators reached 1.38 billion JPY. Major funding agencies include the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW), Japan Science and Technology Agency, Human Frontier Science Program, and National Institutes of Health (USA). IFReC researchers also received a large sum of donations from private sectors including Kishimoto Foundation and a number of pharmaceutical companies (Appendix 3-2).

1-7 Changes in Research Organization in FY2012

The list of principal investigators is shown in Appendix 2. In FY2012, two immunology PIs left IFReC. Miyasaka resigned as PI of IFReC to be a Specially Appointed Professor at the Institute of Academic Initiatives, Osaka University in April and Myoung Ho Jang became an Associate Professor of Laboratory of Gastrointestinal Immunology, POSTECH, South Korea in October, but they continue to collaborate with IFReC. The total number of PIs stood at 26 as of the end of FY2012. There was no change in number of imaging PIs or bioinformatics PIs (Appendix 3-1-1).

2. Advancing fusion of various research fields

2-1 Selected Articles of Fusion Research

One of the most successful examples of the IFReC's fusion research in FY2012 is a work in collaboration between Akira and Yoshioka groups (*Nature* 495:524–8, 2013), showing that Trib1 is critical for adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue-resident M2-like macrophages. It also demonstrates that the supplementation of M2-like macrophages rescues the pathophysiology, indicating that a lack of these macrophages is the cause of lipolysis. Yoshioka group analyzed volume of adipose tissues of mice using MRI imaging technique *in vivo*.

Yoshioka group has been also collaborating with Coban group for imaging of malaria disease, particularly cerebral malaria (CM) by MRI. MRI imaging of CM pathology, especially for early diagnosis of CM complications, is an attractive strategy which may allow a successful treatment window for saving lives. They have found a "vulnerable spot" in brain of mice suffering from CM by using high field MRI which could be a gateway for parasites to cause CM (manuscript in preparation).

Another example is a paper (*Immunity* 37:785-99, 2012) based on research collaboration of Sakaguchi group with informatics scientists of the University of Tokyo, showing that Treg cell development is achieved by the combination of two independent processes, i.e., the expression of Foxp3 and the establishment of Treg cell-specific CpG hypomethylation pattern. This analysis utilizing the techniques of bioinformatics and Super Computer System made a critical contribution to the success of this study. The following are lists of other representative papers coauthored by researchers in different disciplines.

Immunology / Imaging:

- Hayasaka et al., *In vivo* diagnostic imaging using micro-CT: sequential and comparative evaluation of rodent models for hepatic/brain ischemic and stroke. (*PLoS One* 7: e32342, 2012).
- Watabe et al., Intratumoral heterogeneity of F-18 FDG uptake differentiates between gastrointestinal stromal tumors and abdominal malignant lymphomas on PET/CT. (*Ann. Nucl Med*. 26:222-7, 2012).
- Watanabe et al., Distinct modulated pupil function system for real-time imaging of living cells. (*PLoS One* 7:e44028, 2012).

Immunology / Informatics:

- Maruyama et al., The transcription factor Jdp2 controls bone homeostasis and antibacterial immunity by regulating osteoclast and neutrophil differentiation. (*Immunity* 37:1024-36, 2012).
- Vandenbon et al., AA novel unbiased measure for motif co-occurrence predicts combinatorial regulation of transcription. (*BMC Genomics* 13 Suppl 7:S11, 2012).
- Vandenbon et al., A Parzen window-based approach for the detection of locally enriched transcription factor binding sites. (*BMC Bioinformatics* 16:14-26, 2012).

2-2 Strategies of IFReC to Advance Interdisciplinary Research in FY2012

Even though considerable achievements were made, IFReC researchers are well aware of the importance of further advancement of interdisciplinary research by adopting novel strategies. Parts of this campaign are the improvement and installation of research facilities and instruments (see 1-5) and a new program of "the fusion units" (see 2-2-b). The latter is also a reflection of our philosophy of fostering young researchers in an environment where "collision and fusion" is norm to scientific advancement.

a) The program of "fusion research units". This is a new program to advance interdisciplinary research by young researchers at IFReC. The constituent researchers should be different in their research back grounds and/or research fields. The financial and personnel support is provided to the units, which share the research facility with the parent laboratories. In this sense, the units are semi-independent. The first unit beginning operation in April of 2013 is "Quantitative Immunology Research Unit" consisting of two assistant professors, one with research experience in immunology and the other in physics and informatics. Their close collaboration will be expected to open a totally new vista in immunology.

b) Collaboration with other institutions. Interaction of researchers between IFReC and QBiC (see below) was promoted in FY2012. Seven members of IFReC joined the interdisciplinary research seminar series held in QBiC once a week and actively discussed and exchanged opinions. Collaborative researches have also been started among some groups of IFReC and QBiC and some outcome has been already achieved. For an example, Toll like receptor 4 was successfully observed at single molecule level as well as S1P receptor. Biofunctional Laboratory (Yoshioka) of imaging groups in IFReC succeeded in multimodality

imaging of cancer tumors using nanoprobes which was developed in QBiC.

Center for Information and Neural Networks (CiNet) of National Institute of Information and Communications Technology (NICT) constructed a new building in the campus of Osaka University within walking distance from IFReC and it was opened in February, 2013. Having Yanagida, an IFReC's Deputy Director as head of CiNet and Yoshioka as a Vice Director General of Instrument Technologies Section in CiNet, hereafter the collaboration between IFReC and CiNet will be facilitated.

c) Platforms for interdisciplinary research. IFReC has introduced the following programs to further facilitate interdisciplinary research to which IFReC researchers actively commit:

"Discussion Meeting on Mathematical Modeling in Biology and Related Topics" is a monthly seminar series aimed at sharing of knowledge among researchers of various fields since December of 2011. Participants include not only immunologists from IFReC but also theoretical biologists, mathematicians, physicists, and robot scientists from other departments of Osaka University and other institutes including QBiC. In FY2012, 11 researchers were invited to give lecture. A noteworthy outcome of this meeting is an establishment of the new fusion research unit, "Quantitative Immunology Research Unit" (see 2-2 a), and several collaborative researches are ongoing as well.

IFReC Colloquium is a series of discussion meetings only for IFReC members, held on a bimonthly basis. At each colloquium, speakers from IFReC laboratories give talks about their latest research progress which are followed by intensive discussion. Afterwards, participants are able to gather to further the discussions in an informal setting. Six colloquia were held in FY2012 with the average number of attendees of about 100.

Research Support Program for Combined Research Field (Fusion Program) started in FY2009 to financially support research projects, whose members consists of researchers from different IFReC groups/backgrounds. This program provides financial support for the novel idea of bridging research proposal between different research areas. Five projects were newly selected for the FY2012.

Dual Mentor (DM) Program aimed to support graduate students or young post-doctoral fellows engaging in interdisciplinary projects under the supervision of two PIs from different disciplines. It offers extra financial incentives to attract a higher caliber of applicant; financial support will be given to DM recipients and their primary mentor for three years. Financial support and/or other types of incentives will be also given to the secondary mentor if necessary. Post-doctoral Fellow, Takeshi Yoshida, "Visualizing the dynamics of exosomes during various immune responses *in vivo*" from Immune Network Laboratory, was selected as a recipient for the program.

Advanced Seminar Series on Microbiology and Immunology (ASSMI) was organized by the Office of Combined Program on Microbiology and Immunology of Research Institute for Microbial Diseases (RIMD) for students of the Graduate Schools of Medicine and Frontier Biosciences. For FY2012, Melchers, Lymphocyte Development Lab, gave intensive 2-day lecture under the title of "Early lymphocyte development I & II". The program was designed to promote the combined program on microbiology and immunology and put them into practice. Since this is in agreement with IFReC's stance to increase the chance for IFReC researchers to conduct research in different disciplines, IFReC supports the ASSMI by providing IFReC PI's as lecturers and encourages young IFReC researchers to participate in it.

2-3 Medical/clinical immunology

As an earnest effort to create communication environments for medical immunology between IFReC investigators and clinician/physician scientists, Kumanogoh and Takeda (IFReC's PI from the Medical School) in collaboration with H. Yoshikawa (Professor of orthopedics) organized the Osaka University Immunology School for the interaction between clinical and basic research. The school was held twice in FY2012 (July, 2012 and January, 2013). In each case, nearly 200 basic researchers and clinicians participated. Discussion

for construction of a solid platform to exchange views of medical immunology with wide range of researchers was led by Sakaguchi and other PIs at the Medical School, resulting in holding a series of seminar “Immunology Frontier: From Bench to Bed and from Bed to Bench twice a year (the first seminar to be scheduled in May, 2013).

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)

3-1 Approach to Global Visualization

a) Number of overseas researchers. The percentage of overseas researchers at all levels was kept above the WPI target level of 30% throughout the year (Appendix 3-1). For keeping this level, generous support by donations from the Kishimoto Foundation was of great help (see 3-3 b).

b) Number of visitors from abroad. Including top class scientists listed in Appendix 5, the total number of visitors from abroad to IFReC exceeded a hundred, consisting of 47% from Asia/Oceania, 28% from North America and 25% from Europe. Their purpose was mostly scientific, such as giving seminars and making arrangements for research collaborations.

c) Collaborations with government agencies of foreign countries. IFReC was also approached by the Science and Innovation Section of Embassies and Consulates of Foreign countries in Japan aiming to seek collaboration between IFReC and their private companies, universities and government agencies. These include the Embassy of France and Sweden.

d) Research agreements with overseas institutions. As of the end of FY2012, the number of partner institutions was eight, three domestic and five international.

