World Premier International Research Center Initiative (WPI)

Executive Summary (For Extension application screening)

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

A. Progress Report of the WPI Center

I. Summary

In 2007, IFReC set out to integrate imaging and informatics technologies with immunology (IFReC's three **I**s), aiming to unveil spatio-temporal and collective behavior of immune cells and molecules *in vivo* for comprehensive understanding of immune dynamism. While overcoming intellectual and technical perplexities encountered at early stages in collaboration of researchers in different fields or with different backgrounds, through strategical establishment of platforms for such interdisciplinary research, our all-out effort has ultimately resulted in a number of immunologically important discoveries as well as publication of more than 800 papers with an average number of citations of 29.2. Above all, new insight into the immune-regulating mechanism is the foremost achievement attained so far, which is expected to produce new seeds of clinical immunology for diagnosis, therapy and prevention of immune-related diseases.

II. Items

1. Overall Image of Your Center

IFReC has become a globally visible stronghold of top-class immunologists, and imaging and informatics researchers, rallying to comprehensively understand immune dynamism, while advancing frontier researches in their own fields. Considering the spacious laboratories, animal resource facilities, and instalment of highly advanced instruments, the entire research environment of IFReC is of the highest international level. The research support/administration system is also arranged for smooth and effective operation, enabling IFReC researchers to concentrate on research as well as supporting overseas researchers.

2. Research Activities

Research environment Of 27 research groups: immunology (18), imaging (7) and bioinformatics (2), the 16 core groups have spacious laboratories in close collaboration in the Integrated Life Science (ILS) Building and the connected IFReC Research Building. Taking advantage of location on the same site, IFReC and the Research Institute for Microbial Diseases (RIMD) jointly operate facilities including three animal resource center buildings and a core instrumentation facility equipped with top-grade instruments. IFReC is very proud of the establishment of such a cohesive research environment.

Research results to date Research productivity at IFReC has been maintained at very high levels ever since the beginning. More than 800 papers have been published so far, and their quality as a whole is also exceedingly high as indicated not only by their average number of citations but by the fact that Osaka University was ranked 1st in citation impact among the top institutions in immunology all over the world (Essential Science Indicators for 2003-2013 by Thomson Reuters©), to which IFReC researchers made major contribution. Of note is a clear trend in the increase of papers in interdisciplinary ("fusion") research and medical immunology fields (see section A-3). In addition, the 40 "top papers" described in the accompanying progress report can be regarded as achievements of

great importance to clinical immunology.

Competitive and other research funding The number of large-scale government-sponsored competitive grants obtained by our PIs has been increasing annually as demonstrated by a grant to Akira from the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST). Many young researchers, including those from abroad, have also acquired MEXT grants-in-aid for scientific research. These trends are due in part to the high quality of science at IFReC together with the support systems of Osaka University and IFReC that assist researchers to apply for external grants.

Generous donations from the Kishimoto Foundation every year are indispensable both to the reinforcement of research activity by setting up and maintaining a new research laboratory and to the continuation of Kishimoto Fellowship/Scholarship for young researchers from abroad to work at IFReC (see section A-4).

State of joint research Osaka University has exchanged comprehensive research contracts with the National Institute of Information and Communications Technology (NICT) and RIKEN, which resulted in the construction of the Center for Information and Neural Networks (CiNet) of NICT and Quantitative Biology Center (QBiC) of RIKEN at the Suita Campus of the University. Both centers are headed by an IFReC deputy director, Yanagida. IFReC has concluded satellite or partner contracts with many domestic institutions including the National Institute of Biomedical Innovation (NIBIO) and RIKEN Center for Integrative Medical Sciences.

Appraisal by society and scientific organizations Among many awards given to IFReC researchers, the most prestigious are the Crafoord Prize (2009) and the Japan Prize (2011) to Kishimoto and Hirano, and Canada Gairdner International Award to Akira (2011). Akira (2009) and Yanagida (2013) have been accredited as Persons of Cultural Merit of Japan. The National Academy of Sciences of USA elected Akira and Sakaguchi to its foreign associates in 2009 and 2012, respectively.

Feeding research outcomes back into society The number of patent applications has steadily expanded. For medical/clinical immunology, in addition to a steady increase in the number of clinically-oriented papers, many groups have started research projects using clinical samples in collaboration with Osaka University Hospital clinician/physician scientists. Furthermore, a few clinical trials of immune-therapy are in progress.

Outreach activities IFReC has been actively engaged in outreach activities such as introductory seminars and lectures to general citizens and school students. These activities were made successful thanks to the prevailing recognition of their importance within IFReC as indicated by the fact that most researchers willingly participate in the outreach events when requested.

3. Interdisciplinary Research Activities

Undertakings toward creating new interdisciplinary domains Conversion of half of the 3rd floor of the research building into “Live Immune-Imaging facility” is a highlight of IFReC’s determination to aggressively promote “fusion” research. The facility consists of rooms with advanced imaging instruments including 11.7T MRI and the adjacent animal-rearing room in specific pathogen-free environment, enabling researchers to observe immune phenomena in the same animals over a few weeks.

IFReC has established three financial support programs to promote “fusion” research: the “Research Support Program for Combined Research Field” is to encourage researchers with different specialties or research backgrounds to collaborate; the “Dual Mentor Program” is to support graduate students or young post-doctoral fellows engaging in “fusion” projects under the supervision of two PIs from different disciplines; and the “Fusion Research Units Program” is to set up semi-independent groups consisting of talented young researchers selected from different IFReC laboratories. Collaboration of IFReC with CiNet and QBiC has been gradually accelerated, since their methodologies and

technologies are necessary for immunologists to open new vistas in immunology through “fusion” researches as described in B-1.

Results of “fusion” studies The number of “fusion” papers based on outcomes of such studies has gradually increased year by year from 2009 to the present, exceeding 15% of the total publications in 2011, of which, 14 were published in high-impact journals. Such remarkable advancement of “fusion” studies is, in part, due to the IFReC-implemented strategies to promote “fusion” studies as well as a plenitude of research facilities equipped with highly advanced instruments. However, the indefatigable efforts of researchers to improve the performance capacity of their technology for the purpose of immunological experiments should be accorded due appreciation.

4. International Research Environment

The percentage of overseas researchers exceeded the WPI target level of 30% in 2010 and has been maintained (contribution of annual donation from the Kishimoto Foundation is described above). IFReC researchers have started to secure new positions in research institutions both in Japan and overseas. As IFReC has been recognized worldwide, it has drawn interest from institutions overseas. We have academic cooperation agreements with six overseas partner institutions. IFReC also saw many visitors including foreign government officials and pharmaceutical companies seeking interaction or collaboration between researchers. In addition to the annual international symposia we host, IFReC and Singapore Immunology Network have jointly organized the annual Winter School on Advanced Immunology every year since 2012 to globally foster young immunologists.

5. Organizational Reforms

Decision–making system Authorized by Osaka University, the director has made major decisions regarding personnel and budget allocation as well as other administrative matters, to which the Administrative Director has given full support by acting as a coordinator with the Deputy Directors and by executing management actions through the administrative office. This top-down decision-making system, significantly different from the management systems in other faculties and institutes within the University, has been well understood and implemented through the whole organization of IFReC.

Research support system IFReC’s administration system consists of General Affairs and Accounting sections together with the Research Planning and Management Office (RPMO). More than two-thirds of the staff are capable of administrative work in English. RPMO is composed of five PhD holders with research experience and bilingual administrative staff, covering logistics of symposia and seminars, support of grant application, management of intellectual property, purchase procedures for instrumentation, outreach activities, etc. RPMO has proved effective in facilitating communication between researchers and administrative staff.

System reforms Through the aforementioned top-down decision-making system and rapid and flexible execution of administrative procedures, we have established a unique organization in Japan where researchers can devote themselves to their research. The University Support Office for Large-Scale Education and Research Projects (established in FY2009) launched its team of university research administrators taking RPMO as a role model for its support system for international researchers to make successful applications for external competitive funds.

Host institution’s commitment Construction of research centers (CiNet and QBiC) of other national organizations within the campus of Osaka University is a first in national universities. Solid collaboration of IFReC with these centers has made significant impacts on other institutions both inside and outside of the University. In the Second Medium-Term Plan of the University (FY2010-2015), active support to sustain and advance IFReC is given one of the top priorities by the university. The university constructed the ILS Building and gave financial support for construction of a new building of the animal resource center. The university also constructed a new accommodation facility, Kasugaoka

House, for visiting researchers from abroad. Together with these facility improvements and posting of a number of experienced administrative staff, the University has duly committed on the support of IFReC as its host institution.

6. Others

In addition to annual orientation for newcomers, we have implemented a series of seminars/ lectures since FY2013 for faculty and staff development to raise morale and skills as well as consciousness of compliance. In the orientation for researchers, the rules and safety measures to use the facilities at IFReC are emphasized. Researchers with outstanding careers are invited as speakers of the seminars for IFReC staff to learn about different career paths and development, while the lectures are delivered by IFReC faculties for administrative staff to understand outlines of the research being done at IFReC.

World Premier International Research Center Initiative (WPI)
Progress Report of the WPI Center
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** Write your report within 30 pages. (The attached forms are in addition to this page count.) Keep the length of your report within the specified number of pages.*

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

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

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

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

IFReC is a stronghold of researchers in immunology, imaging and informatics, rallying for comprehensive understanding of immune dynamism. While advancing frontier researches in their own fields, they collaborate to reveal spatio-temporal and collective behavior of immune cells and molecules *in vivo*. Outcomes of such studies make great contributions to medical and clinical immunology for human welfare, which then provides new seeds for basic research of immunology and related fields.

IFReC consists of 25 research groups - immunology (15), imaging (8) and bioinformatics (2). Laboratories of the 16 core groups are located in close collaboration in the Integrated Life Science (ILS) building and the connected IFReC Research building. IFReC and the Research Institute for Microbial Diseases (RIMD) jointly operate facilities including three buildings of animal resource center and the core instrumentation facility equipped with top-grade instruments.

In this self-contained research environment, the research at IFReC has been maintained at a very high level in both quantitative and qualitative aspects. More than 800 papers have been published so far with an average number of citations of 29.2. Thus, IFReC researchers made a major contribution to rank Osaka University 1st in citation impact among the top institutions in immunology all over the world (Essential Science Indicators for 2003-2013 by Thomson Reuters©). In addition, the percentage of clinically-oriented papers has been steadily increasing. In collaboration with Osaka University Hospital clinicians/physician scientists, many groups have started research projects using clinical samples, and a few clinical trials of immune-therapy are already in progress.

Among the many awards given to researchers of IFReC since its establishment, the most prestigious are the Crafoord Prize (2009) and the Japan Prize (2011) to Kishimoto and Hirano, and Canada Gairdner International Award to Akira (2011). Akira (2009) and Yanagida (2013) were accredited as Persons of Cultural Merit of Japan. The National Academy of Sciences elected Akira and Sakaguchi to its foreign associates in 2009 and 2011, respectively.

The high quality of science at IFReC has been reflected in the large-scale government-sponsored

grants obtained by our PIs as represented by a grant to Akira from the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST). Many young researchers, including those from abroad, have also acquired MEXT grants-in-aid for scientific research.

Interdisciplinary ("fusion") research activities have increased the number of papers produced by collaborations and the development of new technologies useful for immunology. This is attributable to our efforts to promote "fusion" research including Research Support Program for Fusion of Different Fields, Dual Mentor Program, and Fusion Research Unit, as well as financial start-up support for junior PIs. These programs are all consistent with IFReC's mission of fostering excellent young researchers for the next generation and will benefit the employment of female PIs in the future.

The Center for Information and Neural Networks (CiNet) of the National Institute of Information and Communications Technology (NICT) and Quantitative Biology Center (QBiC) of RIKEN, both headed by an IFRec deputy director Yanagida, were established in Suita Campus of Osaka University. The main focus of CiNet is technological innovation to allow for the direct imaging of the dynamic states of brains, while QBiC focuses on quantitative and comprehensive studies to predict and control biological activities. Thus, their challenges to understand complex systems completely meet research strategies of "fusion" researches at IFReC. The collaboration of IFReC with CiNet and QBiC serves as a role model for a new research structure in Osaka University and Japan's research institutions.

The percentage of overseas researchers exceeded the WPI target level of 30% in 2010 and has been maintained, to which generous support from the Kishimoto Foundation established in 2009 has greatly contributed. Many researchers who left IFReC have secured new positions in research institutions both in Japan and overseas.

As IFReC has been recognized worldwide, it has drawn interest from overseas institutions. At present, we have academic cooperation agreements with four overseas partner institutions. IFReC also sees many visitors including foreign government officials and pharmaceutical companies seeking collaboration between researchers. In addition to the annual international symposia we host, IFReC and Singapore Immunology Network agreed to jointly organize the annual Winter School on Advanced Immunology and has held it successfully every year since 2012 to foster young international immunologists

A top-down decision-making system, differing from the management systems in faculties and institutions within the University, is well understood and implemented through the whole of IFReC. The Research Planning and Management Office (RPMO), consisting of five PhD holders with research experience and bilingual administrative staff, covers logistics of symposia and seminars, support for grant application, management of intellectual property, purchase procedures for instrumentation, outreach activities, etc. The Liaison Office, a team consisting of selected bilingual staff, plays a major role in supporting our international researchers in areas including facility orientation, research funds acquisition, medical treatment and welfare, etc. Through these activities, RPMO serves as a role model for the University Research Administrator (URA) System in Osaka University.

The University has positioned IFReC as a core of scientific development in its mid and long term plans, taking various measures to sustain and advance IFReC. Most notable is construction of the ILS Building, a building of animal resource center, and an accommodation facility—Kasugaoka House—for visiting researchers from abroad. In addition, the University has implemented various new programs compatible with WPI schemes, from which IFReC has received much benefit in various aspects.

2. Research Activities (within 15 pages)

2-1. Research results to date

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

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

[1]
(Papers underscoring the research achievement above and their brief account: [Appendix 2-1] 1-X)

. . .

[10]
(Papers underscoring the research achievement above and their brief account: [Appendix 2-1] XX-40)

The research at IFReC has been maintained at a very high level in both quantitative and qualitative aspects ever since its establishment. Thus, the number of papers by authors affiliated with IFReC in each fiscal year has steadily increased from 2008 onward. More than 800 papers have been published so far, and the average number of citations of these papers was 29.2 and the *h*-index* of IFReC as a whole was 65 (*a measure of both the productivity and impact of the published work of a scientist or organization: Hirsch, J. E., *PNAS* **102**: 16569–72, 2005). Such a high research level at IFReC has made Osaka University ranked 1st in citation impact among the top institutions in immunology all over the world (Essential Science Indicators for 2003-2013 by Thomson Reuters©).

The main trend in the papers being produced is the increase in interdisciplinary research fields (See section 3-3) and medical immunology fields. The 40 “top papers” described in Appendix-2 contain the 14 papers in interdisciplinary research fields in Appendix 3. Papers in medical immunology fields include those on inflammatory diseases (Akira and Arase groups), various autoimmune diseases (Kurosaki, Sakaguchi, Kumanogoh, Kikutani, Kinoshita, Kishimoto, and Hirano groups), infectious diseases (Coban, Ken Ishii, Takeda, and Yamamoto groups), osteoporosis (Masaru Ishii group), adult diseases (Akira group), etc. As will be detailed in section 2-6-1, a number of practical seeds of medical/clinical immunology have been produced from these achievements for development of diagnosis, therapy and prevention of immune-related diseases, and a few clinical trials are already under way in collaboration with Osaka University Hospital.

***[1] Pathogen recognition and innate immune responses**

The primary responses against various pathogens are very important to understand immunological functions and physiology. Akira and IFReC groups have proposed a variety of new models in innate immune systems.

Saito and Akira groups showed that Macrophage-inducible C-type lectin (Mincle), which is expressed mainly in macrophages, selectively associated with the Fc receptor common γ-chain and activated macrophages to produce inflammatory cytokines and chemokines ([Appendix 2-1] 1).

Akira group identified interferon-inducible tripartite-motif (TRIM) 56 as a regulator of double-stranded DNA-mediated type I interferon induction. TRIM56 overexpression enhanced IFN-β promoter

activation after double-stranded DNA stimulation whereas TRIM56 knockdown abrogated it ([Appendix 2-1] 2).

Akira group showed that neutrophil extracellular traps (NETs) capture human immunodeficiency virus (HIV)-1 and promote HIV-1 elimination through myeloperoxidase and α-defensin. They succeeded in the direct observation of NETs-HIV complex by Super-resolution Structured Illumination Microscopy ([Appendix 2-1] 3).

***[2] Formation of inflammasome and inflammation**

In the mechanism of regulation of inflammatory response, inflammasome activation plays crucial roles. Akira group has shown the critical link between inflammasome formation and inflammation.

They identified Atg16L1 (autophagy-related 16-like 1) as an essential component of the autophagic machinery responsible for control of the endotoxin-induced inflammatory immune response ([Appendix 2-1] 4). They showed that activation of NLRP3 inflammasome is promoted by microtubule-driven spatial arrangement of mitochondria. This fact explains functional mechanism of traditional gout medication ([Appendix 2-1] 5).

***[3] New findings on M2 macrophages**

Macrophages are functionally polarized into M1 and M2 cells in response to infection with microorganisms and host mediators. M2 macrophages have important roles in responses to parasite infection, tissue remodeling, angiogenesis and tumor progression.

Akira group has provided new insight into the function of M2 macrophages in immune responses. They showed that the H3K27me3-specific demethylase Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection ([Appendix 2-1] 6). They also showed that a pseudokinase protein Trib1 deficiency causes a severe reduction of M2-like macrophages in various organs, including bone marrow, spleen, lung and adipose tissues. The results suggest that Trib1 is critical for adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue-resident M2-like macrophages ([Appendix 2-1] 7).

***[4] Toward the development of effective vaccines**

For developing optimal vaccines for clinical applications, it is important to understand the mechanisms of the vaccines' actions on immune systems in terms of efficacy as well as safety.

Akira and K. Ishii groups demonstrated *in vivo* that TANK-binding kinase 1, a non-canonical IκB kinase, mediates the adjuvant effect of DNA vaccines and is essential for its immunogenicity in mice ([Appendix 2-1] 8).

K. Ishii group further revealed that DNA released from dying host cells mediates the activity of aluminum-based adjuvants, widely used in human vaccination ([Appendix 2-1] 9).

***[5] New findings in mucosal immunology**

The gastrointestinal tract is constantly exposed to food proteins and commensal bacteria. Studies of the intestinal immune system have yielded key information about immunological tolerance and inflammatory bowel diseases.

Akira group revealed the regulation mechanism of humoral and cellular gut immunity by lamina propria dendritic cells (LPDCs) expressing Toll-like receptor 5. The findings demonstrated unique properties of LPDCs and the importance of TLR5 for acquired immunity in the intestine ([Appendix 2-1]

10).

Takeda group showed the importance of commensal bacteria and ATP for Th17 differentiation in health and disease, and offered an explanation of why Th17 cells specifically present in the intestinal lamina propria ([Appendix 2-1] 11). They also revealed the role of the caecal patch as a major site for generation of IgA-secreting cells (Nat Commun 2014).

***[6] Immune responses to malaria infection**

About 3.4 billion people, half of the world's population, are at risk of malaria. The number of malaria patients tested by microscopic examination was 188 million in 2012 (World Malaria Report 2013, WHO). Countermeasure developments against malaria are the responsibility of developed nations.

Coban group determined that Lipocalin 2, a host protein that sequesters iron, is abundantly secreted during human and mouse blood-stage malaria infections and is essential to control P. *yoelii*NL parasitemia, anemia, and host survival. They concluded Lipocalin 2 has multiple tasks in immunity against malaria ([Appendix 2-1] 12). Furthermore, the group showed that the olfactory bulb is a site for the initiation of cerebral malaria (published in FY2014).