3-2 International Symposia, Workshops and Other Meetings

IFReC held the International Symposium "Dynamism of Immune Reactions & Regulation" on May 22-23, 2012. This was originally scheduled in FY2011 as one of the events in celebration of the 80th anniversary of Osaka University, but it was cancelled due to the Great East Japan Earthquake. In FY2012, the symposium was organized by IFReC with the support of the Kishimoto Foundation and the FIRST Program AKIRA Project. In the symposium, the world's leading scientists discussed current progress in elucidating immune reactions and mechanisms that mediate and regulate immune responses. The number of participants was 500 in total.

Osaka University and Leica Microsystems Corporation have signed a joint research contract and established a joint research and development center, Leica-Osaka University Interdisciplinary Collaboration Hub for Techno-development on bioimaging (LICHT Leica Center) on the 7th floor of the IFReC Research Building. To commemorate its opening, "LICHT Leica Center opening seminar" was held on June 22, 2012. In the seminar, the researchers working in cutting-edge bioimaging area presented their current research progress. The number of participants was 150.

3-3 Strategies to Attract and Foster Talented Young Researchers

a) The 2nd Winter School on Advanced Immunology was held in Singapore from January the 20th to 25th, 2013 jointly by IFReC and Singapore Immunology Network (SIgN) to foster young immunologists. From 256 applications, 54 young researchers from 17 different countries including five young researchers of IFReC (graduate students and post-doctoral fellows with PhD thesis obtained within three

years) were selected by a competitive screening and selection process. The school provided 20 lectures given by prominent immunologists including four IFReC PIs, and opportunities to the participants for oral/poster presentations. It successfully achieved its educational aims both in fostering young researchers 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 in global standards.

b) Kishimoto Foundation Fellowship/Scholarship Program. Throughout FY2012, a few enquiries about this program were made every month. As of March 31, 2013, the program-supported researchers include one Assistant Professor, nine post-doctoral fellows, and one graduate student. Since this program was established in 2009, the total number of researchers supported by this program has reached 41.

c) IFReC Young Scientist Support Program for Research Abroad was established to provide financial support for young researchers to attend conferences or to collaborate with other laboratories abroad. The program supported ten young researchers of IFReC (graduate students, 5; post-doctoral fellow, 4; assistant professor, 1) to attend the international congresses held abroad.

3-4 Improvement of Research Environment for Overseas Researchers

a) Support for overseas researchers to engage in experiments using common facilities of IFReC and RIMD. The orientation for use of facilities commonly available to IFReC and RIMD researchers was held in English again in 2012. This orientation included lectures required by law, and regulations and guidelines for those who wish to engage in specific experiments using living modified organisms, pathogens, animals, etc. The orientation in English helps overseas researchers to conduct experiments in the common facilities as well as in their laboratories.

Also, continuous support for overseas researchers has been given in preparation of application forms and other necessary documents required by law, or stipulated in regulations and guidelines for animal experiments, living modified organisms, biologically hazardous materials, etc. Since animal experiments are under complicated regulations and rules, an English available inquiry counter was opened for overseas researchers in FY2012. Also, notifications frequently sent from animal experiment center are now translated into English by IFReC liaison office and sent to overseas researchers for complete understanding of the rules.

b) Support for overseas researchers to obtain research funds. In FY2012, Research Promotion Division of the university took over and held the seminar, which was initiated by IFReC last fiscal-year, for overseas researchers at Osaka University to promote applications to the Grant-in-Aid for Scientific Research (KAKENHI) (see 4-2). For overseas researchers, there are still many barriers to obtaining competitive funds. Most documents used for the procurement of funds, such as application guidelines and forms, and the completion of reports are required to be prepared in Japanese. IFReC provides several kinds of support; a monthly updated list of funds applicable to the research fields of IFReC researchers in English and Japanese is made available on the IFReC webpage. The application forms and guidelines are translated into English if needed. PhD holders in the Research Planning and Management Office (RPMO) of IFReC can advise on the content and/or expression of research plans in the application forms, and help with the translation into Japanese if required.

3-5 Other Support to Overseas Researchers

Seminars: Seminars for avoiding misuse of research funds, intellectual property, and fire-safety were held in English for overseas researchers to learn and adapt to Japanese systems relating to research activities.

Lodgment: As in preceding years, IFReC continued to subsidize part of the rent from the WPI budget for overseas researchers staying in Kasugaoka House which was constructed in Osaka University in 2010 to provide accommodation of high quality for international researchers/students.

Japanese Language Class: Meeting the request of some overseas researchers to facilitate communication with other laboratory members and locals, IFReC started a Japanese language class for overseas researchers in FY2012. The class targeted beginners and had 20 lessons in a half year. Approximately twelve researchers including FIRST program and QBiC researchers attended the class and improved their Japanese.

Japanese Language Café: Together with the Japanese language class, "Japanese Language Café" was organized where overseas researchers could ask questions about language to a Japanese teacher or talk in Japanese over certain topics in an informal setting.

Casual meetings: Buffet-styled casual meetings ("Happy Hours") were organized and held once a month to promote interaction between researchers in a friendly atmosphere as well as to encourage scientific collaborations.

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 continued various types of efforts to reinforce the organization for smoother management of the facilities as well as offering generous support for overseas researchers in preparation of forms required by law or regulations necessary for their researches.

4-1 Operation of common research facilities

Core instrumentation facility and animal resource center are under joint operation of IFReC and RIMD, where the personnel and the running cost is supported both by IFReC and RIMD. In FY2012, IFReC engaged an administrator holding PhD for smoother management of these facilities as well as for generous support to overseas researchers.

4-2 Development of university research administrators (URA) system in Osaka University

In IFReC administration system, the Research Planning & Management Office (RPMO) has been established since FY2009. RPMO consists of five PhD holders with research experience and headed by the Administrative Director. One of the missions of RPMO is to support researchers to acquire competitive research funds from public agencies and private foundations by providing with administration for application and post-award management. Taking RPMO of IFReC as a role model, the University Support Office for Large-Scale Education and Research Projects (established in FY2009) launched its URA team in FY2012 under the project of MEXT, and is going to expand it for further support.

4-3 Researcher & Staff Development

In November of 2012, Retreat was held with 239 participants of IFReC members and collaborators at a location off campus in an informal setting for the first time. All laboratories participated in presentation and poster session to recognize research conducted by young researcher in different fields. Some of the benefits of Retreat are a boosting of morale of staff, reconfirming the mission of IFReC and deepening the mutual understanding of all members through friendly interaction for research collaborations in order to achieve WPI goals. Administrative staff discussion at Retreat led to a new SD program, "Berlitz-IFReC English Communication course" to further improve the staff's English and communication skills as a member of WPI, which will start in Spring of FY2013.

Researcher Development IFReC has increased opportunities and options for young researcher's individual carrier planning as a scientist through varies seminars and workshops. Associate and Assistant Professors were assigned to be a chair/facilitator of the colloquium or other seminars for training purposes to be a next generation principal investigator candidate to lead forefront research at IFReC.

Staff Development IFReC has encouraged administrative staff to attend the undergraduate introduction classes in immunology conducted by the Institute for Higher Education and Practice of the university, research promotion seminars, and workshops to attain the forefront information of research in other departments of the university.

4-4 Other Ripple Effects of Activities of IFReC

a) Kakenhi-seminar Orientation for overseas researchers working at Osaka University to understand the MEXT Grants-in-Aid for Scientific Research (Kakenhi) system and how to apply for the grant was held in English by Department of Research Promotion of Osaka University in June, 2012. The orientation was originally organized by IFReC in 2011 and was succeeded by the Department. A young PI of IFReC, Coban, who had been awarded several Kakenhi grants, gave a talk about her experience of application.

b) Education and Training Since 2011, IFReC have organized an orientation in English with RIMD consisting of lectures that are required by law, and regulations and guidelines for those who wish to engage in specific experiments using living modified organisms, animals, etc. It provides an opportunity for legally required education and training to overseas researchers belonging to RIMD as well as those of IFReC.

c) Research Administration IFReC provides its initiative activities for supporting research and administration to the Support Office for Large-Scale Education and Research Projects and university research administrators (URA) in the project of MEXT started from 2012 to improve the research supporting system and activities of Osaka University.

d) Support for Application to U.S. funds A PhD holder of the RPMO of IFReC stands in for Osaka University to manage registration and registered information of all belonging to Osaka University to apply to U.S. Funds, such as NIH funds.

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)

Taking the results of the FY2012 site-visit (August of 2012) and follow-up (October of 2012), discussion was repeated about the future plans of IFReC. In view of primary importance of how to sustain the center after the initial WPI program period of 10 years, strategies were discussed for overall organization of the center, further advancement of interdisciplinary research, translational development of outcomes of fundamental research into medical/clinical immunology, and strengthening of the support of Osaka University. Consequently the IFReC Future Planning Committee was set up together with three sub-committees, each handling the continuance of the center, advancement of interdisciplinary research and the promotion of medical and clinical immunology. Points that have been so far confirmed in these discussions are briefly described in 5-1 and strategies of IFReC for Research Collaboration with Institutions inside and outside of Osaka University are shown in Fig. 1. Along with these internal actions, IFReC started discussions for its future plan with the Osaka University in FY2011 (5-2).

5-1 Future prospect of IFReC

Establishment of solid basis of collaboration with RIMD: It is a general consensus both in IFReC and RIMD that studies of immunology and infectious diseases are complementary to each other, and hence both institutions should stand together to further their research activities. At present, several IFReC PIs are RIMD-affiliated and a few WPI-supported academic staff members are collaborating with RIMD academic

staff for joint operation of core research facilities and animal resource center. In future, it is necessary to consider reorganization of IFReC with RIMD together in not only research but also administration system.

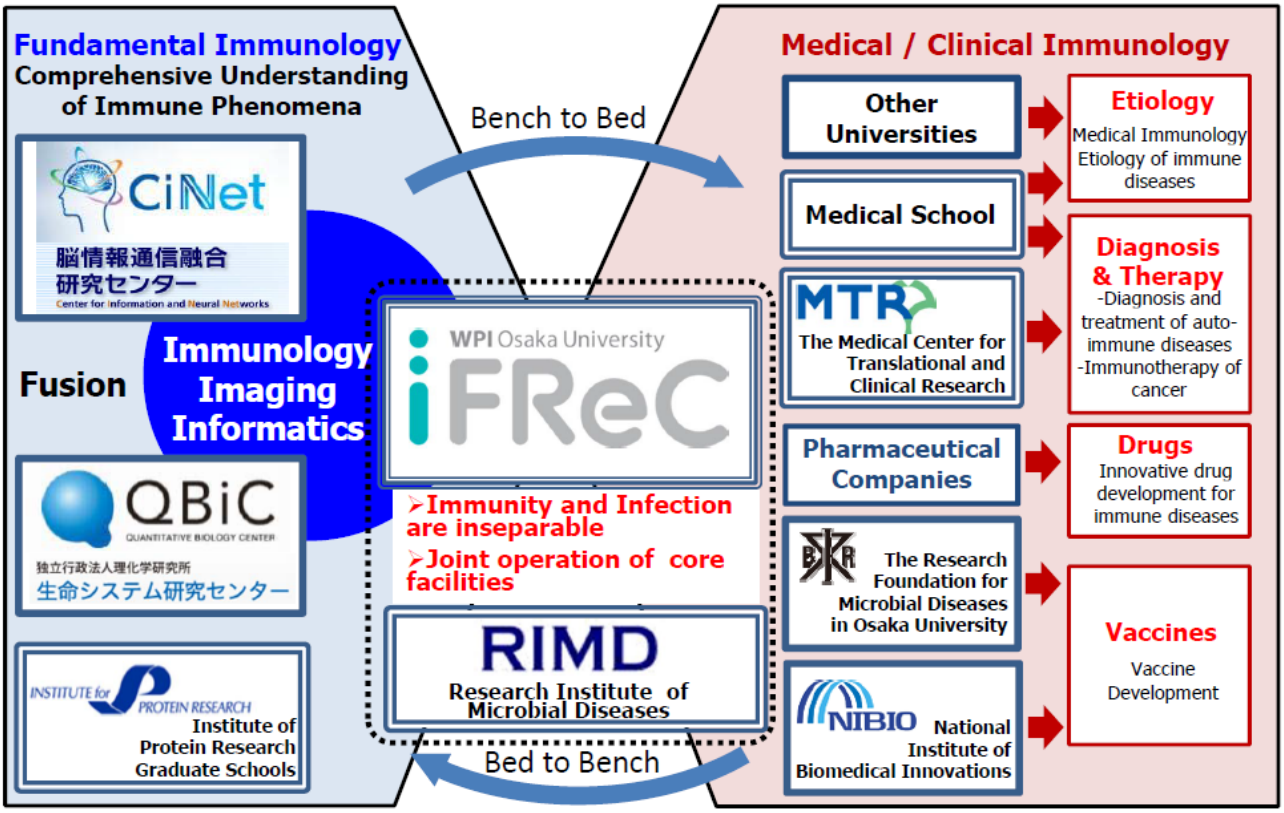

Figure 1 Strategies of IFReC for research collaboration with institutions inside and outside of Osaka University. While furthering close ties with RIMD, IFReC will advance interdisciplinary research in collaboration with QBiC/CiNet and accelerate medical/clinical immunology together with the University Medical School and Hospital and other partner institutions.

Collaboration with QBiC and CiNeT for innovative advancement of interdisciplinary research: Two research centers of large scale, the National Institute of Information and Communications Technology - Center for Information and Neural Networks (CiNet) and the RIKEN - Quantitative Biology Center (QBiC) are now in operation in the same University campus as IFReC. Both centers are headed by Yanagida, an IFReC's Deputy Director. In addition, various research technologies of imaging and informatics employed at these centers are applicable to immunology, though their ultimate goals are different from those of IFReC. Taking advantage of these facts, IFReC, while doing at most its own effort for advancement of interdisciplinary research, will lead to promote research collaboration with these centers in order to advance toward the major goal of IFReC, a "comprehensive understanding of immune dynamism," and create new interdisciplinary research projects.

Medical/clinical immunology: Even before FY2012, researchers of IFReC had been well aware of the importance of translational development of basic immunological research into medical/clinical immunology. As indicated by publication (1-1 and 1-3) and other activities (2-3), a general consensus were gradually formed within IFReC on necessity of more aggressive commitment to medical /clinical immunology or at least research projects with such direction, which is in line with the discussion of IFReC"s future prospect.

5-2 Negotiation with Host Institution

The first action after the WPI follow-up was the Director's appeal at the president-organized university-wide hearing of deans of graduate schools and directors of institutions in January, 2013, where

IFReC asked the University's pledge that the continuing existence of IFReC is a prerequisite in future system plans of the Osaka University. In our view, it is actually a good match not only for Osaka University's 2nd Mid-term Goals (FY 2010 - FY2015), but also for its new plan of "Institute for Academic Initiatives". Focusing on provision of financial and human resources, discussion between IFReC and Osaka University had been repeated on the continuation of IFReC after the initial period of 10 years of WPI program, resulting in the report of Osaka University submitted to the WPI-working group for "*the Dialogues with the Host institutions and Centers*" (scheduled in June, 2013).

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.

In FY2012, IFReC was actively engaged in various types of outreach activities in collaboration more than ever (listed in Appendix 6).

6-1 Outreach Activities

a) Activities of IFReC. IFReC held science café series "Science Café on the Edge" four times in FY2012. The number of participants varied from 30 to 190, and was 350 in total. Two of the Science Cafés were held in the central area of Osaka and Fukuoka cities.

IFReC designed "Lectures for Career-development for younger generation" to let students know about "true scientists" and "scientists' lives". Sugihara and Kohyama, young scientists of IFReC gave talk at Suma Gakuen High & Junior High School (Kobe, Hyogo), and Mukogawa Women's University (Nishinomiya, Hyogo), respectively. The numbers of audience were about 250 in total.

The two IFReC PIs from abroad, Smith and Standley gave talk titled "In touch with Science" at Senri and Osaka International Schools of Kwansei Gakuin (Suita, Osaka).

Akira gave keynote lectures to students and teachers at Shuyukan Senior High School (Fukuoka, Kyushu) and Kozu High School (Osaka). He lectured his audience "The mystery of immunity; a newly opened door to immunology", which explains his achievements in an easy-to-understand manner. The numbers of audience were more than 1500 in total.

At the "FIRST Science Forum 3", an event in Kyoto organized by JST, Akira talked to participants about his school days and what inspired him to become a researcher. The event was broadcasted by NHK educational channel at a later date.

b) Collaboration with other WPI centers. The second WPI joint outreach symposium for the younger generations called "Let's enjoy the world's advanced science!" was held in Tsukuba, Ibaraki on Nov. 24, 2012. Kurosaki of IFReC gave a talk titled "Answer to the mystery behind immune memory", then the students and scientists enjoyed free talking and experiments at each WPI booth. The number of participants including teachers and parents was about 700.

IFReC and five other WPI institutes attended the Annual Meeting of the American Association for the Advancement of Science (AAAS2013 in Boston) as part of the "Japan pavilion" on Feb. 14-18, 2013. The staff from Japan, including WPI members, held a press conference with the title "Japan: Your next career destination", and introduced our internationally-opened institutes to the press. IFReC also participated in "Science Festa in Kyoto 2013" with other WPI institutes on Mar. 16-17, 2013. In the demonstration booth, the researches at IFReC were presented to students, and a biological microscope demonstration was set-up in cooperation with Nikon Instech Co., Ltd. More than 6000 participants visited the Festa over the two days including the Minister of State for Science and Technology Policy, who visited the WPI booths.

6-2 Other Activities

Hatazawa was invited to a technology seminar sponsored by the Senri Life Science Foundation. He and his staff gave lectures on the cutting edge technologies of PET-imaging on October 16th of 2012 at the Osaka University Medical School. An observation tour of the PET-Microdose Clinical Trial Facility in the University Hospital was a post-seminar event for the participants.

7. Center's response to the results of the FY2012 follow-up (including the results of the site visit)

* Note how the center has responded to the results of FY2012 follow-up. However, if you have already provided this information, please indicate where in the report.

7-1 Actions Required and Recommendations (Follow-up)

1) Significant fusion efforts were made, but still seem a unilateral interaction. The provision of urgent and important issues to the imaging sector by immunology group is crucial in more concrete and attractive manners. Effective designs to attract the basic-imaging researchers to specific and important questions in immunology are also needed.

Center's response: For we have been well aware of this important issue, various measures have been adopted as described in 2-2. The challenge is gradually being met as number of collaborative projects between immunology and imaging researchers are in progress both at IFReC and QBiC as described in 2-2 b. In addition, we expect that the construction of "Live Immuno-Imaging Facility" (1-5 a), where an 11.7T MRI device has been installed, on the 3rd floor of IFReC Research Building will be able to attract immunologists for studying various immunological phenomena of mice that can be kept alive for a few weeks.

2) Considering the previous state of medical or fundamental human immunology in Japan, IFReC is expected to be a driving force of the fields. However, the present approaches of IFReC remain rather sporadic. A task force discussing medical immunology may be needed to create steady planning and communication environments between IFReC investigators and clinicians/physician scientists.