***[7] Immune responses to Toxoplasma**

Toxoplasmosis is considered to be a leading cause of death attributed to foodborne illness. More than 60 million people in the USA carry the Toxoplasma parasite. Women newly infected with Toxoplasma during pregnancy and anyone with a compromised immune system should be aware that toxoplasmosis can have severe consequences (Centers for Disease Control and Prevention, USA).

Takeda, Yamamoto, and Standley groups showed that a single polymorphic amino acid on *Toxoplasma gondii* (*T. gondii*) kinase ROP16 determines the direct and strain-specific activation of Stat3 ([Appendix 2-1] 13).

Takeda and Yamamoto groups showed that ATF6β is a host cellular target of the *T. gondii* virulence factor ROP18 ([Appendix 2-1] 14).

Yamamoto group also showed that a cluster of guanylate-binding protein (GBP) genes is required for host cellular immunity against the intracellular parasite *T. gondii*. They identified a cluster of interferon-γ-inducible p65 GTPases playing a critical role in host defense against *T. gondii* ([Appendix 2-1] 15).

***[8] Roles of PILR in immune responses**

Herpes simplex virus-1 (HSV-1) is the prototype of the diverse α-herpesvirus family, which generally causes mucocutaneous lesions but also is involved in lethal encephalitis.

Arase group showed that cellular receptors for both glycoprotein B and glycoprotein D are required for HSV-1 infection and that paired immunoglobulin-like type 2 receptor alpha (PILRα) plays an important role in HSV-1 infection as a coreceptor that associates with glycoprotein B ([Appendix 2-1] 16). The group also demonstrated that neutrophil recruitment in inflammatory responses is regulated by PILRα via modulation of integrin activation ([Appendix 2-1] 17).

***[9] Immune regulation and mRNA decay by Regnase-1**

Immune responses induced by Toll-like receptors (TLRs) are tightly controlled to prevent excessive host inflammation. In the process of innate immune responses, TLR signaling induces the expression of several genes. Therefore, investigation of these TLR-inducible genes is important for clarifying the

control mechanisms of immune reactions. The research groups headed by Akira have tried to reveal a new concept of post transcriptional immune regulation by mRNA decay.

Akira and Standley groups identified the TLR-inducible gene Zc3h12a as an immune response modifier that has an essential role in preventing immune disorders ([Appendix 2-1] 18), and Zc3h12a was renamed regulatory RNase-1 (Regnase-1) thereafter.

Akira group showed that Regnase-1 mRNA is negatively regulated by Regnase-1 itself via a stem-loop region present in its 3' untranslated region. The data demonstrated that Regnase-1 works not only as a 'brake' but also as an 'accelerator' on IL-6 mRNA expression ([Appendix 2-1] 19). Furthermore, Akira group showed that Regnase-1 is essential for preventing aberrant effector CD4+ T cell generation cell autonomously. Their results demonstrated that Regnase-1 is essential for suppressing an unwanted T cell-mediated immune reaction by targeting multiple mRNAs encoding transcription factors, surface molecules, and cytokines. Dynamic regulation of Regnase-1 by TCR signaling contributes to robust T cell activation ([Appendix 2-1] 20).

***[10] Immune regulation and mRNA stabilizing by Arid5a**

IL-6 is a key molecule in various autoimmune diseases. However its post-transcriptional regulation has not been characterized other than ribonuclease Regnase-1 (discovered by Akira), which prevents autoimmunity by destabilizing IL-6 mRNA.

Kishimoto group identified AT-rich interactive domain-containing protein 5A (Arid5a) as a unique RNA binding protein, which stabilizes IL-6 mRNA. Arid5a inhibited the destabilizing effect of Regnase-1 on IL-6 mRNA, which is an opposing function to Regnase-1 ([Appendix 2-1] 10-21).

***[11] Autoimmune diseases and Th17 cells**

Recent evidence suggests that Th17 cells play a key role in autoimmune diseases such as rheumatoid arthritis (RA). How pathogenic self-reactive Th17 cells are generated, activated, and lead to autoimmune disease is a question for the future. Researchers in IFReC have made remarkable achievements in this field.

Sakaguchi group provided evidence that complement activation and C5a (a chief component of complement activation produced via all three complement pathways) production are critically involved in the initiation of certain autoimmune disease, and presumably microbial immunity, by driving Th17 development ([Appendix 2-1] 22).

Kishimoto group demonstrated that Aryl hydrocarbon receptor (Ahr) deficiency in T cells, but not macrophages, suppresses collagen-induced arthritis development as was observed in Ahr KO mice. These effects may result from inhibited Th17 generation and proinflammatory cytokine production. In RA, Ahr mainly functions during Th1 and Th17 cell development, although roles in other cell types may contribute to autoimmune diseases. Their findings indicate that the development of experimental autoimmune arthritis depends on the presence of Ahr in T cells, and that Th1/Th17 balance may be particularly important for this process ([Appendix 2-1] 23).

***[12] Autoimmune diseases and IL-6 amplifier**

It has yet to be elucidated how IL-17A contributes to autoimmune diseases and/or inflammation.

Hirano group offered the new understanding that the IL-17A-triggered positive-feedback loop of IL-6 expression in nonhematopoietic cells may provide a general etiologic mechanism for various

autoimmune diseases ([Appendix 2-1] 24). They also showed that local microbleeding facilitates IL-6 and IL-17 dependent arthritis in the absence of tissue antigen recognition by activated T cells ([Appendix 2-1] 25).

***[13] New findings on regulatory T cells**

$CD25^+CD4^+$ regulatory T cells (T_{reg}s), which specifically express the transcription factor Foxp3, suppress aberrant immune responses, including autoimmune diseases and allergy. Furthermore, reduction or expansion of T_{reg}s can be exploited to provoke effective tumor immunity or transplantation tolerance, respectively.

As a pioneer in this field, Sakaguchi and his colleagues have achieved important results for T_{reg}s' developments and functions. They showed T_{reg}-specific cytotoxic T lymphocyte antigen 4 (CTLA-4) deficiency impairs *in vivo* and *in vitro* suppressive function of T_{reg}s. CTLA-4 is a key molecular target for controlling T_{reg}-suppressive function in both physiological and pathological immune responses including autoimmunity, allergy, and tumor immunity ([Appendix 2-1] 26). They also found that T cell receptor stimulation-induced epigenetic changes and Foxp3 expression are independent and complementary events required for T_{reg} cell development ([Appendix 2-1] 27).

***[14] New findings on semaphorins**

Semaphorins were initially identified as axonal guidance cues during neurogenesis. In addition, they have diverse and important functions in other physiological processes, including heart development, vascular growth, tumor progression, and immune responses. Kumanogoh and IFReC researchers have discovered various immunological and physiological functions of molecules belonging to semaphorin groups.

Kumanogoh group showed the importance of Sema3A-mediated signals in dendritic cells trafficking, particularly for passage through the lymphatics, but has also identified a previously unknown mechanism that promotes actomyosin contraction at the trailing edge of migrating cells ([Appendix 2-1] 28).

Kumanogoh and others also showed that semaphorin 3A (Sema3A) exerts an osteoprotective effect by both suppressing osteoclastic bone resorption and increasing osteoblastic bone formation. Sema3A could be a potential new therapeutic agent in bone and joint diseases ([Appendix 2-1] 29).

Kumanogoh group determined that a point mutation in the semaphorin 4A (Sema4A) gene causes retinal degenerative disease, which is further supported by structural modelling analyses. Furthermore, photoreceptor degeneration could be rescued by Sema4A gene supplementation in an animal model. Their findings provide a novel therapeutic target for retinal degenerative diseases ([Appendix 2-1] 30).

***[15] Discovery of a gateway of immune cells to nerve system**

The central nervous system (CNS) is an immune-privileged environment, protected by the blood-brain barrier (BBB), which is formed by specific vessels tightly attached to each other. However, this barrier is compromised by the invasion of certain pathogens and infections, suggesting that immune cells in the peripheral lymphoid organs contribute to CNS related immune responses.

Hirano/Murakami group searched a gateway for immune cells to cross the BBB, and they found that autoreactive T cells access CNS via the fifth lumbar spinal cord ([Appendix 2-1] 31).

[16] T cell activation and its visualization

In order to induce proper activation of T cells through costimulation, expression of costimulatory receptors and their signals should be regulated in appropriate strength and timing in a dynamic and quantitative fashion.

Saito group found that the accumulation of micro clusters (MC) at the central supramolecular activation cluster (cSMAC) is important for T cell costimulation, which is mediated by the generation of a unique costimulatory compartment in the cSMAC via the dynamic regulation of MC translocation ([Appendix 2-1] 32). They also showed the dynamic mechanism of CTLA-4-mediated T cell suppression at the cSMAC employing the latest bioimaging technique ([Appendix 2-1] 33).

***[17] Factor of memory B cells toward plasma cell differentiation**

During an immune response, B cells create memory cells that are clones of the specific B cells. They remain in the body, holding information about each pathogen. A fundamental question is how the immune system mounts a quicker response, when it encounters the same pathogen again.

Kurosaki group showed repression of the transcription factor Bach2 contributes to predisposition of IgG1 memory B cells toward plasma cell differentiation ([Appendix 2-1] 34).

***[18] Calcium sensors controlling B cell regulatory function in multiple sclerosis**

Multiple sclerosis is an unpredictable, often disabling disease of the central nervous system that disrupts the flow of information within the brain, and between the brain and body (National Multiple Sclerosis Society, USA).

Kurosaki group showed the calcium sensors STIMs control B cell regulatory function through IL-10 production. Their results from a mouse model of multiple sclerosis established STIM-dependent SOC influx as a key signal for B cell regulatory function required to limit autoimmunity ([Appendix 2-1] 35).

***[19] Glycoproteins in cellular homeostasis**

Various kinds of proteins including glycoprotein are indispensable elements for the maintenance of homeostasis in mammalian cells.

Kinoshita group described a novel molecule mechanism involved in Golgi acidification. They discovered a novel Golgi-resident multi-transmembrane protein, named Golgi pH regulator (GPHR). GPHR is an essential regulator for pH homeostasis of Golgi apparatus ([Appendix 2-1] 36). They also showed that GPI (glycosylphosphatidylinositol) glycan remodeling by PGAP5 (post-GPI-attachment to proteins 5) regulates transport of GPI-anchored proteins from the endoplasmic reticulum to the Golgi apparatus ([Appendix 2-1] 37).

***[20] Regulation of osteoclast**

Osteoporosis is a disease of the bones, which happens when we lose too much bone, make too little bone or both. As a result, bones become weak and may break from a minor fall or, in serious cases, even from simple actions, like sneezing or bumping into furniture (National Osteoporosis Foundation, USA). Prevention and developing therapeutic approach for osteoporosis are important tasks for countries that have a rapidly aging population such as Japan.

M. Ishii group developed a novel method for direct *in situ* visualization of cell behavior. They found that sphingosine-1-phosphate, a lipid mediator enriched in blood, controls the movement of osteoclast precursors between the blood and the bone surface ([Appendix 2-1] 38). They also showed a mechanism for active vitamin D in controlling the migratory behavior of circulating osteoclast

precursors, and this action should be conducive to limiting osteoclastic bone resorption in vivo ([Appendix 2-1] 39).

M. Ishii group together with Kumanogoh and Kikuchi groups succeeded in observing cells with distinct motility behaviors and function, with the relative proportion of static – bone resorptive to moving – non-resorptive (published in FY2014)

Akira group showed that Jun dimerization protein 2, which is a member of the AP-1 family, plays pivotal roles in *in vivo* bone homeostasis and host defense by regulating osteoclast and neutrophil differentiation ([Appendix 2-1] 40).

2-2. Research environment including facilities and equipment

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

IFReC and its parent institution, the Research Institute for Microbial Diseases (RIMD) are located on the same site, where the Integrated Life Science (ILS) Building (10 floors, 9,300 m^2) and the IFReC Research Building (9 floors, 6,600 m^2) were constructed in 2009 and in 2011, respectively. These buildings, connected by covered walkways, provide IFReC's 17 core PIs with spacious laboratories that can be arranged for their own specialties, some for experiments using live animals and/or cell and molecular biology and others for advanced imaging.

These two new buildings and the preexisting research buildings of RIMD together constitute a rather large research complex, the IFReC/RIMD complex. The complex also contains the core instrumentation facility and animal resource center, both of which are jointly operated by IFReC and RIMD. The core instrumentation facility is equipped with highly advanced instruments. Under the supervision of a few academic staff from both IFReC and RIMD, skilled technicians provide in-house services such as cell sorting, DNA sequencing, electron microscopy and mass spectrometry.

As for the animal resource center, in addition to its two buildings of RIMD, the third building for specific pathogen-free (SPF) animals was also constructed in 2009, which has resulted in the establishment of a large capacity animal-breeding facility that enables researchers to choose animal rooms suitable for their purpose.

New servers and network system were also installed on the fourth floor of the IFReC Research Building in 2011 to facilitate the flow and availability of data from the imaging, informatics and immunology groups. The cost was covered in part by an internal research support program of Osaka University. Furthermore, the live immune-imaging facility was set up on the 3rd floor of IFReC Research Building in 2012. It contains animal rooms to rear 700 mice together with rooms for an 11.7T Magnetic Resonance Imaging (MRI) and a two-photon microscope in SPF environment, enabling researchers to observe immune phenomena in the same animals over a few weeks. This new experimental system is now opening up a new field in immunological research.

As a whole, the IFReC/RIMD complex can be regarded as self-contained and IFReC researchers are able to effectively and smoothly carry out their experiments and naturally interact with each other leading to their collaboration for "interdisciplinary research" (see Section 3).

Facility guidance orientation both in Japanese and English is held every year for researchers working within the IFReC/RIMD complex and engaged in experiments using radioisotopes, animals

and genetically modified organisms. Emphasis is placed on how to use the facilities at IFReC according to the rules and safety measures. A PhD-holding staff member of IFReC RPMO collaborates with RIMD staff for this researcher-oriented guidance and administrative management of core instrumentation facility and animal resource center.

2-3. Competitive and other funding

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

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

The amount of competitive research funds obtained by IFReC researchers has constantly increased, well exceeding the WPI program subsidy since 2009. This fact indicates that achievements of IFReC researchers are of very high scientific quality and their research purpose and perspective are widely acknowledged to be very important for science and our society. This is particularly the case for our Director Akira. He was selected as one of the 30 core researchers of Funding Program for World-Leading innovative R&D on Science and Technology (Cabinet Office-sponsored FIRST Program, FY2009-FY2013, 2,520 million yen). The project successfully revealed various aspects of dynamics of immune molecules and cells, and also made great contribution to instalment of advanced instruments in IFReC such as a very high magnetic-field MRI instrument which is of critical importance to live imaging of immune phenomena (see section 2-2). In addition, owing to this project fund, IFReC was able to organize the international symposia "Towards Comprehensive Understanding of Immune Dynamism (TCUID)" in 2011, 2012, and 2013 (Section 4-2) and to carry out various outreach activities (Section 2-6-2).

Other IFReC researchers also acquired other large-scale grants as listed in Appendix 2-2. Young talented researchers including relatively recent PI recruits also obtained prestigious research grants including: Funding Program for Next Generation World Leading Researchers (Kumanogoh), Strategic Basic Research Programs of JST (PRESTO, Smith, Hanayama, and Suzuki). It should be noted that a number of overseas researchers also successfully obtained Grant-in-aid for Scientific Research at the same success rate as Japanese researchers. Thus, IFReC researchers have successfully raised funds for their own research.

IFReC also received a large sum of donations from private sectors including Kishimoto Foundation and a number of pharmaceutical companies. The annual donation from the Kishimoto foundation has greatly contributed to enhance research capability and internationalization of IFReC. Thus, the Kishimoto Fellowship/scholarship supported the total of 34 young researchers staying at IFReC for both short and long terms and Kaisho was invited to take an endowed chair as a new PI.

In order to promote successful grant applications, an advisory system of Osaka University, seminar series for research grants, and IFReC's support system for grant application have been established, all of which have proved very effective, especially for overseas researchers. It should be also noted that our administrative system has made it possible to handle overseas grants such as the grant to Akira from the National Institute of Health, USA through budget management and a registry at Osaka University of information required for application.

2-4. State of joint research

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

QBiC and CiNet : Osaka University has concluded cooperative agreements with National Institute of Information and Communications Technology (NICT) and with Riken in 2009 and 2010, respectively. Based on these agreements, two research centers, the Center for Information and Neural Networks (CiNet) of NICT and Quantitative Biology Center (QBiC) of RIKEN have been opened in the University campus, with Yanagida, a deputy director of IFReC, as the director of both centers. CiNet aims to understand brain functions to create a novel principle of human-machine interfaces and information, while QBiC attempts to elucidate the dynamics of fundamental biological systems beyond levels from molecules and cells to organs and individuals. Thus, the missions and goals of these centers may differ from those of IFReC, but the methodologies and technologies are useful for interdisciplinary researches at IFReC, so that our collaboration with CiNet and QBiC have been actively proceeded as described in section 3.

Domestic Satellites: IFReC has established strong collaborative relationships with four domestic research institutions under the satellite agreements; National Institute of Biomedical Innovation (NIBIO), Riken Center for Integrative Medical Sciences (Riken IMS), Kyoto University, and University of Hyogo. A researcher has been invited as an IFReC PI from each of these institutions.

K. Ishii, Project Leader, Adjuvant Innovation Laboratory of NIBIO has been playing a central role to develop safe and effective vaccines and adjuvants. He is also a core member of the “Consortium for Innovative Cancer Immunotherapy” to promote immunotherapy research against cancer. IFReC will join the consortium together with Osaka University Hospital and National Cancer Center Hospital East.

Personnel cooperation with Riken IMS is of crucial importance to IFReC. Kurosaki and Saito, group directors of Riken IMS, are concurrently appointed as our PIs, while Kurosaki mainly conducts his research at IFReC. Kaisho moved from Riken IMS to IFReC as a PI as described in Section 2-3.

Sakaguchi, a former director of Institute of Frontier Medical Sciences of Kyoto University, moved to IFReC as a PI in April 2011, but he still has his laboratory there as a guest professor of Kyoto University. Hata develops novel technologies for imaging and analysis in collaboration with researchers of University of Hyogo.

Others

IFReC also has a tight collaborative relationship with the School of Medicine and the University Hospital. We have jointly operated a sample collection center to stock serum collected from patients at clinics in Osaka area and to supply it for orphan disease research. Furthermore, the University Hospital has been playing a critical role to translational research development of IFReC by providing human biological specimens to IFReC researchers and conducting clinical trials together with IFReC researchers.

In the Akira project of FIRST Program (described in section 2-3), IFReC researchers had close collaborations with imaging and informatics researchers at the University of Tokyo, Hokkaido University, Kyoto University, and Nara Institute of Science and Technology.

2-5. Appraisal by society and scientific organizations

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

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

As shown in Appendix 2-3-1, IFReC scientists have been awarded for their brilliant achievements and significant impact on society. Especially the Canada Gairdner International Award given to Akira and Jules Hoffmann (2011 Nobel laureate) is known as one of world's most prestigious awards. Kishimoto and Hirano were the first Japanese winners of the Crafoord Prize (2009) since its establishment. This award is a tremendous validation of their works not only in basic researches but also in the application to medical care.

In addition, all of these prize-winners gave award lectures on each occasion, Akira and Sakaguchi also received accolades when they were invited to the Royal Society Lecture in London in 2010 and to the Karolinska Research Lectures at Nobel Forum in 2013, respectively.