Center's response: As described partly in 1-1 and mainly 1-3, more than two-thirds of Immunology groups have undertaken research projects that are more or less linked to medical/clinical immunology. In fact, clinical samples supplied from the Osaka University Hospital have been used by several groups. Furthermore, several clinical trials of immune-therapy are planned or actually on-going in collaboration between the hospital clinicians and IFReC researchers. In addition, as described in 2-3, effective platforms for communication between IFReC investigators and clinicians/physician scientists have been gradually arranged. Sakaguchi at IFReC and Kumanogoh at the Hospital are the central figures in these activities.

3) The recruiting of women PIs seems to be especially challenging for this institute. The Director might need to examine some different approaches and get some advice and assistance from institutions which have had more success.

Center's response: In the FY2011, we described IFReC's three strategies to increase the number of female PIs as well as young female researchers: inviting as many female speakers to IFReC-organized scientific meetings as possible; making and using a reservoir of talented young female researchers of international level, utilizing the fact that a number of young female students participated in the Winter Schools (held in January of every year); and more aggressively publicizing the University's support systems such as the Day Care Centers within the premises of Osaka University for child welfare. In addition, exploiting the plan to set up the fusion units (2-2 a), the post of at least one unit will be filled by a young female researcher as a candidate of junior PI in FY2013.

7-2 Actions Required and Recommendations (Site-visit)

1) Facing the termination of the 10-year program in 4 and half years, it is most critical to plan and document a new program/blue print for seeking the third term during the second term of this WPI program. Especially, a budgetary and organization plan to sustain and develop IFReC has to be carefully discussed in depth and presented. For this purpose, a task force should be established to discuss future and directorship of IFReC.

2) At the same time, all parties, including IFReC, JSPS, MEXT and Osaka University, should push forward discussions on IFReC's future. Discussions with IFReC investigators, especially junior PIs, made it clear that this is currently their primary concern, decisions need to be started soon and be clearly articulated so that there will not be an erosion in confidence, potentially compromising the great strides forward IFReC has made to date.

Center's response to the items 1) and 2): Described in this report (5-1 and 5-2)

3) Overall, the activities, publications, and outside exposure of the Imaging Group on its own are still relatively limited, especially in comparison with the Immunology Group, although all the imaging equipment was not functional until just recently. Especially, the new 11.7T MRI has big potential for contributing to our understanding of physiological immune cell migration and interaction. Therefore, the Imaging Group might consider doing ex vivo cell labeling in collaboration with the Immunology Group. Optical imaging including various microscopes is strong and going well; yet, it still needs scientific outcomes and outside exposure. Integration and communication within the Imaging Group still needs to be improved.

Center's response: Described in this report (7-1)

4) It is also important to continuously merge bioinformatics and immunology to foster systems immunology, which will contribute new directions of research associated with both basic and medical immunology.

Center's response: Interaction between immunology and informatics researchers have obviously increased through various activities including the IFReC colloquia and retreat. Of noteworthy is a series of "discussion meetings on Mathematical Modeling in Biology and Related Topics" organized by young researchers in different research fields, and the concept to establish the fusion research units is its fruitful consequence (see 2-2 a and c).

5) It seems that more thought needs to be put into translational efforts. Considering the previous state of medical or fundamental human immunology in Japan, IFReC is expected to be a driving force of the fields. It would make sense for IFReC to capitalize on its strengths to develop novel biomarkers and diagnostics for inflammatory and other immunological diseases, based on its expertise in imaging and systems immunology. In this regard, another task force discussing medical immunology may be needed to create steady planning and communication environments between IFReC investigators and clinicians/physician scientists belonging to University Hospital.

Center's response: Described in this report (7-1)

6) IFReC should not let itself fall behind in CyTOF technology. Given its unique combination of experts in immunology, chemistry, informatics and optics, it stands to be not just an applier of this next-generation technology, but an innovator and driver.

Center's response: IFReC researchers are well aware of the capability and usefulness of the CyTOF technology in immunology research. At present, however, we cannot financially afford to install the instrument, but we are ready to seriously start planning to its introduction in case of increased internal demand to use with scientific rationale.

List of Center's Research Results and Main Awards

A. Refereed Papers

List only the Center's papers published in 2012. (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 2012, 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 2013 may not be aware of this requirement, their papers are treated as "WPI-related papers." From 2014, 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).

C. Previously published important WPI-related papers
List previously published papers that provided the basis for the center's research project plan. (Around 30 papers as a yardstick.)

(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 2012.
- 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

C. Previously published WPI-related papers

A. WPI papers

1. Original articles

1. Abe T, Fukuhara T, Wen X, Ninomiya A, Moriishi K, Maehara Y, Takeuchi O, Kawai T, Akira S, Matsuura Y. CD44 participates in IP-10 induction in cells in which hepatitis C virus RNA is replicating, through an interaction with Toll-like receptor 2 and hyaluronan. *J Virol.* 86:6159-70, 2012.
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4. Baba Y, Kurosaki T. Impact of Ca2+ signaling on B cell function. *Trends in Immunol.* 32(12), 589-594, 2012
5. Bradley LM, Douglass MF, Chatterjee D, Akira S, Baaten BJ. Matrix metalloprotease 9 mediates neutrophil migration into the airways in response to influenza virus-induced toll-like receptor signaling. *PLoS Pathog.* 8:e1002641, 2012.
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11. Dhara K, Hori Y, Baba R, Kikuchi K. A fluorescent probe for detection of histone deacetylase activity based on aggregation-induced emission. *Chem. Commun.* 48:11534-36, 2012.
12. Dong Z, Davidson D, Perez-Quintero LA, Kurosaki T, Swat W, Veillette A. The Adaptor SAP Controls NK Cell Activation by Regulating the Enzymes Vav-1 and SHIP-1 and by Enhancing Conjugates with Target Cells. *Immunity* 36, 974-985, 2012.
13. Fernandez M, Miranda-Saavedra D. Genome-wide enhancer prediction from epigenetic signatures using genetic algorithm-optimized support vector machines. *Nucleic. Acids. Res.* 40(10):e77, 2012.
14. Flores-Langarica A, Marshall JL, Hitchcock J, Cook C, Jobanputra J, Bobat S, Ross EA, Coughlan RE, Henderson IR, Uematsu S, Akira S, Cunningham AF. Systemic flagellin immunization stimulates mucosal CD103+ dendritic cells and drives Foxp3+ regulatory T cell and IgA responses in the mesenteric lymph node. *J. Immunol.* 189:5745-54, 2012.
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2. Review articles

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autoimmune arthritis: insights from mouse and man. *Immunol. Cell Biol.* 90, 277-87, 2012.
136. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. Tanaka T, Kishimoto T. *Int J Biol Sci.* 8(9):1227-36, 2012.
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3. Proceedings

NONE; IFReC does not request researchers to submit conference proceedings.

4. Other English articles

NONE

B. WPI-related papers

NONE

C. Previously published WPI-related papers

NONE

B. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings
- List up to 10 main presentations during FY2012 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	Tomohiro Kurosaki, "B Cell Intrinsic and Extrinsic Mechanisms for Rapid Responsiveness of IgG1 Type Memory B Cells", Keystone Symposia: B Cell Development and Function, Feb. 13, 2013.
2	Ken Ishii, "Intra- and Inter-Cellular Signaling Pathways for DNA Vaccination", DNA vaccine 2012, Dec. 5, 2012.
3	Tadamitsu Kishimoto, "Pathogenesis and treatment of IL-6 dependent autoimmune diseases", French-Japanese Immunology Meeting, Sep. 20, 2012.
4	Shimon Sakaguchi, "Genetic and epigenetic control of regulatory T cell development", 3rd European Congress of Immunology, Sep. 7, 2012.
5	Shizuo Akira "Non-self RNA sensing in virus infected cells and activation of antiviral immunity", The 2012 Les Treilles Meeting France, Aug. 31, 2012.
6	Toshio Yanagida, "Single molecules in vitro and vivo", Gordon Research Conferences -Single Molecule Approaches to Biology, Jul. 18, 2012.
7	Atsushi Kumanogoh, "Immunoregulation by Semaphorins and Their Receptors", The Federation of Clinical Immunology Societies (FOCIS 2012), Jun. 21, 2012.
8	Taroh Kinoshita, "Deficiencies of GPI mannosyltransferases 1 and 2 cause different fates of GPI anchored Proteins", 8th International Symposium on Glycosyltransferases, Jun. 7, 2012.
9	Cevayir Coban, "Innate immunity and malaria parasites", Molecular Immunology & Immunogenetics Congress (MIMIC2012), Apr. 28, 2012.
10	Masaru Ishii, "Roles of S1P in osteoclast regulation and bone physiology", Gordon Research Conferences Italy 2012, Apr. 24, 2012.

C. Major Awards
- List up to 10 main awards received during FY2012 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	Kazuya Kikuchi; Inoue Prize for Science 2012
2	Kenichi Asano, Wataru Ise, Tatsuya Saitoh, Takashi Shichita, and Kazuhiro Suzuki; Young Investigator Award, Japanese Society for Immunology 2012
3	Rikinari Hanayama; Astellas Award for the Best Biomedical Research 2012
4	Atsushi Kumanogoh; Mochida Memorial Science Prize 2012
5	Morihisa Fujita; Young Investigator Award, Japanese Biochemical Society 2012
6	Masanaka Sugiyama; Young Investigator Award, 20th International Symposium on Molecular Cell Biology of Macrophage 2012
7	Shimon Sakaguchi; Foreign Associate of the National Academy of Sciences USA
8	Tomohiro Kurosaki; Prizes for Science and Technology, Minister of Education, Culture, Sports, Science and Technology 2012
9	Shin Mizukami; The Young Scientists' Prize, Minister of Education, Culture, Sports, Science and Technology 2012
10	Tadamitsu Kishimoto; The Royal Decoration from Thai Kingdom

FY 2012 List of Principal Investigators

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

<Results at the end of FY2012>

Principal Investigators Total: 26

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* (60)	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* (73)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	70%	0%	30%	0%	01/11/2007	Usually stays at IFReC	
Hitoshi Kikutani* (62)	Professor, Research Institute for Microbial Diseases, Osaka University	MD, PhD (Immunology)	70%	10%	20%	0%	01/10/2007	Usually stays at IFReC	
Taroh Kinoshita* (61)	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* (46)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	50%	0%	0%	50%	01/10/2007	Usually stays at IFReC	
Kiyoshi Takeda* (46)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	70%	0%	0%	30%	01/11/2007	Usually stays at IFReC	
Hisashi Arase* (47)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	95%	0%	0%	5%	01/10/2007	Usually stays at IFReC	
Shimon Sakaguchi* (62)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	50%	10%	17%	23%	01/12/2007	Usually stays at IFReC	
Takashi Saito* (62)	Group Director, RIKEN, Research Center for Allergy and Immunology	PhD (Immunology)	20%	0%	70%	10%	03/12/2007	usually stays at RIKEN RCAI satellite	
Tomohiro Kurosaki* (57)	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* (76)	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* (66)	Professor, Graduate School of Frontier Biosciences, Osaka University	PhD (Molecular imaging)	25%	0%	65%	10%	01/11/2007	Usually stays at IFReC	
Yoshichika Yoshioka* (59)	Professor, WPI Immunology Frontier Research Center, Osaka University	DSc (Biophysics)	100%	0%	0%	0%	01/02/2008	Usually stays at IFReC	
Yutaka Hata* (51)	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 (45)	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Chemistry)	100%	0%	0%	0%	01/10/2008	Usually stays at IFReC	
Jun Hatazawa* (59)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Nuclear Medicine)	5%	5%	45%	45%	16/01/2009	Usually stays at IFReC	
Masaru Ishii (39)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Bioimaging)	100%	0%	0%	0%	01/12/2008	Usually stays at IFReC	
Kazuya Kikuchi (47)	Professor, Graduate School of Engineering, Osaka University	PhD (Chemical Biology)	28%	2%	50%	20%	01/08/2009	Usually stays at IFReC	

Diego Miranda-Saavedra (37)	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Molecular and Cellular Biology)	100%	0%	0%	0%	16/01/2010	Usually stays at IFReC	
Cevayir Coban (40)	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 (38)	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* (44)	Project Leader, National Institute of Biomedical Innovation (NIBIO)	MD, PhD (Immunology, Vaccine Science)	15%	5%	75%	5%	01/11/2007	He visits his laboratory at IFReC once a week.	
Tsuneyasu Kaisho* (53)	Professor, WPI Immunology Frontier Research Center	MD, PhD (Immunology)	100%	0%	0%	0%	01/03/2011	Usually stays at IFReC	
Kazuhiro Suzuki (37)	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 (38)	Associate Professor, WPI Immunology Frontier Research Center	MD, PhD (Cell Biology)	100%	0%	0%	0%	01/10/2011	Usually stays at IFReC	

Masahiro Yamamoto (34)	Associate Professor, Research Institute for Microbial Diseases, Osaka University	PhD (Immunology)	90%	10%	0%	0%	01/04/2012	Usually stays at IFReC	

Researchers unable to participate in project in FY 2012

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken
Masayuki Miyasaka	Specially Appointed Professor, Institute for Academic Initiatives, Osaka University	01/11/2007	He transferred his position to Specially Appointed Professor, Institute for Academic Initiatives, Osaka University	
Jang Myoung Ho	Associate Professor, Pohang University of Science and Technology, Korea	01/11/2007	He transferred his position to Associate Professor, Pohang University of Science and Technology, Korea	

Biographical Sketch of a New Principal Investigator

Name (Age) *NOTE: Place an asterisk (*) by the name of investigators considered to be ranked among the world's top researchers.*	Masahiro Yamamoto (34)
Current affiliation (Position title, department, organization)	Associate Professor, Department of Immunoparasitology, RIMD, Laboratory of Immunoparasitology, IFReC
Academic degree, specialty	Ph.D. , Immunoparsitology

Research and education history

2006.8-2010.5 Assistant Professor, Dept of Microbiology and Immunology, Graduate school of Medicine, Osaka University

2010.5-2011.12 Associate Professor, Dept of Microbiology and Immunology, Graduate school of Medicine, Osaka University

2012.1 – current Associate Professor, Dept of Immunoparasitology, Research Institute for Microbial Diseases, Osaka University

2012.4 – current Associate Professor, Laboratory of Immunoparasitology, IFReC, Osaka 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.)*

1) He has elucidated the role of TIR domain-containing adaptors in the TLR signaling pathways.

2) He has addressed the functions of nuclear proteins in the TLR-mediated immune responses.

3) He has established molecular analysis of the host-pathogen interface using a parasite T. gondii.

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) **Yamamoto M**. 「Role of GBPs in innate host defense against an intracellular pathogen Toxoplasma gondii」41th Annual meeting of Japanese society of Immunologist (Kobe、Hyogo, Japan、December 5th-7th, 2012)

a) **Yamamoto M**. 「Essential role of interferon-γ-inducible p65 GTPases in host cellular innate immunity against Toxoplasma gondii」 The 11th Awaji International Forum on Infection and Immunity (Awaji Yumebutai International Conference Center on Awaji Island, Hyogo, Japan, September 11th-14th, 2012)

b) None.

c) None.

d) None.

e) None.

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

Grant-in-aid for Young Scientists (A) 30,000,000 yen (2011-2013)

Grant-in-aid for Scientific Research on Innovative area 10,000,000 yen (2012-2013)

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

⑪ **Yamamoto M**, Okuyama M, Ma JS, Kimura T, Kamiyama N, Saiga H, Ohshima J, Sasai M, Kayama H, Okamoto T, Huang DS, Soldati-Favre D, Horie K, Takeda J, Takeda K. A cluster of interferon-γ-inducible p65 GTPases plays a critical role in host defense against Toxoplasma gondii. *Immunity* (2012) 37:302-313. (citation index: 8)

⑩ **Yamamoto M**, Ma JS, Mueller C, Kamiyama N, Saiga H, Kubo E, Kimura T, Okamoto T, Okuyama M, Kayama H, Nagamune K, Takashima S, Matsuura Y, Soldati-Favre D, Takeda K. ATF6β is a host cellular target of the Toxoplasma gondii virulence factor ROP18. *J Exp Med.* (2011) 208:1533-1546. (citation index: 20)

⑨ **Yamamoto M,** Standley DM**,** Takashima S, Saiga H, Okuyama M, Kayama H, Kubo E, Ito H, Takaura M, Matsuda T, Soldati-Favre D, Takeda K. A single polymorphic amino acid on Toxoplasma gondii kinase ROP16 determines the direct and strain-specific activation of Stat3. *J Exp Med.* (2009) 206: 2747-2760. (citation index: 47)

⑧ **Yamamoto M**, Uematsu S, Okamoto T, Matsuura Y, Sato S, Kumar H, Satoh T, Saitoh T, Takeda K, Ishii KJ, Takeuchi O, Kawai T, Akira S. Enhanced TLR-mediated NF-IL6 dependent gene expression by Trib1 deficiency. *J Exp Med.* (2007) 204:2233-9. (citation index: 19)

⑦ **Yamamoto M,** Sato S, Saitoh T, Sakurai H, Uematsu S, Kawai T, Ishii KJ, Takeuchi O, Akira S. Cutting Edge: Pivotal Function of Ubc13 in Thymocyte TCR Signaling. *J Immunol.* (2006) 177:7520-4. (citation index: 38)

⑥ **Yamamoto M**, Okamoto T, Takeda K, Sato S, Sanjo H, Uematsu S, Saitoh T, Yamamoto N, Sakurai H, Ishii KJ, Yamaoka S, Kawai T, Matsuura Y, Takeuchi O, Akira S. Key function for the Ubc13 E2 ubiquitin-conjugating enzyme in immune receptor signaling. *Nat Immunol.* (2006) 7:962-70. (citation index: 136)

⑤ **Yamamoto M**, Yamazaki S, Uematsu S, Sato S, Hemmi H, Hoshino K, Kaisho T, Kuwata H, Takeuchi O, Takeshige K, Saitoh T, Yamaoka S, Yamamoto N, Yamamoto S, Muta T, Takeda K, Akira S. Regulation of Toll/IL-1-receptor-mediated gene expression by the inducible nuclear protein IB. *Nature.* (2004) 430:218-22. (citation index: 202)

④ **Yamamoto M**, Sato S, Hemmi H, Uematsu S, Hoshino K, Kaisho T, Takeuchi O, Takeda K, Akira S. TRAM is specifically involved in the Toll-like receptor 4-mediated MyD88-independent signaling pathway. *Nat Immunol.* (2003) 4:1144-50. (citation index: 512)

③ **Yamamoto M**, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, Takeuchi O, Sugiyama M, Okabe M, Takeda K, Akira S. Role of Adaptor TRIF in the MyD88-Independent Toll-Like Receptor Signaling Pathway. *Science.* (2003) 301:640-3. (citation index: 1324)

② **Yamamoto M**, Sato S, Mori K, Hoshino K, Takeuchi O, Takeda K, Akira S. Cutting Edge: A Novel Toll/IL-1 Receptor Domain-Containing Adapter That Preferentially Activates the IFN- Promoter in the Toll-Like Receptor Signaling. *J Immunol.* (2002) 169:6668-72. (citation index: 695)

① **Yamamoto M**, Sato S, Hemmi H, Sanjo H, Uematsu S, Kaisho T, Hoshino K, Takeuchi O, Kobayashi M, Fujita T, Takeda K, Akira S. Essential role for TIRAP in activation of the signalling cascade shared by TLR2 and TLR4. *Nature.*（2002） 420:324-329. (citation index: 548)

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

None.