The Ministry of Education, Culture, Sports, Science and Technology of Japan elected Akira (2009) and Yanagida (2013) as recipients of Persons of Cultural Merit of Japan for their lengthy career and contributions to society, which has given IFReC three recipients of this very high honor in Japan as Kishimoto was elected as early as 1990. Furthermore, the National Academy of Sciences (NAS) of USA nominated Akira and Sakaguchi as foreign associates of NAS in 2009 and 2012, respectively, resulting in IFReC having three NAS members as Kishimoto had been nominated in 1991.

2-6. Feeding research outcomes back into society

2-6-1. Applications of research results

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

The number of patent applications from IFReC is increasing. The monetary support provided by the FIRST program is a significant contributor to this. Patent applications have been submitted for Kikuchi's highly selective probe technology, imaging technology such as that developed by Yoshioka which dramatically improves MRI performance, adjuvants, vaccines, and other drugs that regulate immunity. As detailed below, a venture startup has been established based on Yoshioka's resonant circuit for MRI; research is advancing at IFReC based on Kishimoto's patent for Tocilizumab (see below), which stands as a great precedent for patents originating at Osaka University, and clinical studies will begin in order to expand the scope of application showing how patented results can be used. In addition, IFReC researchers are promoting collaboration with the private sector and returning research results to society. Many IFReC researchers receive grants from corporations and are implementing research on the basis of joint research contracts formed with corporations.

Translational research

Based on the research achievements of IFReC researchers, translational research has advanced to practical application in medicine. Some research is now undergoing clinical trials.

(1) Clinical Trial: DNA adjuvant (K. Ishi) As Akira elucidated, an effect of vaccines is enhanced by adjuvants, and nucleic acids such as DNA are considered good candidates for adjuvants. K. Ishii has developed a DNA adjuvant for malaria vaccine using CpG sequences. The adjuvants were confirmed to

be sufficiently safe and effective in pre-clinical trials. The phase-I clinical trial for practical use has started, which is the first investigator-driven clinical trial in Osaka University.

(2) Clinical Trial: T_{reg} targeted immunotherapy of cancer (Sakaguchi) Sakaguchi found that tumor-infiltrating T cells in a variety of cancers contained a higher frequency of effector regulatory T cells (T_{reg}s) compared with peripheral blood. These effector T_{reg}s dominantly expressed CCR4 and were depressed by anti-CCR4 monoclonal antibody treatment *in vitro*. An investigator-initiated Pharmaceutical and Medical Devices Agency (PDMA)-approved Phase-I clinical trial of T_{reg}-targeted therapy of solid tumor with anti CCR4 antibody is in progress. An investigator-initiated phase II/III clinical trial of a combination immunotherapy with existing cancer vaccine and anti-CCR4 monoclonal antibody for T_{reg} depression is currently planned. This T_{reg}-targeted therapy will be the first cancer vaccine trial in the world.

(3) Clinical Trial: Extension of Tocilizumab applicable diseases (Kishimoto and Kumonogoh) Tocilizumab, an anti-IL-6 receptor antibody, was first developed as a rheumatoid arthritis therapeutic agent by Kishimoto (trade name “Actemura”, Roche-Chugai Pharmaceutical), which is known as one of “blockbusters” and the first antibody drug developed in Japan to be approved in the rest of the world . Recently it was shown that Tocilizumab was effective for many other refractory autoimmune diseases. Kishimoto and Kumanogoh have completed or are conducting clinical trials in Japan and overseas in collaboration with Chugai Pharmaceutical for amyloid A amyloidosis, systemic sclerosis, Takayasu arteritis, neuromyelitis optica, polymyalgia rheumatic, and polymyositis, and are planning to conduct clinical trials for relapsing polychondritis.

Development of seeds for clinical applications

Research to develop seeds found in basic research to clinical applications for diagnosing, treating, and preventing immune diseases has been facilitated in collaboration with clinical medicine researchers and/or pharmaceutical firms.

(1) Semaphorin targeted antibody drug development (Kumanogoh) Kikutani and Kumanogoh elucidated that semaphorin family involves specific immune diseases. Kumanogoh is developing a semaphorin targeted antibody drug for rheumatoid arthritis and vasculitis in collaboration with Chugai Pharmaceutical.

(2) Identification of a diagnosis marker for autoimmune diseases (Sakaguchi and Kumanogoh) Sakaguchi and Kumanogoh successfully identified a serum marker to diagnose Behçet's disease and interstitial pneumonia with serum of patients stocked in a sample collection center established by IFReC and Osaka University Hospital.

(3) M2 macrophage targeted drug development Akira has started to collaborate with Chugai Pharmaceutical and other pharmaceutical firms for drug development on a basis of new modality with M2 macrophages, of which Akira found new functionalities.

Collaborations with industries to enhance research capability of IFReC

(1) Leica Center A laboratory of Leica Center was installed in the IFReC Research Building in 2012 for collaboration between M.Ishii and Leica Microsystems, a world-leading company of microscopy to

develop with advanced technologies of multi-photon microscopy for *in vivo* observation of various immune responses.

(2) Collaborations with BioLegend Ltd. IFReC and BioLegend (USA) agreed on collaboration to develop monoclonal antibodies, which IFReC researchers require for their research. Followed by the agreement, BioLegend installed its first laboratory in Japan nearby to IFReC in 2013, to enable effective antibody development by close communication with IFReC researchers. A collaborative research project with Sakaguchi has already launched, and four other projects are under discussion.

(3) Establishing a venture to develop and sell extremely sensitive coils for MRI signal detection A former postdoctoral researcher of Yoshioka group founded a venture company (Daimatsu Medical Electronics) in 2013, to develop extremely sensitive coils for MRI signal detection into production and start to sell them. Supported by a grant from Osaka municipal government, further development of coils is in progress in collaboration with Yoshioka group.

(4) Providing genetically modified mice IFReC researchers have generated many genetically modified mice contributing to understand an immune mechanism. They have voluntarily provided the mice to domestic and overseas research institutes with material transfer agreements between Osaka University and the institute. Especially Akira group provides more than hundred mice every year.

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

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

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

Since the establishment of WPI outreach policy in 2010, IFReC has made noticeable progress in PR activities for general citizens and school students. An office staff of IFReC was appointed to a committee of "Outreach Working Group" of Osaka University, and contributed in forming the policy of outreach in Osaka University. In the WPI joint projects, the outreach staff and office members of IFReC participated in various events as core members of the WPI outreach team. We have been trying to explain our research outputs and the raison d'etre of the WPI program to general citizens. At the Science and Technology Festa (Kagaku-Gijyutsu Festa) in Kyoto 2011, and the annual meeting of American Association for the Advancement of Science (AAAS) in 2012, an IFReC outreach staff was chief organizer. Two members of the IFReC office have been officially recognized as "Press Information Officer of the Research Institutes" by AAAS. Other than WPI joint projects such as "Science Talk Lives", Science Agora or AAAS meetings, IFReC has also organized the following public relations activities.

Publishing

- IFReC has put out a media release to Japanese press club 10-15 times per year, resulting in a high rate of publication in major newspapers.
- IFReC has published the original leaflets for introducing IFReC and WPI program (both in English and Japanese), and a total of 10,000 copies were distributed to school students. These leaflets reflected the latest research information, and have been revised every year.
- With supervision by Director Akira, an IFReC staff member published a book titled "Practical guide to innate immunity" for general readers in Japanese. The book has placed highly on the bestselling ranking in the life science field.

- An article by a member of IFReC office (Jpn J Sci Commun 9:65-72, 2011) describes the science communication in the IFReC administrative office, and has been downloaded more than 1400 times.

To general citizens

- IFReC has co-organized “Café on the Edge”, science café series introducing latest researches in IFReC, and has welcomed over 500 participants every year.
- Director Akira gave a lecture, and talk with high school students at “FIRST Science Forum 3” in Kyoto. The lecture was broadcast on the NHK educational TV program.
- Symposium for general audience "Future Medical Treatment Created by Immunology" was co-organized by IFReC and FIRST Program AKIRA Project in Tokyo. In the symposium, opinions from various viewpoints were deeply discussed for creating new medical treatments for cancer, allergic diseases, and others.

To students

- The lecture series “Immunology–from its history to latest findings-” that were held as general liberal arts education in Osaka University, were opened to local high school students. A total of 30 lectures were given by the scientists in various research fields in IFReC.
- "The mystery of life visualized by advanced live imaging technique”, an open school for high school students was held in August, 2010. The original textbook for the school is now open to the public on the web.
- Director Akira gave a memorial lecture to "Super Science High Schools (SSH)" students at "The Congress of SSH” in Kobe in August, 2011. He also gave lectures at two high schools in Fukuoka and Osaka in 2011. His lecture titled "The mystery of immunity; a newly opened door to immunology" explained his brilliant achievements in an easy-to-understand manner to students and teachers.
- IFReC PIs, Smith and Standley, gave talks in English in the science class titled "In touch with Science" at Osaka International School of Kwansei Gakuin, Minoh City in FY2012.
- IFReC co-organized science communication seminars. Guest lecturers from the National Museum of Emerging Science (Miraikan) talked about helpful skills to interpret one’s research effectively and efficiently.
- The three events “Career-development Lectures for younger generation” were organized at a high & junior high school, and the women’s college in 2012. The lectures were designed to let students know about “true scientists” and “scientists’ lives”.
- IFReC has taken a stance of placing importance on students and science teachers at high school. As the result of our efforts, IFReC was featured as “World Leading Institute in Japan” in a popular supplementary reader that is read by many high school students. Moreover, IFReC has decided to provide cooperation for producing TV program for high school students on NHK educational TV after 2013.

3. Interdisciplinary Research Activities (within 3 pages)

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

IFReC has implemented several strategic measures to advance interdisciplinary researches.

Programs to promote fusion research: Research Support Program for Combined Research Fields encourages IFReC researchers with different specialties or research backgrounds to collaborate on challenging new projects. The Dual Mentor Program supports graduate students or young post-doctoral fellows to engage in interdisciplinary projects under the supervision of two PIs from different disciplines. Several projects are selected for financial support every year and evaluated during and after the project period of three years. Since 2009, 26 research projects in total have been selected. Their outcomes have resulted in the publication of several papers.

Fusion research units: This program is to foster young, talented researchers in the next generation. Each unit consists of young researchers of Assistant or Associate Professor level with different research backgrounds and/or experience. Selected from young researchers in IFReC based on their achievement and motivation, they receive some financial and personnel support directly from IFReC and share research facilities with the parent laboratories. Three units have been set up so far.

Live immune-imaging facility: This facility, detailed in section 2-2, has made it possible for IFReC researchers to observe immune reactions in the same animals for as long as a few weeks with high-performance MRI or two-photon microscope under a specific pathogen-free environment. The number of requests for fusion research using this facility is steadily increasing and some of the projects have successfully reached the publication stage.

IFReC colloquium: A series of colloquium has been held bimonthly. Open only to IFReC staff, speakers from two or three IFReC laboratories give talks on their latest research progress including unpublished results. Presentations based on outcomes of interdisciplinary research are most encouraged. After each colloquium, a small social gathering ("Happy Hour") is held for participants to exchange their ideas and discuss future collaborations in a relaxed atmosphere.

Collaboration with CiNet and QBiC: As described in section 2-4, the missions and goals of these centers are different from those of IFReC. However, a fundamental recognition shared by the three institutions is that technological and methodological developments are indispensable for comprehensive understanding of a complex network or system composed with a wide variety of elements. Hence, while CiNet and QBiC researchers are engaged to develop their own technologies to analyze and model multi-element networks, brain and cell as a whole respectively, they are willingly collaborating with IFReC researchers attempting to analyze another multi-element system, the immune system in the body. In other words, the collaboration is never a one-sided game, but is the synergistic effect of innovative efforts being made through respective strengths and resources and is beneficial to all three institutions.

CiNet inaugurated a new building in Suita campus of Osaka University in 2013. Using 3T and 7T MRI instruments installed therein, Yoshioka, who is concurrently appointed as a Vice Director General of Instrument Technologies Section of CiNet, has started collaborative studies with researchers from the Medical School and University Hospital to understand the human immune system. By inviting Ben Seymour of CiNet as a PI (from April, 2014), IFReC is to open a new laboratory "Brain-immune interaction" to understand interaction between immune and psycho-neurological systems, making a scientific approach to the traditional thought that "Illnesses start in mind".

Many IFReC researchers have started collaboration with QBiC researchers since its opening in 2011 within a facility at Osaka University. When construction of its new building adjacent to the CiNet

building is completed in late 2014, far more active collaboration between the three institutions is expected.

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

The Osaka University Immunology School has been organized by Kumanogoh and Takeda to promote interaction between clinical and basic researchers. A seminar series of "Immunology Frontier: From Bench to Bed and from Bed to Bench" has also been started with the initiative taken by Sakaguchi.

"Study Session on Mathematical Modeling in Biology and Related Topics" has been organized voluntarily by some IFReC young researchers. It is a series of seminars to share knowledge among researchers of a wide range of research fields besides immunology such as theoretical biology, mathematics, physics, and robot science. The researchers are from both inside and outside of the University. The researchers from one of the fusion research units described above are core members of this meeting.

3-3. Results of research in fused research fields

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

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

As indicated in Appendix 3, where papers are sorted from newest to oldest, an increasing number of papers have been published on outcomes of interdisciplinary research. In addition, Appendix 2-1, the list of papers mostly published in top journals, includes as many as 14 such papers.

Osteoclast studies by multi-photon microscopy: Masaru Ishii developed the world's first intravital two-photon imaging system and used it to observe dynamic behavior of immune cells to reveal their function. Fully exploiting this system, his group studied osteoclast dynamics and bone homeostasis, where sphingosine-1-phosphate and its receptors play critical roles (Appendixes 3-20, 3-14, 3-5 and 3-3).

MRI for immunology: Yoshioka group has been improving the technology of MRI for non-invasive assessment to unveil precise functions of cells *in vivo*. Using this system, it was shown that Trib1 deficiency causes a severe reduction of M2-like macrophages in various organs, including bone marrow, lung and adipose tissues (Appendix 3-4). Collaborating with Kikuchi group, his group also successfully detected cellular gene expression by ^{19}F-MRI without cell fixation. The technique makes it possible to monitor gene expression *in vivo*, and potentially be utilized for the diagnosis and therapy of various diseases (Appendix 3-9).

Immunology studies using other imaging technologies: Using super-resolution structured illumination microscopy, Akira group showed that neutrophil extracellular traps (NETs) capture human immunodeficiency virus (HIV)-1 and promote HIV-1 elimination through myeloperoxidase and α-defensin (Appendix 3-10). They also succeeded in observing NLRP3 inflammasome formation, in which microtubules mediate the approximation of ASC on mitochondria to NLRP3 on the endoplasmic reticulum in response to stimulation (Appendix 3-2).

Observing transmigration of bone marrow–derived DCs in 3D collagen matrices by confocal time-lapse video-microscopy, Kumanogoh group showed plexin-A1 is crucially involved in the entry of dendritic cells (DCs) into the lymphatics, and that the semaphorin 3A is required for DC transmigration. (Appendix 3-17).

Saito group developed total internal reflection fluorescence microscopy and showed that the

dynamic mechanism of CTLA-4-mediated T cell suppression at the central-supramolecular activation cluster (cSMAC), and that the dynamic behavior of CTLA-4 in its real-time competition with CD28 at cSMAC results in the dislocalization of protein kinase C-θ and CARMA1 scaffolding protein. (Appendix 3-16).

Using a Raman spectroscopy method elaborated by Smith group, Coban group successfully monitored changes in erythrocytes and plasma during Plasmodium infection in mice, following malaria disease progression over the course of seven days and showed that plasma analysis has significant potential for early, quantitative and automated detection of malaria (Appendix 3-6).

Bioinformatics approach to immunology: Informatics groups of IFReC, Standley group in particular, have made a substantial contribution to deepening of our understanding of immune dynamism. The group covers a wide range of aspects of structure/function relationship of important molecules in immune system, which is most beneficial to many findings made by Akira group. The following are typical examples.

- The TLR-inducible gene Regnase-1 (also known as Zc3h12a) -deficient mice were found to suffer from fatal anemia. Regnase-1 is an essential RNase that prevents immune disorders by directly controlling the stability of inflammatory genes. (Appendix 3-19).
- Jumonji domain containing-3 (Jmjd3) is essential for M2 macrophage polarization in response to helminth infection and chitin, though Jmjd3 is dispensable for M1 responses. (Appendix 3-15).
- The inhibitor of transcription factor NF-κB (IκBk) kinase (IKK) complex controlled the stability of mRNA for IL-6 by phosphorylating Regnase-1 in response to stimulation via the IL-1 receptor or TLR. (Appendix 3-13).
- An AP-1 family transcription factor Jdp2(-/-) mice was generated. The factor plays crucial roles not only in bone metabolism but also in differentiation of neutrophils. Jdp2(-/-) mice exhibited osteopetrosis resulting from impaired osteoclastogenesis. (Appendix 3-7).
- Regnase-1 is essential for preventing aberrant effector $CD4^+$ T cell generation cell autonomously (Appendix 3-1).
- On the basis of stochasticity and heterogeneity, rather than on biochemical reactions, a coarse-grained formulation for modeling was developed for the dynamic behavior of immune cells. The system can be analytically represented by a finite set of ordinary linear differential equations, which provides a continuous time course prediction of each molecular state (Appendix 3-12).
- Collaborating with Standley group, Takeda group generated highly polymorphic parasite-derived kinase ROP16-deficient type I parasites, and found a severe defect in parasite-induced Stat3 activation, culminating in enhanced production of interleukin (IL) 6 and IL-12 p40 in the infected macrophages (Appendix 3-18).

The following two publications are also good examples that methodology of informatics is of great merit to elucidation of various immune phenomena.

Sakaguchi group showed that T_{reg} cell development was achieved by the combination of two independent processes, i.e., the expression of Foxp3 and the establishment of T_{reg} cell-specific CpG hypomethylation pattern. The calculation for DNA methylation was done by bioinformatics methods using the super computer system (Appendix 3-8).

Miranda-Saavedra group described a systematic approach to identify the elusive STAT3-controlled effectors of the anti-inflammatory response (AIR). This is the first in-depth study of the AIR by next-generation sequencing and provides an unprecedented degree of detail into this fundamental physiologic response (Appendix 3-11).

4. International Research Environment (within 4 pages)

4-1. International Circulation of Best Brains

4-1-1. Center's record of attracting and retaining top-world researchers from abroad

Describe the participation of top-world researchers as PIs and the residing of joint researchers at the Center.

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

Diego Miranda-Saavedra, a bioinformatics specialist, joined IFReC as a junior PI (Bioinformatics and Genomics) in 2011 and left to take up a post of reader at Institute of Cellular Medicine, Newcastle University, UK in 2013. Nineteen papers were published from his laboratory.

Fritz Melchers, an overseas PI of IFReC and the former director of the Basel Institute of Immunology, stayed at IFReC for two weeks in 2012 to exchange views on various aspects of immunological research with Akira and other PIs. Abbas Ghaderi (Professor, Shiraz University of Medical Science, Iran) stayed to work with Kishimoto for four months in 2010. Michel L. Tremblay (Professor, McGill University, Canada) stayed for five months in 2012 and collaborated with Kurosaki and Miranda-Saavedra. Florent Ginhoux (Senior Principal Investigator, Singapore Immunology Network) also collaborated with Kaisho for a month in 2014.

In addition, a number of researchers of world-top class have taken the opportunity to visit IFReC on occasion of attending symposia and other scientific meetings held in Japan. Some of them have been invited to IFReC seminars as speakers and/or to discuss potential collaboration with our researchers.

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

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

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

The high level of research activities at IFReC seems to have attracted many capable young researchers as indicated by the fact that IFReC has received 296 applications so far in total for 39 postdoctoral positions in the open recruitment.

Every year IFReC accepts a few JSPS-supported postdoctoral fellows from abroad. The Kishimoto Foundation Fellowship for the recruitment of overseas researchers has greatly contributed to the internationalization of IFReC and 16 overseas researchers have been accepted from 10 countries since its establishment in 2009.

In principle, the employment term for postdoctoral researchers in IFReC is limited to three years. However, 13 have been promoted to assistant professors and one to an associate professor.

As listed in Appendix 4-4, a number of postdoctoral researchers who left IFReC have found more senior positions in their new places, suggesting that their research accomplishments and experience in IFReC were highly appreciated. It is notable that seven associate professors in their early forties were promoted to professors in their new institutions.

Active recruitment of young researchers as PIs resulted in the average age of PI being 53 years as of March 2014, about 2 years younger than that of April 2008.

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

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

At the very beginning (2007), IFReC formed contracts with six world famous bioimaging institutions in USA as satellites and posted a postdoctoral researcher in each satellite to become familiar with their cutting-edge technologies. These include National Institute of Allergy and Infectious Diseases (NIAD) and University of California, San Francisco (UCSF). The partnerships ended successfully with the publication of 20 collaborative papers. Our PIs, M. Ishii and Suzuki were recruited from NIAD and UCSF, respectively.

As listed in Appendix 4, we have the cooperative research agreements with four institutions or organization. Among various activities with these institutions, notable ones are "IFReC-New Zealand (NZ) Immunology Workshop" held in 2010 and an international symposium on immunologic Diseases jointly organized IFReC, Convergent Research Consortium for Immunologic Diseases (CRCID) and Pohang University of Science and Technology (POSTECH) in 2011.

Above all, one of the most successful cooperative activities with overseas organization is "Singapore Immunology Network (SIgN)-IFReC Joint Symposium" in 2009, which resulted in the establishment of 'Network of Immunology Frontier (NIF)'. Its major goal is to globally foster young researchers who will lead immunology in the next generation. Toward this end, "NIF Winter School on Advanced Immunology" has been organized every winter since 2012 (details in section 4-4).

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

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

Since its foundation, IFReC has organized a large number of international symposia and workshops, as shown in Appendix 2-5. Topics in these events were not only immunology, but also other fields, such as imaging, bioinformatics, and parasitology and malaria. Active communication between participants is expected to enhance their collaboration including interdisciplinary studies. Young researchers are encouraged to present posters, providing good opportunities to discuss their research with top scientists.

IFReC organizes or co-organizes a major international symposium every year, in which guest speakers, from young to senior, are invited to activate lively discussion on the latest topics in immunology. After the symposia in 2009 and 2010, to which young speakers were eagerly invited, IFReC arranged individual meetings for young researchers in IFReC to talk with guest speakers.

IFReC also co-organized five international symposia with overseas organizations such as the international symposia "Towards Comprehensive Understanding of Immune Dynamism (TCUID)" cooperatively with FIRST Program, AKIRA Project in 2011, 2012, and 2013. Although the research fields of the participants ranges from immunology to bioinformatics, lively discussion was made beyond individual fields of expertise at the symposia.

4-3. System for supporting the research activities of overseas researchers

Describe the Center's preparations to provide an environment conducive for overseas research to concentrate on their work, including for example living support in various languages or living support for their families.

Several bilingual staffs are positioned in accounting and general affairs sections in administrative office, and a one-stop service counter called "liaison office" has been set up to provide comprehensive support for overseas researchers. It consists of about five bilingual staff that help overseas researchers to settle in Japan with issues such as finding a room to stay, opening a bank account etc. The office also responds to inquiries on family matters such as children's education, visa application, and emergencies.

The Liaison Office created a website to provide information necessary for life in Japan, which is useful not only to overseas researchers who are already settled but also to newly accepted researchers preparing for their new lives in Japan.

The Liaison Office organizes two levels of Japanese language classes by a qualified Japanese teacher every week to encourage communication among foreign and Japanese researchers, other staff and locals. The classes are held inside the IFReC building in the evening, which is good for researchers balancing a class with their work. A Japanese language café is also held periodically to learn Japanese in a casual manner. IFReC foreign researchers are quite satisfied with these approaches, according to questionnaire surveys.

IFReC organizes orientation, which are compulsory lectures providing information on how to conduct experiments, in English every year for foreign researchers to ensure that regulations and rules are adhered to.

Grant information, and application forms when requested, is translated by RPMO as well as the liaison office staff. Ph.D holders in RPMO also act as consultants to support grant applications.

4-4. Others

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

IFReC set up 'Young Scientist Support Program for Research Abroad' in 2013 to encourage young researchers to participate in international conferences held overseas or to collaborate with overseas research groups. Nine young researchers have utilized the program. IFReC also preferentially provided young IFReC researchers with opportunities to attend Winter School (WS), briefly described in section 4-1-3, for discussing ideas and forging friendships with overseas peers.

The purpose of WS is to foster young researchers of the world, who are expected to be leaders in the next generation in the field of immunology. The WS usually receives more than 200 applications (about 50 countries) ranging from PhD students to postdoctoral fellows within three years of receiving their PhD, and about 50 applicants are selected as participants. The WS program consists of lectures by world top immunologists and short oral and poster presentations by participants, lasting 4 to 5 days. WS was highly appreciated by the participants as an excellent educational program for better understanding of cutting-edge immunology as well as to fuel networking and future collaborations. IFReC introduces its high research quality and world standard research environment to the participants in WS to raise its international visibility. It is expected that talented young researchers, who participated in the School, will join IFReC to pursue their research careers.

5. Organizational Reforms (within 3 pages)

5-1. Decision–making system in the center

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

Authorized by Osaka University, the director makes major decisions regarding personnel and budget allocation as well as other administrative matters, to which the Administrative Director gives full support by acting as a coordinator with the Deputy Directors and by executing management actions through the administrative office. This top-down decision-making system is significantly different from the management systems in other faculties and institutions within the University and has been well understood and implemented through the whole organization of IFReC.

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

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

We have established an organization where researchers can devote themselves to their research in a research environment and infrastructure that is of an international standard.

(1) Headed by the Administrative Director, a professor with extensive experience in not only scientific research but also the planning and management of research, IFReC has set up an administration system composed of General affairs and Accounting sections together with the Research Planning and Management Office (RPMO). Each office has several English-speaking staff with administrative experience in the university.

(2) With the Administrative Director at the head, RPMO consists of associate and assistant professors (two each) with PhD degrees and research experience. With the support of bilingual staff, RPMO is responsible for planning and organizing various seminars, symposia, and outreach activities, the management of intellectual properties, and safety and hygiene issues.

(3) The bilingual staff of the Liaison Office within RPMO provides full support for researchers from abroad as detailed in 5-3.

(4) In orientation for newcomers held at the beginning of each fiscal year, the outline of the WPI program, mission and ultimate goal of IFReC are explained together with the organization and operation of IFReC. This raises awareness of the mission and objectives of the staff in the interest of promoting the smooth flow of operations.

5-3. System reforms advanced by WPI program and their ripple effects

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

(1) RPMO has assisted international researchers in making successful applications to external competitive research funds and post-award management, in particular, the MEXT Grants-in-Aid for Scientific Research. This effort was highly appreciated by the university and has prompted the Department of Research Promotion to organize a university-wide orientation since 2012.

(2) Taking RPMO as a role model, the University Support Office for Large-Scale Education and Research Projects (established in FY2009) launched its URA team, and has consolidated a research

support system of the university.

(3) Annual salary of all staff members is determined based on evaluation of scientific achievements, work performance, contribution to WPI program, etc.

(4) RPMO edited “A manual for organizing Science Café” and provided it to other departments of Osaka University and other universities to help with their outreach activities.

(5) IFReC and RIMD jointly operate the animal resource center and core instrumentation facility. An administrator with PhD degree has been appointed to be in charge of the facilities. In addition to an English online reservation system and preparation of English user manuals for the core facilities, orientations are annually organized both in Japanese and English for researchers who engage in specific experiments using living modified organisms, pathogens and animals, where emphasis is placed on the importance of research activity being in compliance with laws, regulations and safety measures. IFReC is often asked for information and advice from other faculties and institutions of Osaka University that intend to hold similar orientations in English for their facilities.

(6) The Liaison Office consisting of a PhD holder and bilingual staff, was set up to provide sufficient support for international researchers and their families such as visa-related procedures, accommodations, daily life, health and welfare. The experience and knowledge that has been accumulated has had a substantial influence on the Support Office of Osaka University and contributed to improve the service for international staff and students of the university. In fact, various notifications from the University Office are usually translated into English for overseas researchers at IFReC, but the translated versions are often sent back to the Office on request.

(7) Osaka University concluded research agreements with the National Institute of Information and Communications Technology (NICT) and RIKEN. The effect of these agreements is described in section 2-4. Achievements and information released from those pioneering and world-leading research institutions have significant impacts on other institutions.

5-4. Support by Host Institution

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

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

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

(1) Osaka University constructed the Integrated Life Science building in 2009 to provide IFReC PIs with sufficient space to set up their laboratory. It also secured a site to construct a new IFReC research building, which was completed in 2011. These two buildings made it possible for IFReC's core researchers to assemble together.

(2) All of the indirect expenses in the WPI budget, which were granted during 2007-2010, were allocated to IFReC.

(3) When constructing the IFReC animal resource center for specific pathogen-free animals, the university created a new lending system to support the center financially.

(4) Osaka University responded to a request from IFReC and other faculties by constructing a new

accommodation facility of an international standard, Kasugaoka House.

(5) The university set up the Support Office for International Students and Scholars in 2008 to provide a one-stop service for researchers from overseas to assist visa applications. The Support office has been of great assistance for IFReC to accept many researchers from abroad.

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

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

(1) IFReC was selected as one of the WPI research centers and started operations during the latter half of the Osaka University Medium-term Plans for the 1st Period (1st MTP, FY2004 - FY2009). IFReC was primarily required to achieve the world premier status and was added to the university's medium-term strategy. As shown in Appendix 5, Attachment (1), in the Second Medium-Term Plan (2nd MTP, FY2010-2015), the university has positioned "Immunology being promoted mainly by the leading role of the world premier research center" as one of the projects that it would put more emphasis on. Therefore, active support to sustain and advance IFReC is one of the top priorities of the measures for the development of the University.

(2) In 2011, the Osaka University Institute for Academic Initiatives (IAI 2012-2015) was set up in order to promote interdisciplinary cross-boundary education and research, which was based on the view that modern society faces many challenges that require creative approaches requiring scholarship from more than one field. Thus, under the strong leadership of the President, the IAI aims to promote such cross-border, medium- and long-term learning and research, strategies for a future viewed as a whole. Along this basic stance, there are moves to cultivate research organizations that will become new WPI-like research centers, where IFReC, which has inherited the University's long tradition in the field of immunology, is regarded as their role model (Appendix 5, Attachment (2)).

5-5. Others

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

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

(1) We initiated "Junior PI program for young researchers", in which newly recruited young PIs are provided with financial support for their startup for the first three years.

(2) Programs to enhance interdisciplinary research at IFReC (sections 3-1 and 3-2) are also meant to encourage young researchers to challenge new but difficult project tasks, for which it would otherwise be hard to obtain financial support from outside sources.

(3) IFReC implemented three strategies below to increase the number of female researchers:

1) targeted a number of excellent female students who participated in annual Winter School in January, we advertised to recruit world-class female researchers;

2) more aggressively publicizing the university's support systems such as day care centers within the premises of Osaka University for child welfare;

3) it is expected that the program of the fusion units (section 2-2 a) would encourage young, talented female researchers to join IFReC as PI candidates in the future.

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.*

Faculty & Staff Development Within the formation of a visible international research center, one of the goals of the WPI program, it is vital that research support staff fulfill their roles at the highest of levels. In order for them to do so, clear delineation of roles and positions is required as well as awareness of the importance of one's own responsibilities, how that contributes to the development of IFReC, and that continual improvement is crucial. Based on this, IFReC has placed an emphasis on annual orientations for newcomers, which provides them with explanation on WPI's philosophy and outline of IFReC both in English and in Japanese to raise our staff's morale and consciousness of compliance.

In addition, a series of seminars and lectures for staff development have been implemented since 2013. Female researchers with outstanding careers were invited as speakers in seminars in FY2013 to encourage women to envision a future as a researcher. These include Yoshie Harada (iCeMS, Kyoto University), Michiko Go (Research Organization of Information and Systems) and Junko Tanaka (Hiroshima University). Post-event surveys made after each meeting indicated the participants had a feeling of satisfaction. The lectures are meant to deepen understanding of the research being done at IFReC by providing knowledge of fundamental immunology. The lecture was held only once in FY2013, however we plan to invite our young researchers (assistant professors or postdocs) to give lectures in future.

Another effort for our staff development is that administrative staff in general affairs and accounting sections have been encouraged to join IFReC's supporting team for the Winter Schools and outreach activities, both of which are thought to be good opportunities for them to learn different approaches at other institutions.

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

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

7-1 Recommendations in FY 2013 Follow-up of WPI Program by Program Committee

(1) It is highly recommended to establish junior positions for excellent young researchers with scientific independence and a possible tenure track. These young researchers should be selected based on their scientific vision, originality, excellence and project proposal. They will not only bring fresh ideas into the institute but also change the science culture in Japan.

<Center's Response> IFReC has introduced supporting programs for young researchers: the Research Support Program for Fusion of Different Fields and the Dual Mentor Program, where research activities of promising assistant professors and postdocs are supported and nurtured with the supervision and evaluation of senior researchers; the other is the Fusion Unit Program, under which excellent young researchers are given an opportunity to embark on new endeavors in their research (see section 3). Those programs exactly correspond to recommendation (1). Out of the postdocs belonging to IFReC, several of those who have made outstanding achievements have been promoted to assistant professors.

(2) Clinical immunology is becoming an important future goal of IFReC during extended period. As a matter of fact, Japan is behind in this field and no research center for clinical/medical immunology is available. Therefore, movement of IFReC, a world leading institute in basic immunology, to this direction is most welcome. Progress report claimed about two-thirds of the groups are now involved in clinical immunology. However, their researches still remain at the level of translational research of individual PIs. IFReC should propose a general principle, institutional strategy and their future perspectives.

<Center's Responses>

1) With Sakaguchi, who is responsible for the medical/clinical immunology at IFReC, Kumanogo (Graduate school of medicine), and Ken Ishi (NIBIO) as core members, "the Consortium for Innovative Cancer Immunotherapy" (tentative translation) was established in May, 2014. The participant institutions include Osaka University Hospital, National Cancer Center Hospital East, NIBIO and IFReC. Composed of fundamental researchers with clear vision for applying their research to clinical field and physicians with sufficient experience of both success and failure in new therapies, complementing each other, the Consortium aims to advance innovative research of cancer immunotherapy in Japan and achieving a world-leading position. It is also a research organization capable of launching a large-scale research project under the Health and Labour Sciences Research Grant.

2) In April 2014, IFReC launched the Brain-immune Interaction Laboratory with Ben Seymour, a visiting researcher at CiNet from the University of Cambridge, as a new PI (visiting professor), aiming to advance toward psychoneuroimmunology. The kick-off seminar for the laboratory was held on May 14, 2014, with participation of many IFReC researchers.

3) Led by Sakaguchi and Kumanogoh, active discussion ensued on strategic measures to accelerate researches for medical/clinical immunology through collaboration with clinicians of Osaka

University Hospital and IFReC researchers. As a result, a number of researchers belonging to IFReC, together with clinicians and corporate researchers, got involved in the establishment of seven research units in the Center of Medical innovation and Translational Research, which was inaugurated in April 2014.

4) The fact that clinical trials based on the achievements at IFReC, although still at the individual level, have come to fruition shows that the initial scheme of IFReC (promoting interdisciplinary researches → comprehensive understanding of immune system → evolving to medical/clinical immunology) was not an unachievable goal.

7-2 Actions required and recommendations by the Site-visit team

(1) In order to make IFReC more attractive for gifted young scientists both nationally and internationally, the following is recommended: Set up junior positions for excellent postdocs giving them complete scientific independence, including an institutional core budget; access to all core facilities and some technical support, possibly a PhD student; and a five-year duration with the possibility of tenure track following an interim evaluation. These postdocs should be selected based on their scientific vision, originality, excellence and project proposal. Ten or, better, more such junior groups would not only bring fresh ideas into the institute but also change the science culture in Japan.

<Center's Response> Replied in 7-1-(1)

(2) There appears to be a need for a high-level internal strategic committee or the recently created "Future Planning Committee of the Center" to discuss the future with Osaka University's central administration.

<Center's Response> Executive members of IFReC including the director, deputy directors and administrative director have frequently discussed the matters relating to its future plan, and important issues have been brought to the University's administration via the trustee of the University responsible for research advancement.

(3) IFReC should continue its current efforts to recruit highly talented foreign and female scientists at the levels of PI and junior faculty.

<Center's Response> Replied in section 5-5. Section 6 contains descriptions about staff development for female researchers.

(4) IFReC's efforts in enhancing the research environment for interdisciplinary study and Human/Medical Immunology should be continued, and all of the investigators affiliated with IFReC should share its missions so that they can make further progress on their global appearance. In this context, IFReC's interaction with QBiC and CiNET looks very interesting and even exciting, but they need to be better formulated.

(5) Regarding the imaging group, by taking advantage of the collaboration with QBiC and CiNET, it is now time to obtain sufficient scientific products that will greatly improve IFReC's overall evaluation and chances of getting a 5-year extension.

<Center's Response to (4) and (5) together> For the internal programs to promote

interdisciplinary research, replied in 7-1-(1); for Human immunology, replied in 7-1-(2)

・**Collaboration with QBiC** : Represented by Yanagida group (Fujita and Yamaguchi) and the Research Fusion Unit (Kumagai and Teraguchi), a number of collaborations between QBiC and IFReC are actively conducted. Researchers of both institutions have participated in research events such as seminars held by each center.

・**Collaboration with CiNet :** Following the Yoshioka laboratory, Seymour laboratory has been recently established. Now, with the world-class highly sensitive MRI of 11.7T, 7T, 3T, which enables researchers to observe objectives ranging from small animals to humans, we are ready to move toward psychoneuroimmunology.

(6) Furthermore, attempts to establish more systematic and collaborative national and international networks with the clinical and industrial sectors are advised for further acceleration of medical/clinical immunology program at IFReC, however, it should not be forgotten that there are several places sink into mediocrity when incorporating too much activity, while not being professional about it.

<Center's Response> Replied in 7-1-(2)

(7) Because almost two-thirds of immunology groups are now involved more or less in clinical immunology and it is a promising target of research during extended period, a comprehensive strategy should be drafted in more details for the creation of scientific platform for continuous advancement of human immunology.

<Center's Response> Replied in 7-1-(2)

(8) Since majority of medical graduates in Japan has an increased preference to become physician instead of researcher, it is expected that IFReC makes effort to attract young medical students to do research in the fields of immunology, imaging science and bioinformatics for guiding them to become physician-scientist in the field of basic health science.

<Center's Response> IFReC offers many research opportunities for the medical students of Osaka University. Last year, IFReC accepted 20 out of 100 medical students for the 6-month Lab Exposure Program at the Medical School. Some of them got interested in the research and continued to work in the IFReC laboratories even after the expiration of the program period. The "MD Researcher Development Program (Special Education Program for Cultivating Basic Medical Researchers)" has recently been started at the Medical School, and several medical students have chosen IFReC as their host laboratories.

As described in section 2-6-2 regarding the outreach activities to students, IFReC held a series of lectures entitled "Immunology–from its history to latest findings-" as a course of general liberal arts education in Osaka University in 2013, where many premedical students attended lectures given by young associate and assistant professors of IFReC. We also encourage them to take the opportunity offered by events such as campus festivals held in the University to introduce their researches.