Records of FY2012 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 and the estimated date for achieving it [OO month, OO year].

	Goal set in the "Post-interim evaluation revised center project"	Results at end of FY 2012	Final goal (Date: March, 2017)
Researchers	180 <61, 34%> [38, 21%]	183 <55, 30%> [39, 21%]	180 <61, 34%> [38, 21%]
Principal investigators	30 <8, 27%> [3, 10%]	26 <5, 19 %> [1, 4%]	30 <8, 27%> [3, 10%]
Other researchers	150 <53, 35%> [35, 23%]	157 <50, 32%> [38, 24%]	150 <53, 35%> [35, 23%]
Research support staffs	50	75	50
Administrative staffs	30	28 (24, 86%)	30 (20, 67%)
Total	260	286	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.

＜Employment of researchers＞

Hiroaki Hemmi, Associate Professor, Immunology Group, Laboratory of Kaisho from Associate Professor, IFReC,2012.4

Etsushi Kuroda, Associate Professor, Immunology Group, Laboratory of K. Ishii from the University of Occupational and Environmental Health, 2012.8

Hideaki Fujita, Associate Professor, Imaging Group, Laboratory of Yanagida, from RIKEN Quantitative Biology Center (QBiC), 2012.8

Tatsuya Saito, Associate Professor, Immunology Group, Laboratory of Akira from the Research Institute for Microbial Diseases (RIMD), Osaka University, 2012.8

Keiji Hirota, Associate Professor, Immunology Group, Laboratory of Sakaguchi, from Specially Appointed Researcher, IFReC, 2012.10

Ayako Isotani, Associate Professor, Animal Resource Center for Infectious Diseases, from the Research Institute for Microbial Diseases (RIMD) , Osaka University, 2012.8

Miki Mrorimatsu, Assistant Professor, Core Instrumentation Facility, from the Graduate School of Frontier Biosciences, Osaka University. 2012.4

＜Major examples of position transfer from IFReC to world-renowned research institutions＞

Satoshi Uematsu, Associate Professor, concurrent position (2009.11-2012.6),
→ Professor, The Institute of Medical Science, the University of Tokyo
Jang Myung-Ho, Associate Professor, (2007.11-2012.10)
→ Associate Professor, Laboratory of Gastrointestinal Immunology, POSTECH, South Korea
Naoki Takemura, Specially Appointed Researcher (Full Time), (2010.4-2012.10)
→ Specially Appointed Assistant Professor, The Institute of Medical Science, the University of Tokyo
Taro Kawai, Associate Professor, concurrent position (2007.11-2013.03)
→ Associate Professor, Nara Institute of Science and Technology

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 Research Center for Allergy and Immunology	Takashi Saito	
Kyoto University, Institute for Frontier Medical Sciences		
The National Institute of Biomedical Innovation	Ken Ishii	

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
Institute for Systems Biology, USA		
Division of Life Science & Division Of Integrative Bioscience and Biotechnology, Pohang University of Science and Technology (POSTECH)		
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)		
Maurice Wilkins Center, The University of Auckland, New Zealand		

2. Securing competitive research funding

- Competitive and other research funding secured in FY2012: Total: 1,383 Million yen

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

＜Major external funds in FY2012＞

Agency	Name of Program	Name of Recipient	Amount / Million	Support Period
Cabinet Office	Government of Japan Funding Program for World-Leading Innovative R&D on Science and Technology(The FIRST Akira Project)	Shizuo Akira	450	FY2008-FY2012
MEXT	Strategic Funds for the Promotion of Science and Technology	Tadamitsu Kishimoto	68	FY2010-FY2014
JSPS	KAKENHI, Specially Promoted Research	Shizuo Akira	159	FY2008-FY2012
JSPS	KAKENHI, Specially Promoted Research	Shimon Sakaguchi	71	FY2008-FY2012
JSPS	KAKENHI, Scientific Research (S)	Tomoniro Kurosaki	36	FY2009-FY2013
JSPS	KAKENHI on Innovative Areas	Tsuneyasu Kaisho	22	FY2009-FY2013
JSPS	KAKENHI on Innovative Areas	Masaru Ishii	13	FY2010-FY2014
JST	PRESTO･Sakigake program	Nick Smith	16	FY2009-FY2012
JST	CREST	Tomohiro Kurosaki	78	FY2009-FY2014
JST	CREST	Masaru Ishii	83	FY2011-FY2015
JST	CREST･Sakigake	Kazuhiro Suzuki	14	FY2011-FY2015
HFSP	Carrier Development Award	Rikinari Hanayama	19	FY2011-FY2014
MEXT	National BioResource Project Platform for Drug Discovery, Informatics, and Structural Life Science	Daron Standley	20	**FY2012**-FY2016
MEXT	Research Fund for Cooperation between Industry and Academia Program for Fostering Regional Innovation	Ken Ishii	13	**FY2012-**
MHLW	Health Labour Sciences Research Grant	Coban Cevayir	30	**FY2012**-
MHLW	Health Labour Sciences Research Grant	Yoshihiro Nishikawa (Experimental Immunology)	20	**FY2012-**
MHLW	Health Labour Sciences Research Grant	Masaru Ishii	20	**FY2012-**
MHLW	Health Labour Sciences Research Grant	Daron Standley	10	**FY2012-**
MHLW	Health Labour Sciences Research Grant	Rikinari Hanayama	8	**FY2012-**
JST	CREST	Shimon Sakaguchi	53	**FY2012**-FY2017

KAKENHI: Grants-in-Aid for Scientific Research MHLW: Ministry of Health, Labour and Welfare JST: Japan Science and Technology Agency

（Unit: million yen)

<Major Donation from Private Sectors>

	（Unit: million yen)
Kishimoto Foundation	223
Takeda Science Foundation	17
The Sumitomo Foundation	17
HFSPO	16
Chugai Pharmaceutical Co.	5

<Major Joint Research with Private Sector>

	（Unit: million yen)
Takeda Pharmaceutical Company Limited	21
JapanTobacco inc	7.1
Eizai Co.Ltd	5.7
Shionogi & Co., Ltd.	3.6
Nitto Denko Corporation	3.4

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

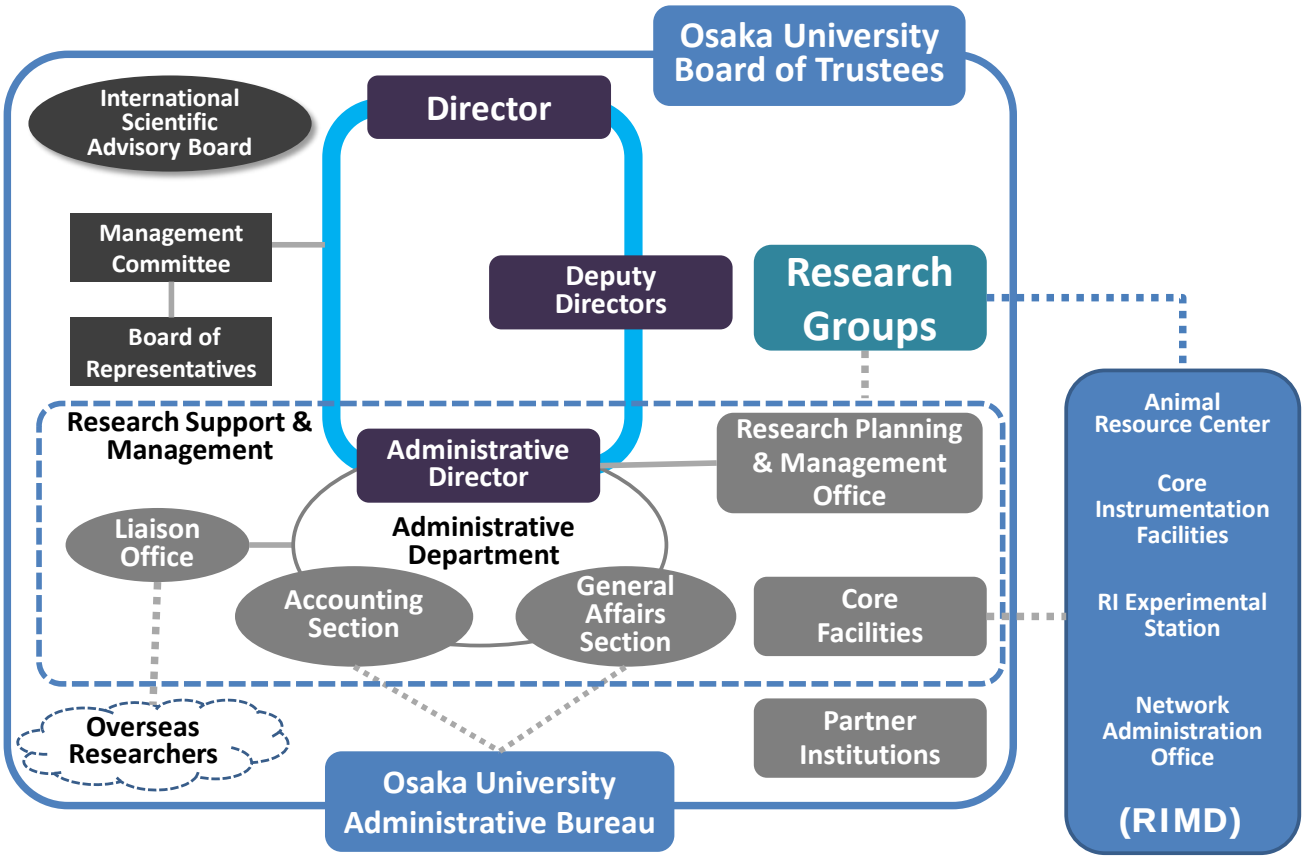
- Indicate the number of international research conferences or symposiums held in FY2012 and give up to three examples of the most representative ones using the table below.