World Premier International Research Center Initiative (WPI)

1. FY 2013 List of Principal Investigators

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

<Results at the end of FY2013>

Principal Investigators Total: 25

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* (61)	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* (74)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	70%	0%	30%	0%	01/11/2007	Usually stays at IFReC	
Hitoshi Kikutani* (63)	Professor, Research Institute for Microbial Diseases, Osaka University	MD, PhD (Immunology)	70%	10%	20%	0%	01/10/2007	Usually stays at IFReC	
Taroh Kinoshita* (62)	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* (47)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	50%	0%	0%	50%	01/10/2007	Usually stays at IFReC	
Kiyoshi Takeda* (47)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	70%	0%	0%	30%	01/11/2007	Usually stays at IFReC	
Hisashi Arase* (48)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	95%	0%	0%	5%	01/10/2007	Usually stays at IFReC	
Shimon Sakaguchi* (63)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	50%	10%	17%	23%	01/12/2007	Usually stays at IFReC	
Takashi Saito* (63)	Group Director, RIKEN, Research Center for Integrative Medical Sciences	PhD (Immunology)	20%	0%	70%	10%	03/12/2007	Usually stays at RIKEN IMS satellite	
Tomohiro Kurosaki* (58)	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* (77)	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* (67)	Professor, Graduate School of Frontier Biosciences, Osaka University	PhD (Molecular imaging)	25%	0%	65%	10%	01/11/2007	Usually stays at IFReC	
Yoshichika Yoshioka* (60)	Professor, WPI Immunology Frontier Research Center, Osaka University	DSc (Biophysics)	100%	0%	0%	0%	01/02/2008	Usually stays at IFReC	
Yutaka Hata* (52)	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 (46)	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Chemistry)	100%	0%	0%	0%	01/10/2008	Usually stays at IFReC	
Jun Hatazawa* (60)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Nuclear Medicine)	5%	5%	45%	45%	16/01/2009	Usually stays at IFReC	

Masaru Ishii (40)	Professor, Graduate School of Frontier Biosciences, Osaka University	MD, PhD (Bioimaging)	30%	0%	70%	0%	01/12/2008	Usually stays at IFReC	
Kazuya Kikuchi (48)	Professor, Graduate School of Engineering, Osaka University	PhD (Chemical Biology)	28%	2%	50%	20%	01/08/2009	Usually stays at IFReC	
Cevayir Coban (41)	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 (39)	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* (45)	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* (54)	Professor, WPI Immunology Frontier Research Center	MD, PhD (Immunology)	100%	0%	0%	0%	01/03/2011	Usually stays at IFReC	

Kazuhiro Suzuki (38)	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 (39)	Associate Professor, WPI Immunology Frontier Research Center	MD, PhD (Cell Biology)	100%	0%	0%	0%	01/10/2011	Usually stays at IFReC	
Masahiro Yamamoto (35)	Professor, Research Institute for Microbial Diseases, Osaka University	PhD (Immunol ogy)	90%	10%	0%	0%	01/04/2012	Usually stays at IFReC	

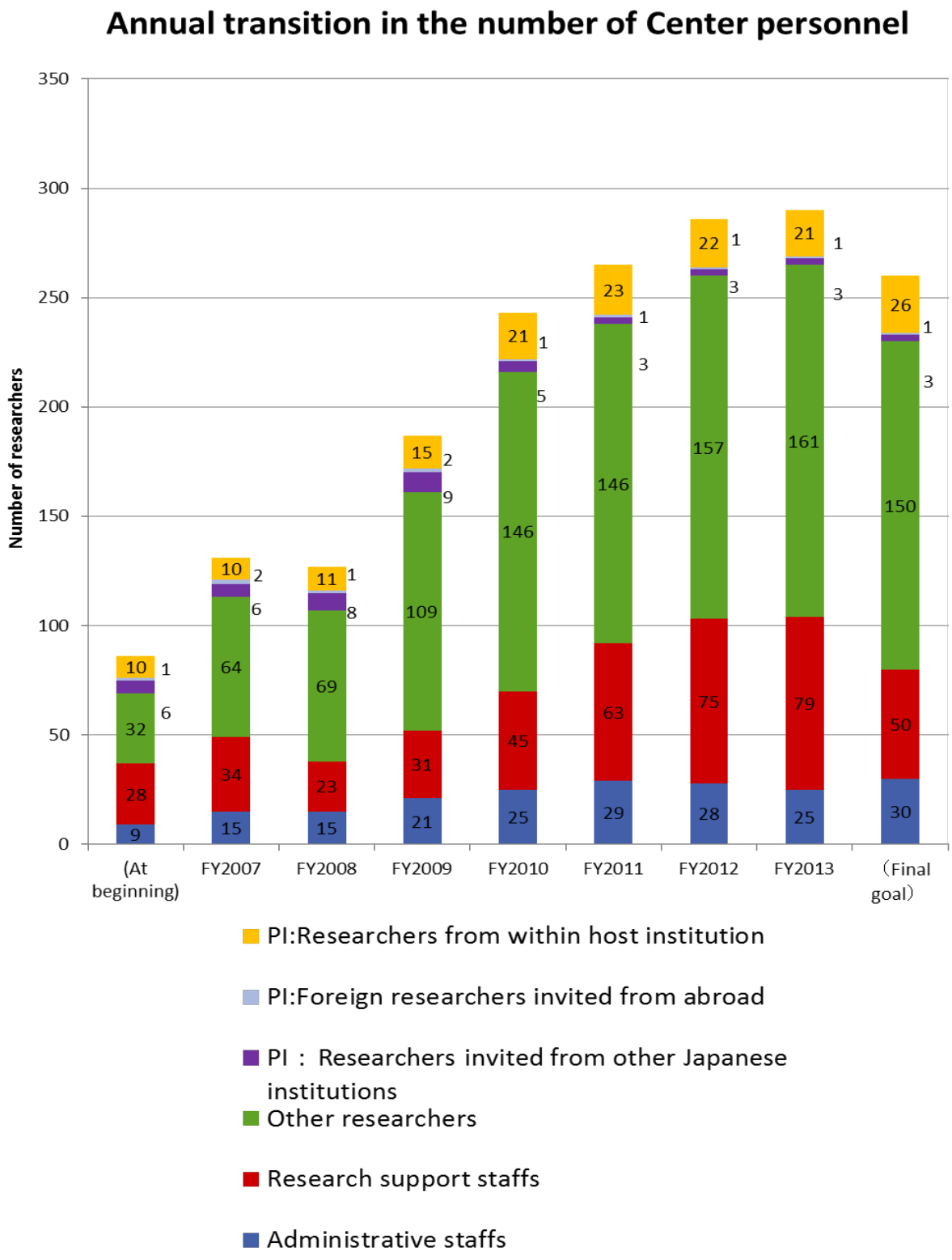
Researchers unable to participate in project in FY 2013

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken
Diego Miranda-Saavedra	Team Leader, Institute of Cellular Medicine, Newcastle University Medical School, UK	16/1/2010	He transferred his position to Team Leader, Institute of Cellular Medicine, Newcastle University Medical School, UK	

World Premier International Research Center Initiative (WPI)

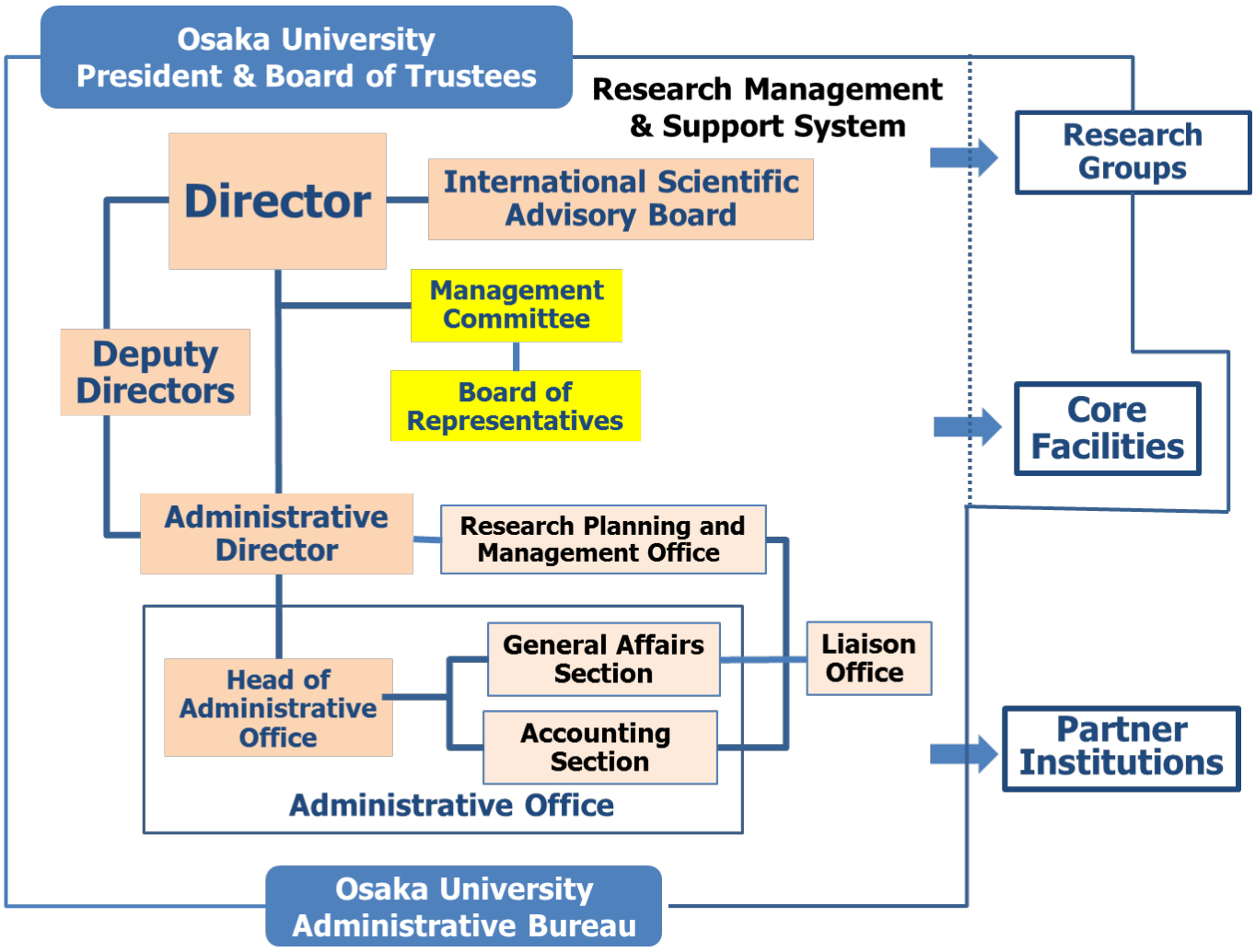
2. Annual transition in the number of Center personnel

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



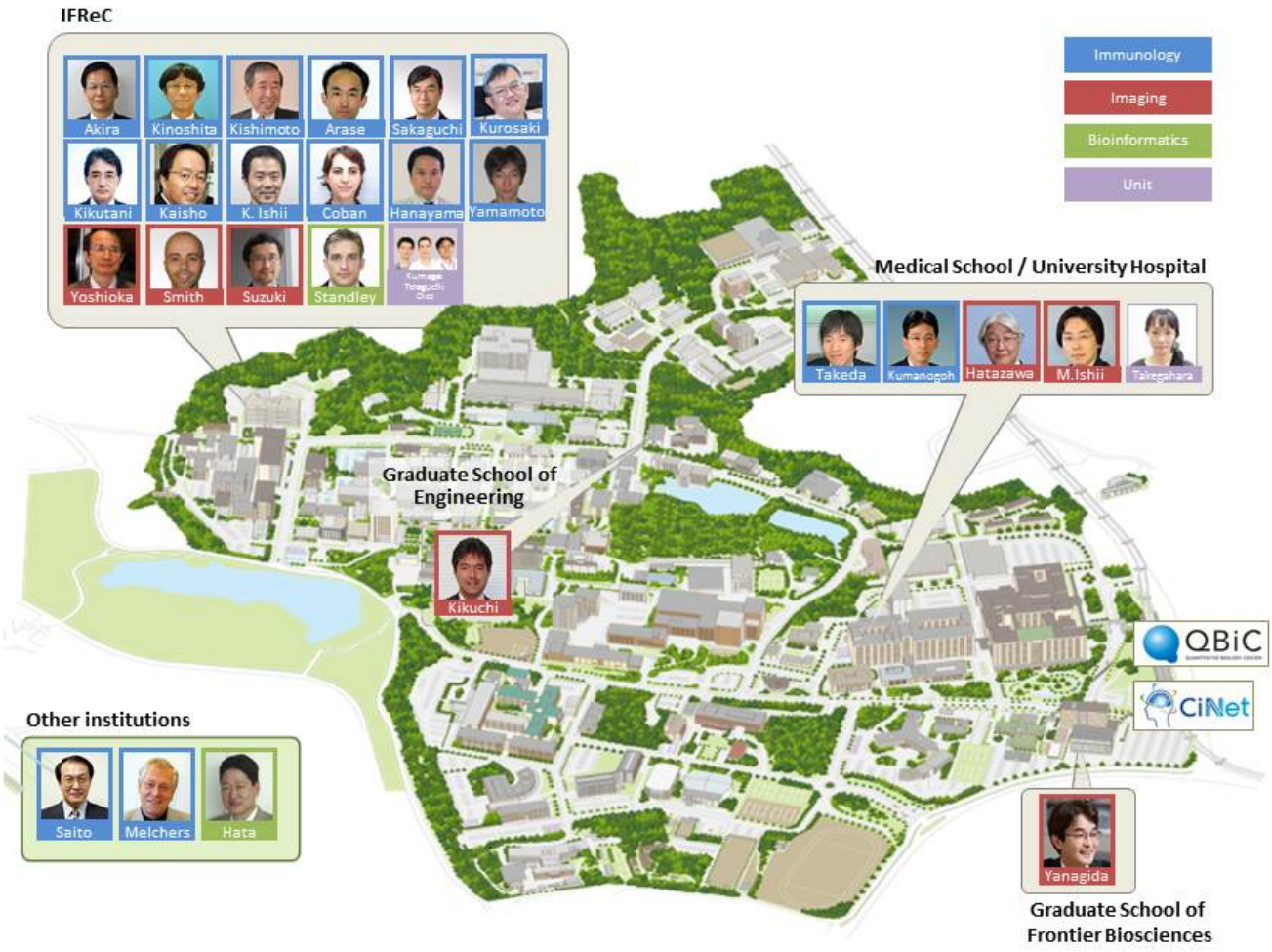
World Premier International Research Center Initiative (WPI)

3. Diagram of management system



World Premier International Research Center Initiative (WPI)

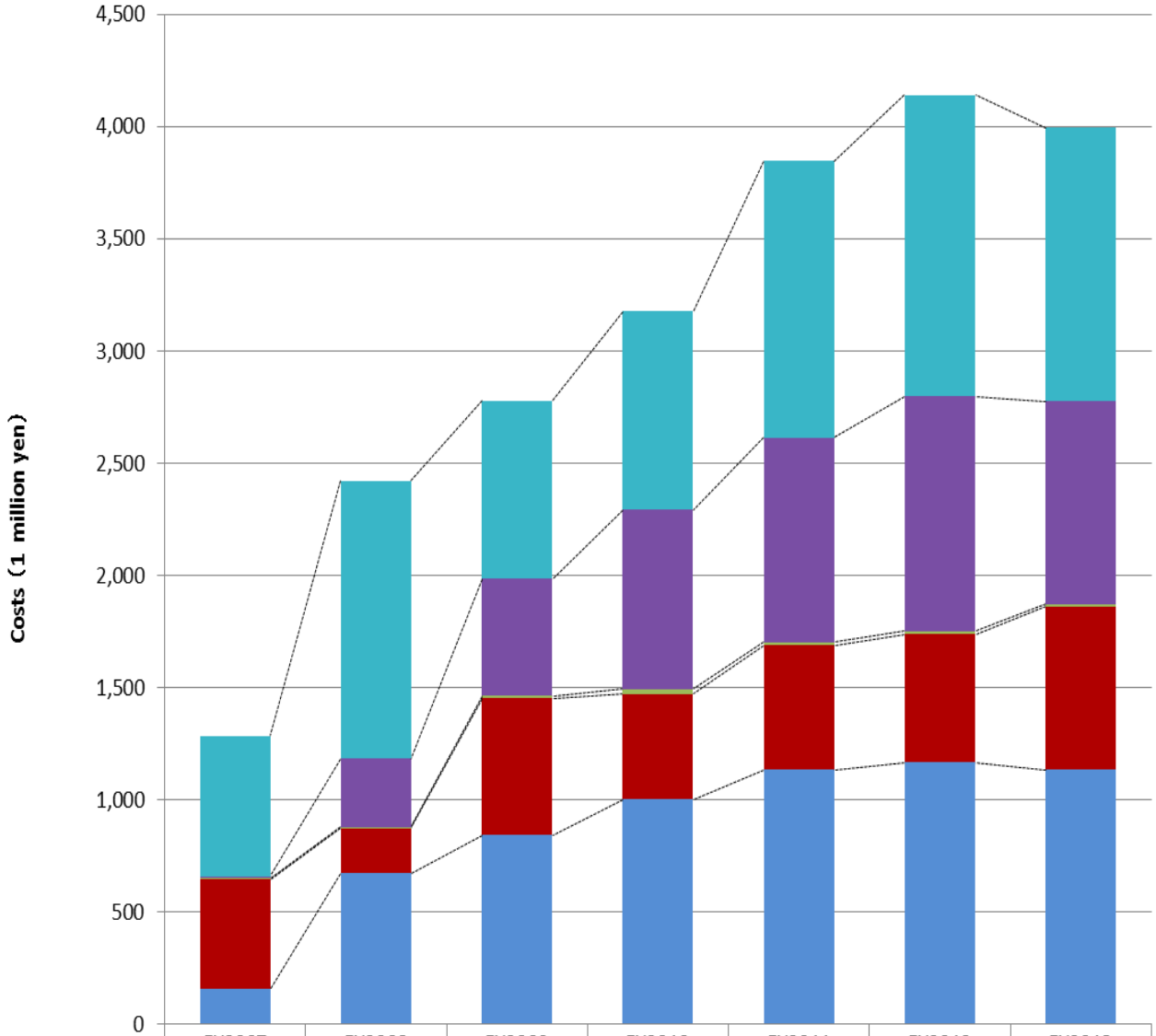
4. Campus map



World Premier International Research Center Initiative (WPI)

5. Annual transition in the amounts of project funding

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



	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013
Research projects	625	1,237	794	882	1,230	1,342	1,219
Equipment	8	305	521	800	912	1,046	903
Travel	7	4	12	23	14	12	9
Project activities	489	201	609	467	553	572	727
Personnel	157	674	843	1,004	1,136	1,167	1,136

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

Overall project funding

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	29
	Principal investigators (no. of persons): 21	161
	Other researchers (no. of persons): 152	599
	Research support staffs (no. of persons): 66	234
	Administrative staffs (no. of persons): 22	113
	Total	1136
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons): 0	0
	Cost of dispatching scientists (no. of persons): 17	17
	Research startup cost (no. of persons): 1	19
	Cost of satellite organizations (no. of satellite organizations): 0	0
	Cost of international symposiums (no. of symposiums): 1	1
	Rental fees for facilities	8
	Cost of consumables	4
	Cost of utilities	62
	Other costs	616
	Total	727
Travel	Domestic travel costs	1
	Overseas travel costs	3
	Travel and accommodations cost for invited scientists (no. of domestic scientists): 0 (no. of overseas scientists): 5	4
	Travel cost for scientists on secondment (no. of domestic scientists): 1 (no. of overseas scientists): 1	1
	Total	9
Equipment	Depreciation of buildings	290
	Depreciation of equipment	613
	Total	903
Other research projects	Projects supported by other government subsidies, etc.	37
	Commissioned research projects, etc.	998
	Grants-in-Aid for Scientific Research, etc.	184
	Total	1219
Total		3994

Ten thousand dollars

WPI grant 1344

Costs of establishing and maintaining facilities 0

Establishing new facilities
(Number of facilities: , m²) Costs paid:

Repairing facilities
(Number of facilities: , m²) Costs paid:

Others

Cost of equipment procured 99

Name of equipment: Next generation sequencer system upgrade
Number of units: 1 Costs paid: 12
Name of equipment: Bio imaging navigator
Number of units: 1 Costs paid: 6
Name of equipment: 561 nm laser upgrade kit
Number of units: 1 Costs paid: 9
Name of equipment: Air spring vivration isolation system
Number of units: 1 Costs paid: 1
Name of equipment: Inverted microscope
Number of units: 1 Costs paid: 1
Name of equipment: STP120-2 spin tissue processor
Number of units: 1 Costs paid: 3
Name of equipment: Ultra freezer
Number of units: 1 Costs paid: 2
Name of equipment: Tissue embedding console system
Number of units: 1 Costs paid: 1
Name of equipment: Cryomicrotome
Number of units: 1 Costs paid: 5
Name of equipment: 13C 1H volume resonator
Number of units: 1 Costs paid: 6
Name of equipment: 11.7T 1H RES QD T/R type RF coil
Number of units: 1 Costs paid: 3
Name of equipment: Imaging chamber (mouse bed)
Number of units: 1 Costs paid: 1
Name of equipment: GaAsP NDD EPI unit
Number of units: 1 Costs paid: 6
Name of equipment: Individually Ventilated Cage system
Number of units: 1 Costs paid: 12
Name of equipment: Stage top incubator
Number of units: 1 Costs paid: 1
Name of equipment: Electron multiplying digital CCD Camera
Number of units: 1 Costs paid: 3
Name of equipment: Nanoparticles analysis system
Number of units: 1 Costs paid: 8
Name of equipment: Cell Analyzer EC800
Number of units: 1 Costs paid: 7
Name of equipment: Ultra compact solid state yellow laser
Number of units: 1 Costs paid: 1
Name of equipment: Confocal scanner unit
Number of units: 1 Costs paid: 6
Others 5

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (no. of persons): 1	
	Other researchers (no. of persons): 2	
	Research support staffs (no. of persons): 4	
	Administrative staffs (no. of persons): 0	
	Total	11
Project activities		
Travel		
Equipment		
Other research projects		59
Total		70

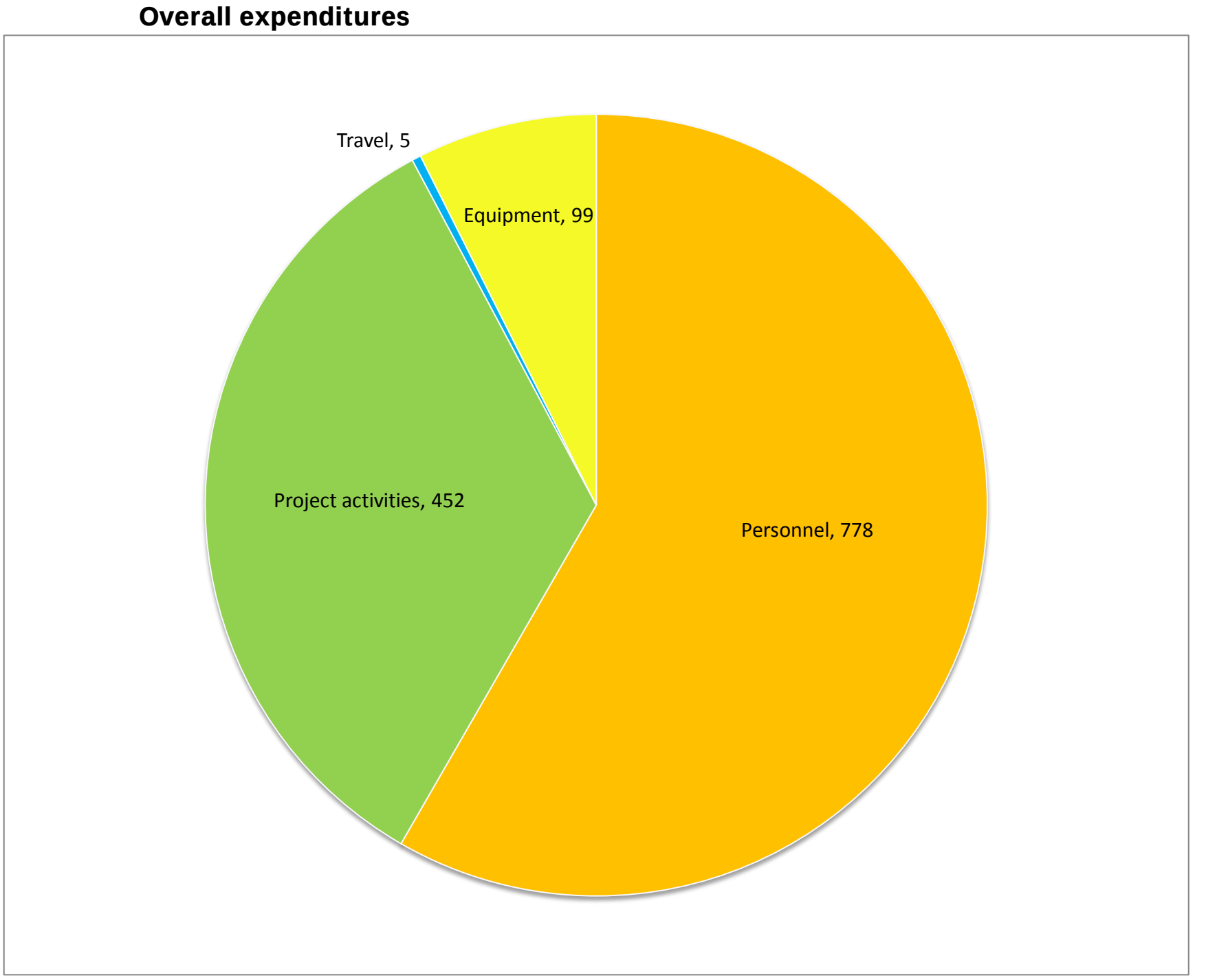
7.FY2013 WPI Grant Expenditures (the exchange rate used: 1USD=100JPY)

i) Overall expenditures

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	29
	Principal investigators (no. of person): 12	107
	Other researchers (no. of person): 102	372
	Research support staffs (no. of person): 56	213
	Administrative staffs (no. of person): 11	57
	Total	778
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of person): 0	0
	Cost of dispatching scientists (no.10 of person): 10	17
	Research startup cost (no. of person): 1	19
	Cost of satellite organizations (no. of satellite organization): 0	0
	Cost of international symposiums (no. of symposiums): 1	1
	Rental fees for facilities	8
	Cost of consumables	4
	Cost of utilities	62
	Other costs	341
	Total	452
Travel	Domestic travel costs	1
	Overseas travel costs	3
	Travel and accommodations cost for invited scientists (no.0 of domestic scientists): 0 (no.0 of overseas scientists): 0	0
	Travel cost for scientists on secondment (no. of domestic scientists): 1 (no. of overseas scientists): 1	1
	Total	5
Equipment	Cost of equipment procured	99
	Total	99
Total		1334

ii) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (no. of person): 1	
	Other researchers (no. of person): 1	
	Research support staffs (no. of person): 4	
	Administrative staffs (no. of person): 0	
	Total	9
Project activities		0
Travel		0
Equipment		0
Total		9



World Premier International Research Center Initiative (WPI)

1. List of papers underscoring each research achievement

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

***[1] Pathogen recognition and innate immune responses**

1. Yamasaki, Sho; Ishikawa, Eri; Sakuma, Machie; Hara, Hiromitsu; Ogata, Koji; Saito, Takashi. Mincle is an ITAM-coupled activating receptor that senses damaged cells. Nature Immunology 9:1179-1188, 2008.

Macrophage-inducible C-type lectin (Mincle) is expressed mainly in macrophages and is induced after exposure to various stimuli and stresses. Saito and Akira's group showed that Mincle selectively associated with the Fc receptor common gamma-chain and activated macrophages to produce inflammatory cytokines and chemokines. Mincle-expressing cells were activated in the presence of dead cells, and they identified SAP130, a component of small nuclear ribonucloprotein, as a Mincle ligand that is released from dead cells. To investigate whether Mincle is required for normal responses to cell death in vivo, they induced thymocyte death by irradiating mice and found that transient infiltration of neutrophils into the thymus could be blocked by injection of Mincle-specific antibody. Their results suggest that Mincle is a receptor that senses nonhomeostatic cell death and thereby induces the production of inflammatory cytokines to drive the infiltration of neutrophils into damaged tissue.

*2. Tsuchida, Tetsuo; Zou, Jian; Saitoh, Tatsuya; Kumar, Himanshu; Kawai, Taro; Akira, Shizuo. The ubiquitin ligase TRIM56 regulates innate immune responses to intracellular double-stranded DNA. Immunity 33:765-776, 2010.

The innate immune system detects pathogen- and host-derived double-stranded DNA exposed to the cytosol and induces type I interferon (IFN) and other cytokines. Akira's group identified interferon-inducible tripartite-motif (TRIM) 56 as a regulator of double-stranded DNA-mediated type I interferon induction. TRIM56 overexpression enhanced IFN-β promoter activation after double-stranded DNA stimulation whereas TRIM56 knockdown abrogated it. TRIM56 interacted with STING and targeted it for lysine 63-linked ubiquitination. This modification induced STING dimerization, which was a prerequisite for recruitment of the antiviral kinase TBK1 and subsequent induction of IFN-β. Taken together, these results indicate that TRIM56 is an interferon-inducible E3 ubiquitin ligase that modulates STING to confer double-stranded DNA-mediated innate immune responses.

*3. Saitoh, Tatsuya; Komano, Jun; Saitoh, Yasunori; Misawa, Takuma; Takahama, Michihiro; Kozaki, Tatsuya; Uehata, Takuya; Iwasaki, Hidenori; Omori, Hiroko; Akira, Shizuo. Neutrophil Extracellular Traps mediate a host defense response to Human Immunodeficiency Virus-1. Cell Host & Microbe 12:109-116, 2012.

Although neutrophil extracellular traps (NETs) express antiviral factors, such as myeloperoxidase

and α-defensin, the involvement of NETs in antiviral responses remains unclear. Akira's group showed that NETs capture human immunodeficiency virus (HIV)-1 and promote HIV-1 elimination through myeloperoxidase and α-defensin. Neutrophils detect HIV-1 by Toll-like receptors (TLRs) TLR7 and TLR8, which recognize viral nucleic acids. Engagement of TLR7 and TLR8 induces the generation of reactive oxygen species that trigger NET formation, leading to NET-dependent HIV-1 elimination. However, HIV-1 counteracts this response by inducing C-type lectin CD209-dependent production of interleukin (IL)-10 by dendritic cells to inhibit NET formation. IL-10 suppresses the reactive oxygen species-dependent generation of NETs induced upon TLR7 and TLR8 engagement, resulting in disrupted NET-dependent HIV-1 elimination. Therefore, NET formation is an antiviral response that is counteracted by HIV-1.

***[2] Formation of inflammasome and inflammation**

*4. Saitoh, Tatsuya; Fujita, Naonobu; Jang, Myoung Ho; Uematsu, Satoshi; Yang, Bo-Gie; Satoh, Takashi; Omori, Hiroko; Kawai, Taro; Takeuchi, Osamu; Yoshimori, Tamotsu; Akira, Shizuo. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1 beta production. Nature 456:264-268, 2008.

The mechanism underlying the regulation of inflammatory response by autophagy is poorly understood. Akira's group showed that Atg16L1 (autophagy-related 16-like 1), which is implicated in Crohn's disease, regulates endotoxin-induced inflammasome activation in mice. Atg16L1-deficiency disrupts the recruitment of the Atg12-Atg5 conjugate to the isolation membrane, resulting in a loss of microtubule-associated protein 1 light chain 3 (LC3) conjugation to phosphatidylethanolamine. Consequently, both autophagosome formation and degradation of long-lived proteins are severely impaired in Atg16L1-deficient cells. Following stimulation with lipopolysaccharide, a ligand for Toll-like receptor 4, Atg16L1-deficient macrophages produce high amounts of the inflammatory cytokines IL-1β and IL-18. Their results demonstrate that Atg16L1 is an essential component of the autophagic machinery responsible for control of the endotoxin-induced inflammatory immune response.

*5. Misawa, Takuma; Takahama, Michihiro; Kozaki, Tatsuya; Lee, Hanna; Zou, Jian; Saitoh, Tatsuya; Akira, Shizuo. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. Nature Immunology 14:454-460, 2013.

NLRP3 forms an inflammasome with its adaptor ASC, and its excessive activation can cause inflammatory diseases. However, little is known about the mechanisms that control assembly of the inflammasome complex. Akira's group showed that microtubules mediated assembly of the NLRP3 inflammasome. Inducers of the NLRP3 inflammasome caused aberrant mitochondrial homeostasis to diminish the concentration of the coenzyme NAD+, which in turn inactivated the NAD+-dependent α-tubulin deacetylase sirtuin 2; this resulted in the accumulation of acetylated α-tubulin. Acetylated α-tubulin mediated the dynein-dependent transport of mitochondria and subsequent apposition of ASC on mitochondria to NLRP3 on the endoplasmic reticulum. Therefore, in addition to direct activation of NLRP3, the creation of optimal sites for signal transduction by microtubules is required for activation of the entire NLRP3 inflammasome.

***[3] New findings about M2 macrophages**

*6. Satoh, Takashi; Takeuchi, Osamu; Vandenbon, Alexis; Kumagai, Yutaro; Miyake, Tohru; Saitoh, Tatsuya; Standley, Daron M.; Akira, Shizuo. The Jmjd3-Irf4 axis regulates M2 macrophage polarization

and host responses against helminth infection. Nature Immunology 11:936-944, 2010.

Polarization of macrophages to M1 or M2 cells is important for mounting responses against bacterial and helminth infections, respectively. Jumonji domain containing-3 (Jmjd3), a histone 3 Lys27 (H3K27) demethylase, has been implicated in the activation of macrophages. Akira's group showed that Jmjd3 is essential for M2 macrophage polarization in response to helminth infection and chitin, though Jmjd3 is dispensable for M1 responses. Furthermore, Jmjd3 (also known as Kdm6b) is essential for proper bone marrow macrophage differentiation, and this function depends on demethylase activity of Jmjd3. Jmjd3 deficiency affected trimethylation of H3K27 in only a limited number of genes. Among them, they identified Irf4 as encoding a key transcription factor that controls M2 macrophage polarization. Collectively, these results show that Jmjd3-mediated H3K27 demethylation is crucial for regulating M2 macrophage development leading to anti-helminth host responses.

*7. Satoh, Takashi; Yamamoto, Masahiro; Takemura, Naoki; Yoshioka, Yoshichika; Takeuchi, Osamu; Akira, Shizuo. Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. Nature 495:524-528, 2013.

Akira's group showed Trib1, an adaptor protein involved in protein degradation is critical for the differentiation of F4/80+MR+ tissue-resident macrophages (M2-like macrophages), and eosinophils but not for the differentiation of M1 myeloid cells. Trib1 deficiency causes a severe reduction of M2-like macrophages in various organs, including bone marrow, lung and adipose tissues. Mice lacking Trib1 in haematopoietic cells show diminished adipose tissue mass accompanied by evidence of increased lipolysis, even when fed a normal diet. Supplementation of M2-like macrophages rescues the pathophysiology. In response to a high-fat diet, mice lacking Trib1 in haematopoietic cells develop hypertriglyceridaemia and insulin resistance, together with increased proinflammatory cytokine gene induction. Their results demonstrate Trib1 is critical for adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue-resident M2-like macrophages.

***[4] Toward the developments of effective vaccines**

*8. Ishii, Ken J.; Kawagoe, Tatsukata; Koyama, Shohei; Kumar, Himanshu; Kawai, Taro; Uematsu, Satoshi; Takeuchi, Osamu; Coban, Cevayir; Akira, Shizuo. TANK-binding kinase-1 delineates innate and adaptive immune responses to DNA vaccines. Nature 451:725-729, 2008.

Ken Ishii and Akira's group demonstrated in vivo that TANK-binding kinase 1 (TBK1), a non-canonical IkappaB kinase, mediates the adjuvant effect of DNA vaccines and is essential for its immunogenicity in mice. Plasmid-DNA-activated, TBK1-dependent signaling and the resultant type-I interferon receptor-mediated signaling was required for induction of antigen-specific B and T cells, which occurred even in the absence of innate immune signaling through a well-known CpG DNA sensor-TLR9 or Z-DNA binding protein 1. Moreover, bone-marrow-transfer experiments revealed that TBK1-mediated signaling in haematopoietic cells was critical for the induction of antigen-specific B and CD4(+) T cells, whereas in non-haematopoietic cells TBK1 was required for CD8(+) T-cell induction. These data suggest that TBK1 is a key signaling molecule for DNA-vaccine-induced immunogenicity, by differentially controlling DNA-activated innate immune signaling through haematopoietic and non-haematopoietic cells.

*9. Marichal, Thomas; Ohata, Keiichi; Kobiyama, Kouji; Lekeux, Pierre; Coban, Cevayir; Akira,

Shizuo; Ishii, Ken J.; Desmet, Christophe J. DNA released from dying host cells mediates aluminum adjuvant activity. Nature Medicine 17:996-1002, 2011.

Ken Ishii's group reported that, in mice, alum (Aluminum-based adjuvants) causes cell death and the subsequent release of host cell DNA, which acts as a potent endogenous immunostimulatory signal mediating alum adjuvant activity. Furthermore, they propose that host DNA signaling differentially regulates IgE and IgG1 production after alum-adjuvanted immunization. They suggest that, on the one hand, host DNA induces primary B cell responses, including IgG1 production, through interferon response factor 3 (Irf3)-independent mechanisms. On the other hand, they suggest that host DNA also stimulates 'canonical' T helper type 2 (T(H)2) responses, associated with IgE isotype switching and peripheral effector responses, through Irf3-dependent mechanisms. The finding that host DNA released from dying cells acts as a damage-associated molecular pattern that mediates alum adjuvant activity may increase our understanding of the mechanisms of action of current vaccines and help in the design of new adjuvants.

***[5] New findings about mucosal immunology**

*10. Uematsu, Satoshi; Jang, Myoung Ho; Yang, Bo-Gie; Kiyono, Hiroshi; Miyasaka, Masayuki; Ishii, Ken J.; Akira, Shizuo. Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5. Nature Immunology 9:769-776, 2008.

Akira's group identified a subset of CD11chiCD11bhi lamina propria dendritic cells (LPDCs) that expressed Toll-like receptor 5 (TLR5) in the small intestine. When stimulated by the TLR5 ligand flagellin, TLR5+ LPDCs induced the differentiation of naive B cells into immunoglobulin A–producing plasma cells by a mechanism independent of gut-associated lymphoid tissue. In addition, by a mechanism dependent on TLR5 stimulation, these LPDCs promoted the differentiation of antigen-specific interleukin 17–producing T helper cells and type 1 T helper cells. Unlike spleen DCs, the LPDCs specifically produced retinoic acid, which, in a dose-dependent way, supported the generation and retention of immunoglobulin A–producing cells in the lamina propria and positively regulated the differentiation interleukin 17–producing T helper cells. Their findings demonstrate unique properties of LPDCs and the importance of TLR5 for adaptive immunity in the intestine.