FY2012: 2 meetings

Major examples (meeting title and place held)	Number of participants
Dynamism of Immune Reactions & Regulation May 22-23, 2012, Osaka International Convention Center (OICC GRAND CUBE OSAKA) Conference Hall, Osaka	From domestic institutions: 350 From overseas institutions: 150
LICHT Leica Center opening seminar June 22, 2012,Taniguchi Memorial Hall, Osaka University	From domestic institutions: 70 From overseas institutions: 30

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)



5. Campus Map

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

6. FY2012 Project Expenditures (the exchange rate used: 1USD= 80JPY)

i) Overall project funding

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	37
	Principal investigators (no.22 of persons):	230
	Other researchers (no. 135 of persons):	767
	Research support staffs (no. 51 of persons):	274
	Administrative staffs (no. 27 of persons):	152
	Total	1460
Project activities	Gratuities and honoraria paid to invited principal investigators (no.0 of persons):	0
	Cost of dispatching scientists (no.8 of persons):	16
	Research startup cost (no. 0 of persons):	0
	Cost of satellite organizations (no.0 of satellite organizations):	0
	Cost of international symposiums (no.1 of symposiums):	15
	Rental fees for facilities	6
	Cost of consumables	5
	Cost of utilities	64
	Other costs	608
	Total	714
Travel	Domestic travel costs	1
	Overseas travel costs	6
	Travel and accommodations cost for invited scientists (no. 0 of domestic scientists): (no. 3 of overseas scientists):	6
	Travel cost for scientists on secondment (no. 2 of domestic scientists): (no. 4 of overseas scientists):	2
	Total	15
Equipment	Depreciation of buildings	503
	Depreciation of equipment	804
	Total	1307
Other research projects	Projects supported by other government subsidies, etc.	55
	Commissioned research projects, etc.	1005
	Grants-in-Aid for Scientific Research, etc.	617
	Total	1677
Total		5173

Ten thousand dollars

WPI grant		16800
		0
Cost of equipment procured		130
BD FACSVerse flow cytometer system Number of units: 1	Costs paid:	15
confocal laser scanning microscope Number of units: 1	Costs paid:	15
405nm laser system for upgread Number of units:	Costs paid:	5
server system Number of units:1	Costs paid:	1
retortome Number of units: 1	Costs paid:	1
cooled centrihuges Number of units: 1	Costs paid:	1
vabration removal board for TCSMP5 Number of units: 1	Costs paid:	13
file server system Number of units:1	Costs paid:	12
405nm laser source kit Number of units:1	Costs paid:	8
LipidSearch academic lisense Number of units:1	Costs paid:	4
mouse cage system Number of units: 1	Costs paid:	46
individually ventilated cage system Number of units: 1	Costs paid:	5
others		4

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (no. 0 of persons):	
	Other researchers (no. 1 of persons):	
	Research support staffs (no. 0 of persons):	
	Administrative staffs (no. 0 of persons):	
	Total	9
Project activities		0
Travel		0
Equipment		0
Other research projects		64
Total		73

Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY2012 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.

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 FY2012. 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: NONE

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2012					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2012					

Overseas Satellite 2: NONE

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2012					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2012					

FY 2012 Visit Records of World Top-caliber Researchers from Abroad

Researchers Total: 29

Name (Age)	Current 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)
Michel L.Tremblay (61)	Professor, Rosalind and Morris Goodman Cancer Research Center, McGill University	PhD Oncology:Biochemistry	Fellow of the Royal Society of Canada Prix Victor-Morin 1974 the Prix France-Québec 1984 Chalmers Award 1994Molson Prize	April 1,2012– August 31, 2012 152 days	Stay for joint research;Seminar
Xuetao Cao (49)	President of Chinese Academy of Medical Sciences; President of FIMSA (Federation of Immunological Societies of Asia-Oceania)	PhD Immunobiology; immunotherapy	2006 First-class Prize of Chinese medical science and technology Awards; 2002 First-class Prize of Shanghai Science and Technology Progress Awards; 1998 First-class Prize of Military Science and Technology Progress Awards	May 21-24, 2012 4 days	Participation in Symposium
Max Cooper (80)	Professor of Pathology and Laboratory Medicine and Emory Vaccine Center, Emory University School of Medicine, USA	MD Immunology; Virology; Immune system ontogeny and phylogeny	3M Life Sciences Award; Sandoz Prize for Immunology; American Association of Immunologists Lifetime Achievement Award; Avery-Landsteiner Prize; American College of Physicians Award; Life 'Member d'Honneur' of the French Society of Immunology	May 21-24, 2012 4 days	Participation in symposium
Mark Davis (-)	Director, Stanford Institute for Immunity, Transplantation and Infection, Stanford University, USA	MD, PhD, Biophysics; Immunology; Microbiology;	1989 Gairdner Foundation International Award; 1993 Member, National Academy of Sciences;	May 21-24, 2012 4 days	Participation in symposium

			1996 Alfred P. Sloan Prize from the General Motors Cancer Research Foundation; 1998 Novartis Prize for Basic Immunology; 2000 American Academy of Arts and Sciences; 2000 William B. Coley Award from the Cancer; Research Institute The Rose Payne Award, American Society for Histocompatibility and Immunogenetics; 2003 The Ernst W. Bertner Memorial Award		
Michael Dustin (-)	Muriel G and George W Singer Professor of Molecular Immunology Co-director, NYU Cancer Institute; Director, NYU Cancer Institute Flow Cytometry Core, USA	PhD Vaccination; autoimmunity; cancer immunotherapy	Fellow of the American Association for the Advancement of Science (AAAS)	May 21-24, 2012 4 days	Participation in symposium
Scott Fraser (-)	Rosen Professor of Biology and Professor of Engineering and Applied Science at the California Institute of Technology, USA	PhD Biophysics	1990 American Association for the Advancement of Science; 1984–87McKnight Scholar Award; 1983Kaiser-Permanente Award	May 21-24, 2012 4 days	Participation in symposium
Ronald Germain (65)	Chief, Laboratory of Systems Biology, Chief, Lymphocyte Biology Section, LSB National Institutes of Health, National Institute of Allergy and Infectious Diseases, USA	MD, PhD Systems Biology	2008 Associate (foreign) member of EMBO; 2008 Landsteiner Medal of the Austrian Society for Allerology and Immunology Distinguished Lecturer; 2006 American Association of Immunologists	May 21-24, 2012 4 days	Participation in symposium

Diane Mathis (-)	Professor Harvard Medical School, Senior Investigator at Joslin Diabetes Center; Associate Member at the Broad Institute, USA	PhD Immunology; Immunogenetics	2012 Columbia Awards; 2003 National Academy of Sciences Romancon Prize; Foundation Athena Research Prize	May 21-24, 2012 4 days	Participation in symposium
Josef Penninger (49)	Senior Scientist and Scientific Director, Institute of Molecular Biotechnology, Austria	PhD Immunology; Molecular Biology;	2007 Ernst Jung-Preis for Medicine; 2006 Descartes Prize 2007 Austrian Academy of Sciences; 2008 Carus Medal from the German Academy of Sciences Leopoldina; 2008 Karl Landsteiner prize;	May 21-24, 2012 4 days	Participation in symposium
Fiona Powrie (-)	Head of Nuffield Department of Medicine -Exp Medicine; Group Head/PI and Unit Director University of Oxford, UK	PhD Immunology; Infectious Disease	2011 Inaugural Sidney Truelove Professor of Gastroenterology within the Nuffield Department of Clinical Medicine in Oxford; Fellow of the Royal Society; 2012Louis-Jeantet Prize for Medicine	May 21-24, 2012 4 days	Participation in symposium
Alexander Rudensky (-)	Investigator, Memorial Sloan-Kettering Cancer Center; Howard Hughes Medical Institute (HHMI), USA	PhD Immunology; Immuno therapy	American Association of Immunologist, Searle Scholar Award; Pharmingen Investigator Award from the American Association of Immunologists; Sandler Foundation Senior Investigator award; NIH Merit Award; NAS associate	May 21-24, 2012 4 days	Participation in symposium
Eric Betzig (-)	Janelia Farm Research Scientist, Howard Hughes Medical Institute(HHMI), USA	PhD Applied & engineering physics	William L. McMillan Award; National Academy of Sciences Award for Initiatives in Research	June 1 2012 1 day	Seminar

Michael C. Carroll (63)	Senior Investigator, PCMM at Boston Children's Hospital; Professor of Pediatrics, Harvard Medical School, USA	PhD Immunology	1999-2000 Member Basel Institute for Immunology	August 22. 2012 1 day	Seminar
Dominique Soldati-Favre (-)	Vice Dean, Basic Research, Faculty of Medicine, University of Geneva, Switzerland	PhD Molecular biology; Parasitology	2012 HHMI Senior International Research Scholar; 2011 Nomination as EMBO Member	September 9-16, 2012 8 days	Research meeting
Antonio Lanzavecchia (62)	Professor and Director, Institute for Research in Biomedicine, Human Immunology, ETH Zurich, Switzerland	MD Immunology; Molecular Biology	1988 EMBO gold medal; 1999 Cloëtta Award, Zurich, Switzerland; 2001 Cavaliere della Repubblica, Italy Italian Society for Immunology, Clinical Immunology and Allergology (SIICA); European Molecular Biology Organization (EMBO); Henry Kunkel Society (HKS) Royal College of Physicians; Swiss Society for Immunology and Allergology (honorary member); American Society for Immunology (honorary member)	September 10, 2012 1 day	Participation in symposium
Peter Sarnow (-)	Professor and Chair, Dept. of Microbiol and Immunology, School of Medicine, Stanford University, USA	PhD Microbiology; Immunology	2010 Fellow, American Association for the Advancement of Science; 2006 The Sidney and Skippy Frank Prize, Institute for Immunity, Transplantation and Infection,	September 10, 2012 1 day	Participation in symposium