*11. Atarashi, Koji; Nishimura, Junichi; Shima, Tatsuichiro; Umesaki, Yoshinori; Yamamoto, Masahiro; Onoue, Masaharu; Yagita, Hideo; Ishii, Naoto; Evans, Richard; Honda, Kenya; Takeda, Kiyoshi. ATP drives lamina propria T(H)17 cell differentiation. Nature 455:808-812, 2008.

Takeda's group showed that adenosine 5′-triphosphate (ATP) derived from commensal bacteria activates a subset of lamina propria cells, CD70highCD11clow cells, leading to the differentiation of TH17 cells. Germ-free mice exhibit much lower concentrations of luminal ATP, accompanied by fewer lamina propria TH17 cells, compared to specific-pathogen-free mice. Systemic or rectal administration of ATP into these germ-free mice results in a marked increase in the number of lamina propria TH17 cells. A CD70highCD11clow subset of the lamina propria cells expresses TH17-prone molecules, such as IL-6, IL-23p19 and transforming-growth-factor-β-activating integrin-αV and -β8, in response to ATP stimulation, and preferentially induces TH17 differentiation of co-cultured naive CD4+ T cells. Their observations highlight the importance of commensal bacteria and ATP for TH17 differentiation in health and disease, and offer an explanation of why TH17 cells specifically present in the intestinal lamina propria.

***[6] Immune responses to Malaria infection**

*12. Zhao, Hong; Konishi, Aki; Fujita, Yukiko; Yagi, Masanori; Ohata, Keiichi; Aoshi, Taiki; Noha H.; Horii, Toshihiro; Akira, Shizuo; Ishii, Ken J.; Coban, Cevayir. Lipocalin 2 bolsters innate and adaptive immune responses to blood-stage Malaria infection by reinforcing host iron metabolism. Cell Host & Microbe 12:705-716, 2012.

Although Plasmodium parasites require host iron for replication, how host iron homeostasis and responses to these fluxes affect Plasmodium infection are incompletely understood. Coban's group determined that Lipocalin 2 (Lcn2), a host protein that sequesters iron, is abundantly secreted during human (P. vivax) and mouse (P. yoeliiNL) blood-stage malaria infections and is essential to control P. yoeliiNL parasitemia, anemia, and host survival. During infection, Lcn2 bolsters both host macrophage function and granulocyte recruitment and limits reticulocytosis, or the expansion of immature erythrocytes, which are the preferred target cell of P. yoeliiNL. Additionally, a chronic iron imbalance due to Lcn2 deficiency results in impaired adaptive immune responses against Plasmodium parasites. Thus, Lcn2 exerts antiparasitic effects by maintaining iron homeostasis and promoting innate and adaptive immune responses.

***[7] Immune responses to Toxoplasma**

*13. Yamamoto, Masahiro; Standley, Daron M.; Kayama, Hisako; Matsuda, Tadashi; Soldati-Favre, Dominique; Takeda, Kiyoshi. A single polymorphic amino acid on Toxoplasma gondii kinase ROP16 determines the direct and strain-specific activation of Stat3. Journal of Experimental Medicine 206:2747-2760, 2009.

Takeda, Yamamoto, and Standley's groups generated a highly polymorphic parasite-derived kinase ROP16-deficient type I parasites by reverse genetics and found a severe defect in parasite-induced Stat3 activation, culminating in enhanced production of interleukin (IL) 6 and IL-12 p40 in the infected macrophages. Furthermore, overexpression of ROP16 but not ROP18 in mammalian cells resulted in Stat3 phosphorylation and strong activation of Stat3-dependent promoters. In addition, kinase-inactive ROP16 failed to activate Stat3. Comparison of type I and type II ROP16 revealed that a single amino acid substitution in the kinase domain determined the strain difference in terms of Stat3 activation. Moreover, ROP16 bound Stat3 and directly induced phosphorylation of this transcription factor. These results formally establish an essential and direct requirement of ROP16 in parasite-induced Stat3 activation and the significance of a single amino acid replacement in the function of type II ROP16.

*14. Yamamoto, Masahiro; Ma, Ji Su; Mueller, Christina; Kamiyama, Naganori; Kayama, Hisako; Matsuura, Yoshiharu; Soldati-Favre, Dominique; Takeda, Kiyoshi. ATF6 beta is a host cellular target of the Toxoplasma gondii virulence factor ROP18. Journal of Experimental Medicine 208:1533-1546, 2011.

Takeda and Yamamoto's groups showed that ROP18 kinase targets the host endoplasmic reticulum–bound transcription factor ATF6β. Disruption of the ROP18 gene severely impairs acute toxoplasmosis by the type I RH strain. Because another virulence factor ROP16 kinase modulates immune responses through its N-terminal portion, they focus on the role of the N terminus of ROP18 in the subversion of host cellular functions. The N-terminal extension of ROP18 contributes to ATF6β-dependent pathogenicity by interacting with ATF6β and destabilizing it. The kinase activity of ROP18 is essential for proteasome-dependent degradation of ATF6β and for parasite virulence. Consistent with a key role for ATF6β in resistance to this intracellular pathogen, ATF6β-deficient mice

exhibit a high susceptibility to infection by ROP18-deficient parasites. The results reveal that interference with ATF6β-dependent immune responses is a novel pathogenic mechanism induced by ROP18.

*15. Yamamoto, Masahiro; Okuyama, Megumi; Ma, Ji Su; Kimura, Taishi; Kamiyama, Naganori; Sasai, Miwa; Kayama, Hisako; Huang, David C. S.; Soldati-Favre, Dominique; Takeda, Kiyoshi. A cluster of Interferon-gamma-inducible p65 GTPases plays a critical role in host defense against Toxoplasma gondii. Immunity 37:302-313, 2012.

Yamamoto's group showed that a cluster of guanylate-binding protein (Gbp) genes was required for host cellular immunity against the intracellular parasite Toxoplasma gondii. They 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. Furthermore, Gbpchr3-deleted macrophages were defective in IFN-γ-mediated suppression of T. gondii intracellular growth and recruitment of IFN-γ-inducible p47 GTPase Irgb6 to the parasitophorous vacuole. In addition, some members of Gbpchr3 restored the protective response against T. gondii in Gbpchr3-deleted cells. Their results suggest that Gbpchr3 play a pivotal role in anti-T. gondii host defense by controlling IFN-γ-mediated Irgb6-dependent cellular innate immunity.

***[8] Roles of PILR in immune responses**

*16. Satoh, Takeshi; Arii, Jun; Suenaga, Tadahiro; Wang, Jing; Kogure, Amane; Uehori, Junji; Arase, Noriko; Spear, Patricia G.; Lanier, Lewis L.; Arase, Hisashi. PILR alpha is a herpes simplex virus-1 entry coreceptor that associates with glycoprotein B. Cell 132:935-944, 2008.

Glycoprotein B (gB) is one of the essential components for infection by herpes simplex virus-1 (HSV-1). Although several cellular receptors that associate with glycoprotein D (gD), such as herpes virus entry mediator (HVEM) and Nectin-1, have been identified, specific molecules that mediate HSV-1 infection by associating with gB have not been elucidated. Arase's group found that paired immunoglobulin-like type 2 receptor (PILR) α associates with gB, and cells transduced with PILRα become susceptible to HSV-1 infection. Furthermore, HSV-1 infection of human primary cells expressing both HVEM and PILRα was blocked by either anti-PILRα or anti-HVEM antibody. Their results demonstrate that cellular receptors for both gB and gD are required for HSV-1 infection and that PILRα plays an important role in HSV-1 infection as a coreceptor that associates with gB. These findings uncover a crucial aspect of the mechanism underlying HSV-1 infection.

*17. Wang, Jing; Shiratori, Ikuo; Uehori, Junji; Ikawa, Masahito; Arase, Hisashi. Neutrophil infiltration during inflammation is regulated by PILR alpha via modulation of integrin activation. Nature Immunology 14:34-40, 2013.

Acute inflammatory responses are important in host defense, whereas dysregulated inflammation causes life-threatening complications. Arase's group found that paired immunoglobulin-like type 2 receptor alpha (PILRα), an inhibitory receptor containing immunoreceptor tyrosine-based inhibitory motifs (ITIMs), negatively regulated neutrophil infiltration during inflammation. Pilra−/− mice had increased neutrophil recruitment to inflammatory sites and were highly susceptible to endotoxin shock. Pilra−/− neutrophils showed enhanced transmigration ability and increased adhesion to the β2 integrin ligand ICAM-1. PILRα expressed on neutrophils constitutively associated in cis with its ligands, resulting

in clustering of PILRα during stimulation with a chemoattractant. Clustering of PILRα enhanced ITIM-mediated signaling, thus modulating β2 integrin inside-out activation. These data demonstrate that neutrophil recruitment in inflammatory responses is regulated by PILRα via modulation of integrin activation.

***[9] Immune regulation and mRNA decay by Regnase-1**

*18. Matsushita, Kazufumi; Takeuchi, Osamu; Standley, Daron M.; Kumagai, Yutaro; Kawagoe, Tatsukata; Miyake, Tohru; Satoh, Takashi; Nakamura, Haruki; Akira, Shizuo. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Nature 458:1185-1190, 2009.

Akira and Standley's groups showed that the TLR-inducible gene Zc3h12a-deficient mice suffered from severe anaemia, and most died within 12 weeks. Zc3h12a-/- mice also showed augmented serum immunoglobulin levels and autoantibody production, together with a greatly increased number of plasma cells, as well as infiltration of plasma cells to the lung. Macrophages from Zc3h12a-/- mice showed highly increased production of interleukin (IL)-6 and IL-12p40, in response to TLR ligands. Although the activation of TLR signaling pathways was normal, Il6 messenger RNA decay was severely impaired in Zc3h12a-/- macrophages. Overexpression of Zc3h12a accelerated Il6 mRNA degradation via its 3′-untranslated region, and destabilized RNAs with 3′-UTRs for genes including Il6, Il12p40 and the calcitonin receptor gene Calcr. These results indicate that Zc3h12a is an essential RNase that prevents immune disorders by directly controlling the stability of a set of inflammatory genes.

*19. Iwasaki, Hidenori; Takeuchi, Osamu; Teraguchi, Shunsuke; Uehata, Takuya; Kuniyoshi, Kanako; Satoh, Takashi; Saitoh, Tatsuya; Standley, Daron M.; Akira, Shizuo. The I kappa B kinase complex regulates the stability of cytokine-encoding mRNA induced by TLR-IL-1R by controlling degradation of regnase-1. Nature Immunology 12:1167-1175, 2011.

Toll-like receptor (TLR) signaling activates the inhibitor of transcription factor NF-κB (IκB) kinase (IKK) complex, which governs NF-κB-mediated transcription during inflammation. The RNase regnase-1 serves a critical role in preventing autoimmunity by controlling the stability of mRNAs that encode cytokines. Akira's group showed that the IKK complex controlled the stability of mRNA for interleukin 6 (IL-6) by phosphorylating regnase-1 in response to stimulation via the IL-1 receptor (IL-1R) or TLR. Phosphorylated regnase-1 underwent ubiquitination and degradation. Regnase-1 was reexpressed in IL-1R- or TLR-activated cells after a period of lower expression. Regnase-1 mRNA was negatively regulated by regnase-1 itself via a stem-loop region present in the regnase-1 3′ untranslated region. Their data demonstrate that the IKK complex phosphorylates not only IκBα, thereby activating transcription, but also regnase-1, thereby releasing a 'brake' on IL-6 mRNA expression.

*20. Uehata, Takuya; Iwasaki, Hidenori; Vandenbon, Alexis; Hernandez-Cuellar, Eduardo; Kuniyoshi, Kanako; Satoh, Takashi; Mino, Takashi; Standley, Daron M.; Takeuchi, Osamu; Akira, Shizuo. Malt1-induced cleavage of Regnase-1 in CD4(+) Helper T cells regulates immune activation. Cell 153:1036-1049, 2013.

Although Regnase-1 (also known as Zc3h12a) inactivation leads to development of an autoimmune disease characterized by T cell activation and hyperimmunoglobulinemia in mice, the mechanism of Regnase-1-mediated immune regulation has remained unclear. Akira's group showed that Regnase-1 is essential for preventing aberrant effector CD4+ T cell generation cell autonomously. Moreover, in T cells, Regnase-1 regulates the mRNAs of a set of genes, including c-Rel, Ox40, and Il2,

through cleavage of their 3′ UTRs. Interestingly, T cell receptor (TCR) stimulation leads to cleavage of Regnase-1 at R111 by Malt1/paracaspase, freeing T cells from Regnase-1-mediated suppression. Furthermore, Malt1 protease activity is critical for controlling the mRNA stability of T cell effector genes. Collectively, these results indicate that dynamic control of Regnase-1 expression in T cells is critical for controlling T cell activation.

***[10] Immune regulation and mRNA stabilizing by Arid5a**

*21. Masuda, Kazuya; Ripley, Barry; Nishimura, Riko; Mino, Takashi; Takeuchi, Osamu; Shioi, Go; Kiyonari, Hiroshi; Kishimoto, Tadamitsu. Arid5a controls IL-6 mRNA stability, which contributes to elevation of IL-6 level in vivo. Proceedings of National Academy of Sciences USA 110:9409-9414, 2013.

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. Kishimoto's group 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 TH17 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.

***[11] Autoimmune diseases and Th17 cells**

*22. Hashimoto, Motomu; Teradaira, Shin; Akizuki, Shuji; Prieto-Martin, Paz; Sakaguchi, Noriko; Koehl, Joerg; Heyman, Birgitta; Takahashi, Minoru; Fujita, Teizo; Mimori, Tsuneyo; Sakaguchi, Shimon. Complement drives Th17 cell differentiation and triggers autoimmune arthritis. Journal of Experimental Medicine 207:1135-1143, 2010.

Sakaguchi's group showed that granulocyte/macrophage colony-stimulating factor (GM-CSF) secreted by activated T cells enhanced in vitro IL-6 production by C5a-stimulated macrophages. In vivo, C5a receptor (C5aR) deficiency in SKG mice inhibited the differentiation/expansion of Th17 cells after mannan or beta-glucan treatment, and consequently suppressed the development of arthritis. Transfer of SKG T cells induced Th17 cell differentiation/expansion and produced arthritis in C5aR-sufficient recombination activating gene (RAG)-/- mice but not in C5aR-deficient RAG-/- recipients. In vivo macrophage depletion also inhibited disease development in SKG mice. Collectively, the data suggest that complement activation by exogenous or endogenous stimulation can initiate Th17 cell differentiation and expansion in certain autoimmune diseases and presumably in microbial infections. Blockade of C5aR may thus be beneficial for controlling Th17-mediated inflammation and autoimmune disease.

*23. Nakahama, Taisuke; Kimura, Akihiro; Nam Trung Nguyen; Chinen, Ichino; Hanieh, Hamza; Nohara, Keiko; Fujii-Kuriyama, Yoshiaki; Kishimoto, Tadamitsu. Aryl hydrocarbon receptor deficiency in T cells suppresses the development of collagen-induced arthritis. Proceedings of National Academy of Sciences USA 108:14222-14227, 2011.

The contributions of aryl hydrocarbon receptor (Ahr) to the pathogenesis of rheumatoid arthritis have not been elucidated. Kishimoto's group showed that Ahr deficiency ameliorated collagen-induced arthritis, a mouse model of RA. Collagen-immunized Ahr KO mice showed decreased serum levels of

such proinflammatory cytokines as IL-1β and IL-6. The Th17 and Th1 cell populations in lymph nodes from these mice decreased and increased, respectively, whereas the percentage of regulatory T cells was unchanged. Interestingly, a lack of Ahr specifically in T cells significantly suppressed collagen-induced arthritis development, whereas Ahr deficiency in macrophages had no effect. These finding indicate that the development of experimental autoimmune arthritis depends on the presence of Ahr in T cells, and that Th1/Th17 balance may be particularly important for this process.

***[12] Autoimmune diseases and IL-6 amplifier**

*24. Ogura, Hideki; Murakami, Masaaki; Okuyama, Yuko; Tsuruoka, Mineko; Kitabayashi, Chika; Iwakura, Yoichiro; Hirano, Toshio. Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via Interleukin-6 induction. Immunity 29:628-636, 2008.

Dysregulated cytokine expression and signaling are major contributors to a number of autoimmune diseases. Interleukin-17A (IL-17A) and IL-6 are important in many disorders characterized by immune self-recognition, and IL-6 is known to induce the differentiation of T helper 17 (Th17) cells. Hirano and Murakamis's group described an IL-17A-triggered positive-feedback loop of IL-6 signaling, which involved the activation of the transcription factors nuclear factor (NF)-kappaB and signal transducer and activator of transcription 3 (STAT3) in fibroblasts. Importantly, enhancement of this loop caused by disruption of suppressor of cytokine signaling 3 (SOCS3)-dependent negative regulation of the IL-6 signal transducer gp130 contributed to the development of arthritis. Because this mechanism also enhanced experimental autoimmune encephalomyelitis (EAE) in wild-type mice, it may be a general etiologic process underlying other Th17 cell-mediated autoimmune diseases.

*25. Murakami, Masaaki; Okuyama, Yuko; Ogura, Hideki; Asano, Shogo; Arima, Yasunobu; Sawa, Yukihisa; Iwakura, Yoichiro; Takatsu, Kiyoshi; Kamimura, Daisuke; Hirano, Toshio. Local microbleeding facilitates IL-6- and IL-17-dependent arthritis in the absence of tissue antigen recognition by activated T cells. Journal of Experimental Medicine 208:103-114, 2011.

Hirano and Murakami's group showed that in the model with F759 mice, transfer of in vitro polarized Th17 cells combined with the induction of experimental microbleeding resulted in CCL20 production, the accumulation of T cells in the joints, and local production of IL-6. Disease induction required IL-17A production by transferred T cells, IL-6 and CCL20 expression, and STAT3 signaling in type I collagen-expressing cells. Their data suggest a model in which the development of autoimmune disease in F759 mice depends on four events: CD4(+) T cell activation regardless of antigen specificity, local events that induce T cell accumulation, enhanced sensitivity to T cell-derived cytokines in the tissue, and activation of IL-6 signaling in the tissue. This model provides a possible explanation for why tissue-specific antigens recognized by activated CD4(+) T cells have not been identified in many autoimmune diseases, especially those associated with class II MHC molecules.

***[13] New findings about regulatory T cells**

26. Wing, Kajsa; Prieto-Martin, Paz; Yamaguchi, Tomoyuki; Miyara, Makoto; Fehervari, Zoltan; Nomura, Takashi; Sakaguchi, Shimon. CTLA-4 control over Foxp3(+) regulatory T cell function. Science 322:271-275, 2008.

Naturally occurring Foxp3+CD4+ regulatory T cells (Tregs) are essential for maintaining immunological self-tolerance and immune homeostasis. Sakaguchi's group showed that a specific deficiency of cytotoxic T lymphocyte antigen 4 (CTLA-4) in Tregs results in spontaneous development

of systemic lymphoproliferation, fatal T cell-mediated autoimmune disease, and hyperproduction of immunoglobulin E in mice, and it also produces potent tumor immunity. Treg-specific CTLA-4 deficiency impairs in vivo and in vitro suppressive function of Tregs-in particular, Treg-mediated down-regulation of CD80 and CD86 expression on dendritic cells. Thus, natural Tregs may critically require CTLA-4 to suppress immune responses by affecting the potency of antigen-presenting cells to activate other T cells.