			Stanford University; 1992-1997Faculty Research Award, American Cancer Society		
Renato Zenobi (52)	Professor, Department of Chemistry and Applied Bioscience, ETH Zurich, Switzerland	PhD Biochemistry	2009 Honorary membership of the Israel Chemical Society; 2006 Michael Widmer Award; 2005 Theophilus Redwood Lectureship; 1998 Emanuel Merck-Prize	September 14, 2012 1 day	Seminar
Ahmet Yildiz (34)	Assistant Professor, Department of Physics, and Molecular Cell Biology, University of California, Berkeley, USA	PhD Biophysics	2011Hellman Faculty Award; 2009-2013 Ellison Medical Foundation New Scholar Award in Aging; 2006-2009 Grand Prize Winner of the Young Scientist Award, AAAS and GE Healthcare; 2003 First Prize Winner of Gregory Weber International Prize in Biological Fluorescence;	September 25, 2012 1 day	Seminar
Gerald Pollack (-)	Professor, University of Washington, USA	PhD Biomedical Engineering	2005 Honorary Professor, Russian Academy of Sciences	October 10, 2012 1 day	Seminar
Thomas T. Perkins (-)	Principal Investigator JILA, National Institute of Standards and Technology , University of Colorado, USA	PhD Single molecule Biophysics	American Physical Society (2012) Marinus Smith Award	November 2, 2012 1 day	Seminar
Zoltan Fehervari (-)	Senior Editor, Nature Immunology, Nature Publishing Group	PhD Immunology; Public Understanding of science	-	November 1, 2012 1 day	Seminar
Robert A. Cross (-)	Professor and Director, Centre for Mechanochemical Cell Biology, Warwick Medical	PhD Cell Biology; Molecular Biology	EMBO Fellow; Honorary Professor in Molecular Cell Biology, University of Kent at Canterbury	November 2, 2012 1 day	Seminar

	School, UK				
Jeroen Roose (-)	Assistant Professor, Department of Anatomy, University of California San Francisco, USA	PhD Immunology; Molecular Biology	2012 Gabrielle's Angel Foundation for Cancer Research Award	November 17-18, 2012 2 days	Seminar
Ludovic Jullien (50)	Professor, Ecole Normale Supérieure, Département de Chimie, France	PhD Chemistry	2012 Prix du Dr. et de Mme Henri Labbé de l'Académie des Sciences (Chemical Biology)	November 22, 2012 1 day	Research meeting, Seminar
Michel C. Nussenzweig (-)	Investigator, Howard Hughes Medical Institute; Senior Physician, Sherman Fairchild Professor, The Rockefeller University, USA	MD, PhD Molecular Immunology	2011 The U.S. National Academy of Sciences and the Brazilian Academy of Sciences; 2008 Lee C. Howley Sr. Prize for Arthritis Research Member of the American Academy of Arts and Sciences (2011)	December 1-4, 2012 4 days	Research meeting, Seminar
Lawrence Steinman (66)	Professor, Neurology and Neurological Sciences, Pediatrics, and Genetics; Chair of the Program in Immunology, Stanford University, USA	MD Neurological Sciences	1994 Dr. Friedrich Sasse Award for Outstanding Contributions in Immunology from the Free University of Berlin; 2004 John M. Dystel Prize for Outstanding Contributions in Multiple Sclerosis Research, National MS Society & the American Academy of Neurology; 2004 Outstanding Inventor Stanford University; 2009 Elected to Institute of Medicine, National Academy of Sciences USA;	December 3-4, 2012 2 days	Research meeting, Seminar
Suzanne Cory (71)	Research Professor, Molecular Genetics of Cancer	PhD Molecular Biology	2010 Colin Thomson Medal; President of the 2010 Australian	December 22, 2012 1 day	Seminar

	Division at The Walter and Eliza Hall Institute of Medical Research (WEHI) Vice-Chancellor's Fellow, The University of Melbourne, Australia		Academy of Science; 2002 Royal Medal of the Royal Society; 2002 Associate Foreign Member of the French Academy of Sciences; 2001 Foreign Member of the American Academy of Arts and Sciences; 2001 L'Oréal-UNESCO Women in Science Award; Foreign Member of the US National Academy of 1997 Sciences of the US		
Jerry Adams (73)	Joint-Head of the Molecular Genetics of Cancer Division, The Walter and Eliza Hall Institute of Medical Research (WEHI) Australia	PhD Molecular Biology	2007 Member of the Medical Research Advisory Committee at the Australian Cancer Research Foundation (ACRF)	December 22, 2012 1 day	Seminar
Roman Jerala (51)	Professor, Laboratory for Biotechnology, National institute of chemistry, Slovenia	PhD Biochemistry; Synthetic biology; structural biology	Zois award (highest Slovenian national scientific award); 2009 National Institute of Chemistry Pregl award for exceptional scientific achievements; 2008 Slovenian Science Foundation Prometheus of Science award	March 27-30, 2013 4 days	short-term stay for joint research

State of Outreach Activities

- Using the table below, show the achievements of the Center's outreach activities in FY2012 (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 FY2012 resulting from press releases and reporting.

Activities	FY2012(number of activities, times held)
PR brochure, pamphlet	4
Lectures, seminars for general public	3
Teaching, experiments, training for elementary and secondary school students	2
Science cafe	7
Open houses	5
Participating, exhibiting in events	4
Press releases	13

Special Achievements

- The two IFReC PIs from abroad, Dr. Smith and Dr. Standley gave talk titled "In touch with Science" at Senri and Osaka International Schools of Kwansei Gakuin (Suita, Osaka).
- Out of the seven science cafes, three events were organized as "Career-development Lectures for younger generation" at Suma Gakuen High & Junior High School, and Mukogawa Women's University. The lectures were designed to let students know about "true scientists" and "scientists' lives".
- Director Akira talked to students and parents about his school days and what inspired him to become a researcher at "FIRST Science Forum 3 in Kyoto". The event was broadcasted by NHK educational channel at a later date.
- A member of Research Planning and Management Office at IFReC was appointed a committee of "Outreach Working Group" of Osaka University. He formed a series of recommendations about the policy of outreach activities of the University with other 8 committee members.

FY 2012 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	2012.4.21 2012.4.23	Asahi Shimbun Kobe Shimbun	Science Café will be held "Dendritic Cells are key players in the immune system" (Prof. Kaisho)
2	2012.4.23	Yomiuri Shimbun	Discovery of innate immune cells (Prof. Sakaguchi, Prof. Takeda)
3	2012.6.7 2012.6.21	Asahi Shimbun	Vol.1 Treatment for serious disease Vol.2 Fostering young human resources by showing my back (Prof. Kishimoto)
4	2012.6.14	Nikkei Shimbun	Pursuit to clarify whole picture of immune system (IFReC)
5	2012.8.6	Yomiuri Shimbun	Semaphorin plays a pivotal role in cell activation (Prof. Kumanogoh, Associate Prof. Toyofuku)
6	2012.8.8	Nikkei Shimbun	Kansai area leads medical research in Japan (Prof. Akira)
7	2012.10.7	Yomiuri Shimbun	Nominees for the Nobel Prize in Physiology of Medicine are laureates of other international awards (Prof. Akira)
8	2012.10.9	Nikkei Shimbun	Fundamental research got long-awaited prize. The number of Japanese researchers awarded international medical prizes has been increased since year 2000 (Prof. Akira)
9	2012.10.9	Nikkei Shimbun	Profile of Dr. Yamanaka (Prof. Kishimoto)
10	2012.10.9	Nikkei Shimbun	Nobel Prize for Japanese scientist enhances confidence of young researchers (Prof. Kishimoto)
11	2012.10.10	Nikkei Shimbun	iPS cells lead new era in science, text books will be rewritten (Prof. Kishimoto)

12	2012.10.18	Mainichi Shimbun	Three turning points (vol.2) The way to reach Nobel Prize (Prof. Kishimoto)
13	2012.10.23	Mainichi Shimbun	Elucidation of activity of regulatory T-cells (Prof. Sakaguchi)
14	2012.11.22 2012.11.25	Mainichi Shimbun Yomiuri Shimbun	Protein that regulates inflammation has been detected (Prof. Arase)
15	2012.11.24	Yomiuri Shimbun	Llipocalin2 suppresses activity of malaria parasite (Associate Prof. Coban)
16	2012.12.3	Mainichi Shimbun	What is science café that began to take root in Japan? (IFReC)
17	2012.12.21	Yomiuri Shimbun	Formation of world premier international center initiatives proceeds well.
18	2013.1.17 2013.1.18	Nikkei Shimbun, Mainichi Shimbun Asahi Shimbun	Development of therapeutic medicine for osteoporosis is expected (Prof. M. Ishii)
19	2013.2.18	Yomiuri Shimbun	Two types of osteoclastic cells have been detected (Prof. M. Ishii)
20	2013.3.17 2013.3.22	Nikkei Shimbun Yomiuri Shimbun	Mechanism of inflammation related with gout has been clarified (Prof. Akira, Associate Prof. Saito)
21	2013.3.21	Yomiuri Shimbun Nikkan Kogyo Shimbun	Research team at Osaka University discovered a gene that controls fat accumulation (Prof. Akira, Assistant Prof. Sato)
22	2013.3.28	Yomiuri Shimbun	Discovery of regulatory T cell that suppress immune reaction (Prof. Sakaguchi)