*27. Ohkura, Naganari; Hamaguchi, Masahide; Morikawa, Hiromasa; Tanaka, Atsushi; Nakai, Kenta; Sakaguchi, Shimon. T cell receptor stimulation-snduced epigenetic changes and Foxp3 expression are independent and complementary events required for Treg cell development. Immunity 37:785-799, 2012.

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. Sakaguchi's group showed that Treg cell development was 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. The Treg cell-type CpG hypomethylation began in the thymus and continued to proceed in the periphery and could be fully established without Foxp3. The hypomethylation was required for Foxp3(+) T cells to acquire Treg cell-type gene expression, lineage stability, and full suppressive activity. Thus, those T cells in which the two events have concurrently occurred are developmentally set into the Treg cell lineage. This model explains how Treg cell fate and plasticity is controlled and can be exploited to generate functionally stable Treg cells.

***[14] New findings about semaphorins**

*28. Takamatsu, Hyota; Takegahara, Noriko; Friedel, Roland H.; Rayburn, Helen; Tessier-Lavigne, Marc; Okuno, Tatsusada; Mizui, Masayuki; Kang, Sujin; Nojima, Satoshi; Toyofuku, Toshihiko; Kikutani, Hitoshi; Kumanogoh, Atsushi. Semaphorins guide the entry of dendritic cells into the lymphatics by activating myosin II. Nature Immunology 11:594-600, 2010.

The recirculation of leukocytes is essential for proper immune responses. However, the molecular mechanisms that regulate the entry of leukocytes into the lymphatics remain unclear. Kumanogoh's group shows that plexin-A1, a principal receptor component for class III and class VI semaphorins, was crucially involved in the entry of dendritic cells (DCs) into the lymphatics. Additionally, they show that the semaphorin Sema3A, but not Sema6C or Sema6D, was required for DC transmigration and that Sema3A produced by the lymphatics promoted actomyosin contraction at the trailing edge of migrating DCs. Their findings not only demonstrate that semaphorin signals are involved in DC trafficking but also identify a previously unknown mechanism that induces actomyosin contraction as these cells pass through narrow gaps.

*29. Hayashi, Mikihito; Nakashima, Tomoki; Taniguchi, Masahiko; Kodama, Tatsuhiko; Kumanogoh, Atsushi; Takayanagi, Hiroshi. Osteoprotection by semaphorin 3A. Nature 485:69-74, 2012.

Kumanogoh's group shows 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-kB ligand (RANKL)-induced osteoclast differentiation by inhibiting the immunoreceptor tyrosine-based activation motif (ITAM) and RhoA signalling pathways. In addition, Sema3A and Nrp1 binding stimulated

osteoblast and inhibited adipocyte differentiation through the canonical Wnt/b-catenin signalling pathway. The osteopenic phenotype in Sema3a2/2mice was recapitulated by mice in which the Sema3A-binding site of Nrp1 had been genetically disrupted. Intravenous Sema3A administration in mice increased bone volume and expedited bone regeneration. Thus, Sema3A is a promising new therapeutic agent in bone and joint diseases.

*30. Nojima, Satoshi; Toyofuku, Toshihiko; Okuno, Tatsusada; Takamatsu, Hyota; Ito, Daisuke; Kang, Sujin; Ikawa, Masahito; Takahashi, Masayo; Kumanogoh, Atsushi. A point mutation in Semaphorin 4A associates with defective endosomal sorting and causes retinal degeneration. Nature Communications 4:-1406, 2013.

Semaphorin 4A (Sema4A) has an essential role in photoreceptor survival. In humans, mutations in Sema4A are thought to contribute to retinal degenerative diseases. Kumanogoh's group generate a series of knock-in mouse lines with corresponding mutations (D345H, F350C or R713Q) in the Sema4A gene and find that Sema4AF350C 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. Additionally, protein structural modelling reveals that the side chain of the 350th amino acid is critical to retain the proper protein conformation. Furthermore, Sema4A gene transfer successfully prevents photoreceptor degeneration in Sema4AF350C/F350C and Sema4A−/− mice. Thus, our 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.

***[15] Discovery of a gateway of immune cells to nerve system**

*31. Arima, Yasunobu; Harada, Masaya; Kamimura, Daisuke; Park, Jin-Haeng; Iwakura, Yoichiro; Marquez, Gabriel; Blackwell, Timothy S.; Hirano, Toshio; Murakami, Masaaki. Regional Neural Activation Defines a Gateway for Autoreactive T Cells to Cross the Blood-Brain Barrier. Cell 148:447-457, 2012.

Although it is believed that neural activation can affect immune responses, very little is known about the neuroimmune interactions involved, especially the regulators of immune traffic across the blood-brain barrier which occurs in neuroimmune diseases such as multiple sclerosis (MS). Using a mouse model of MS, experimental autoimmune encephalomyelitis, Hirano & Murakami's group shows that autoreactive T cells access the central nervous system via the fifth lumbar spinal cord. This location is defined by IL-6 amplifier-dependent upregulation of the chemokine CCL20 in associated dorsal blood vessels, which in turn depends on gravity-induced activation of sensory neurons by the soleus muscle in the leg. Impairing soleus muscle contraction by tail suspension is sufficient to reduce localized chemokine expression and block entry of pathogenic T cells at the fifth lumbar cord, suggesting that regional neuroimmune interactions may offer therapeutic targets for a variety of neurological diseases.

[16] T cell activation and its visualization

32. Yokosuka, Tadashi; Kobayashi, Wakana; Sakata-Sogawa, Kumiko; Takamatsu, Masako; Hashimoto-Tane, Akiko; Dustin, Michael L.; Tokunaga, Makio; Saito, Takashi. Spatiotemporal regulation of T cell costimulation by TCR-CD28 microclusters and protein kinase C theta translocation. Immunity 29:589-601, 2008.

T cell activation is mediated by microclusters (MCs) containing T cell receptors (TCRs), kinases,

and adaptors. Although TCR MCs translocate to form a central supramolecular activation cluster (cSMAC) of the immunological synapse at the interface of a T cell and an antigen-presenting cell, the role of MC translocation in T cell signaling remains unclear. Saito's group found that the accumulation of MCs at cSMAC was important for T cell costimulation. Costimulatory receptor CD28 was initially recruited coordinately with TCR to MCs, and its signals were mediated through the assembly with the kinase PKCθ. The accumulation of MCs at the cSMAC was accompanied by the segregation of CD28 from the TCR, which resulted in the translocation of both CD28 and PKCθ to a spatially unique subregion of cSMAC. Thus, costimulation is mediated by the generation of a unique costimulatory compartment in the cSMAC via the dynamic regulation of MC translocation.

33. Yokosuka, Tadashi; Kobayashi, Wakana; Takamatsu, Masako; Sakata-Sogawa, Kumiko; Zeng, Hu; Hashimoto-Tane, Akiko; Yagita, Hideo; Tokunaga, Makio; Saito, Takashi. Spatiotemporal basis of CTLA-4 costimulatory molecule-mediated negative regulation of T cell activation. Immunity 33:326-339, 2010.

T cell activation is positively and negatively regulated by a pair of costimulatory receptors, CD28 and CTLA-4, respectively. Because these receptors share common ligands, CD80 and CD86, the expression and behavior of CTLA-4 is critical for T cell costimulation regulation. Saito's group demonstrate the dynamic behavior of CTLA-4 in its real-time competition with CD28 at the central-supramolecular activation cluster (cSMAC), resulting in the dislocalization of protein kinase C-θ and CARMA1 scaffolding protein. CTLA-4 translocation to the T cell receptor microclusters and the cSMAC is tightly regulated by its ectodomain size, and its accumulation at the cSMAC is required for its inhibitory function. The CTLA-4-mediated suppression was demonstrated by the in vitro anergy induction in regulatory T cells constitutively expressing CTLA-4. These results show the dynamic mechanism of CTLA-4-mediated T cell suppression at the cSMAC.

***[17] Factor of memory B cells toward plasma cell differentiation**

*34. Kometani, Kohei; Nakagawa, Rinako; Shinnakasu, Ryo; Kaji, Tomohiro; Rybouchkin, Andrei; Moriyama, Saya; Furukawa, Koji; Koseki, Haruhiko; Takemori, Toshitada; Kurosaki, Tomohiro. Repression of the transcription factor Bach2 contributes to predisposition of IgG1 memory B cells toward plasma cell differentiation. Immunity 39:136-147, 2013.

Memory B cells are essential for generating rapid and robust secondary antibody responses. It has been thought that the unique cytoplasmic domain of IgG causes the prompt activation of antigen-experienced IgG memory B cells. To assess this model, Kurosaki's group have generated a mouse containing IgG1 B cells that have never encountered antigen. They found that, upon challenge, antigen-experienced IgG1 memory B cells rapidly differentiated into plasma cells, whereas nonexperienced IgG1 B cells did not, suggesting the importance of the stimulation history. In addition, Their results suggest that repression of the Bach2 transcription factor, which results from antigen experience, contributes to predisposition of IgG1 memory B cells to differentiate into plasma cells.

***[18] Calcium sensors controlling B cell regulatory function in multiple sclerosis**

*35. Matsumoto, Masanori; Fujii, Yoko; Baba, Akemi; Hikida, Masaki; Kurosaki, Tomohiro; Baba, Yoshihiro. The calcium sensors STIM1 and STIM2 control B cell regulatory function through Interleukin-10 production. Immunity 34:703-714, 2011.

A chief Ca2+ entry pathway in immune cells is store-operated Ca2+ (SOC) influx, which is

triggered by depletion of Ca2+ from the endoplasmic reticulum (ER). However, its physiological role in B cells remains elusive. Kurosaki's group showed that ER calcium sensors STIM1- and STIM2-induced SOC influx is critical for B cell regulatory function. B cell-specific deletion of STIM1 and STIM2 in mice caused a profound defect in B cell receptor (BCR)-induced SOC influx and proliferation. However, B cell development and antibody responses were unaffected. Remarkably, B cells lacking both STIM proteins failed to produce the anti-inflammatory cytokine IL-10 because of defective activation of nuclear factor of activated T cells (NFAT) after BCR stimulation. This resulted in exacerbation of experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis. Their data establish STIM-dependent SOC influx as a key signal for B cell regulatory function required to limit autoimmunity.

***[19] Detailed analysis for the protein functions in cell biology**

*36. Maeda, Yusuke; Ide, Toru; Koike, Masato; Uchiyama, Yasuo; Kinoshita, Taroh. GPHR is a novel anion channel critical for acidification and functions of the Golgi apparatus. Nature Cell Biology 10:1135-1145, 2008.

The organelles within secretory and endocytotic pathways in mammalian cells have acidified lumens, and regulation of their acidic pH is critical for the trafficking, processing and glycosylation of cargo proteins and lipids, as well as the morphological integrity of the organelles. How organelle lumen pH is regulated has been largely unknown. Kinoshita's group describes a novel molecule involved in Golgi acidification. First, mutant cells defective in Golgi acidification were established that exhibited delayed protein transport, impaired glycosylation and Golgi disorganization. Using expression cloning, a novel Golgi-resident multi-transmembrane protein, named Golgi pH regulator (GPHR), was identified as being responsible for the mutant cells. After reconstitution in planar lipid bilayers, GPHR exhibited a voltage-dependent anion-channel activity that may function in counterion conductance. Thus, GPHR modulates Golgi functions through regulation of acidification.

*37. Fujita, Morihisa; Maeda, Yusuke; Ra, Moonjin; Yamaguchi, Yoshiki; Taguchi, Ryo; Kinoshita, Taroh. GPI Glycan Remodeling by PGAP5 Regulates Transport of GPI-Anchored Proteins from the ER to the Golgi. Cell 139:352-365, 2009.

Many eukaryotic proteins are attached to the cell surface via glycosylphosphatidylinositol (GPI) anchors. How GPI-anchored proteins (GPI-APs) are trafficked from the endoplasmic reticulum (ER) to the cell surface is poorly understood, but the GPI moiety has been postulated to function as a signal for sorting and transport. Kinoshita's group established mutant cells that were selectively defective in transport of GPI-APs from the ER to the Golgi. They identified a responsible gene, designated PGAP5 (post-GPI-attachment to proteins 5). PGAP5 belongs to a dimetal-containing phosphoesterase family and catalyzed the remodeling of the glycan moiety on GPI-APs. PGAP5 catalytic activity is a prerequisite for the efficient exit of GPI-APs from the ER. Their data demonstrate that GPI glycan acts as an ER-exit signal and suggest that glycan remodeling mediated by PGAP5 regulates GPI-AP transport in the early secretory pathway.

***[20] Regulation of osteoclast**

38. Ishii, Masaru; Egen, Jackson G.; Klauschen, Frederick; Meier-Schellersheim, Martin; Saeki, Yukihiko; Vacher, Jean; Proia, Richard L.; Germain, Ronald N. Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. Nature 458:524-528, 2009.

Masaru Ishii's group reported sphingosine-1-phosphate (S1P), a lipid mediator enriched in blood,

induces chemotaxis and regulates the migration of osteoclast precursors not only in culture but also in vivo, contributing to the dynamic control of bone mineral homeostasis. Cells with the properties of osteoclast precursors express functional S1P(1) receptors and exhibit positive chemotaxis along an S1P gradient in vitro. Intravital two-photon imaging of bone tissues showed that a potent S1P(1) agonist, SEW2871, stimulated motility of osteoclast precursor-containing monocytoid populations in vivo. Osteoclast/monocyte (CD11b) lineage-specific conditional S1P(1) knockout mice showed osteoporotic changes due to increased osteoclast attachment to the bone surface. Their data showed that S1P controls the migratory behavior of osteoclast precursors, dynamically regulating bone homeostasis, and identifies a critical control point in osteoclastogenesis having potential as a therapeutic target.

*39. Kikuta, Junichi; Kawamura, Shunsuke; Okiji, Fumie; Shirazaki, Mai; Sakai, Sadaoki; Saito, Hitoshi; Ishii, Masaru. Sphingosine-1-phosphate-mediated osteoclast precursor monocyte migration is a critical point of control in antibone-resorptive action of active vitamin D. Proceedings of National Academy of Sciences USA 110:7009-7013, 2013.

Masaru Ishii's group showed that calcitriol, the hormonally active form of vitamin D, and its therapeutically used analog, eldecalcitol, inhibit bone resorption by modulating this mechanism. Vitamin D analogs have been used clinically for treating osteoporosis, although its pharmacologic action remains to be fully elucidated. They found active vitamin D reduced the expression of S1PR2, a chemorepulsive receptor for blood S1P, on circulating osteoclast precursor monocytes both in vitro and in vivo. Calcitriol- or eldecalcitol-treated monocytoid RAW264.7 cells, which display osteoclast precursor-like properties, migrated readily to S1P. Concordantly, the mobility of circulating CX3CR1(+) osteoclast precursor monocytes was significantly increased on systemic administration of active vitamin D. The results show a mechanism for active vitamin D in controlling the migratory behavior of circulating osteoclast precursors, and this action should be conducive to limiting osteoclastic bone resorption in vivo.

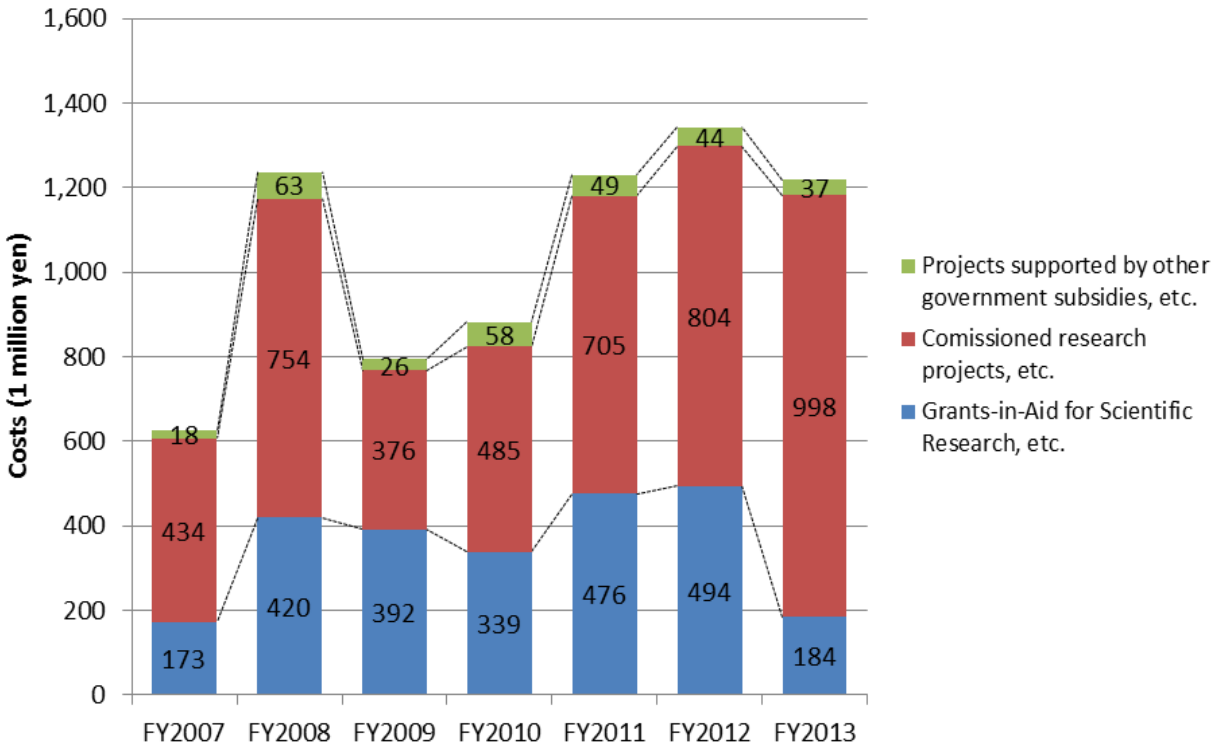
*40. Maruyama, Kenta; Fukasaka, Masahiro; Vandenbon, Alexis; Saitoh, Tatsuya; Kawasaki, Takumi; Kondo, Takeshi; Standley, Daron; Takeuchi, Osamu; Akira, Shizuo. The transcription factor Jdp2 controls bone homeostasis and antibacterial immunity by regulating osteoclast and neutrophil differentiation. Immunity 37:1024-1036, 2012.

Jdp2 is an AP-1 family transcription factor that regulates the epigenetic status of histones. Previous in vitro studies revealed that Jdp2 is involved in osteoclastogenesis. However, the roles of Jdp2 in vivo and its pleiotropic functions are largely unknown. Akira's group generated Jdp2(-/-) mice and discovered its crucial roles not only in bone metabolism but also in differentiation of neutrophils. Jdp2(-/-) mice exhibited osteopetrosis resulting from impaired osteoclastogenesis. Jdp2(-/-) neutrophils were morphologically normal but had impaired surface expression of Ly6G, bactericidal function, and apoptosis. They also found that ATF3 was an inhibitor of neutrophil differentiation and that Jdp2 directly suppresses its expression via inhibition of histone acetylation. Strikingly, Jdp2(-/-) mice were highly susceptible to Staphylococcus aureus and Candida albicans infection. Thus, Jdp2 plays pivotal roles in in vivo bone homeostasis and host defense by regulating osteoclast and neutrophil differentiation.

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

*Make a graph of the annual transition in non-WPI project funding (grants).

*Describe external funding warranting special mention.



[External funding warranting special mention]

Grantor	Program	Grantee	Amount (million JPY)	Term
Cabinet Office	Funding Program for World-Leading Innovative R&D on Science and Technology	Akira	2,520	2009-2013
JSPS	Grant-in-Aid for Specially Promoted Research	Akira	873	2008-2012
		Sakaguchi	460	2008-2012
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kikuchi	219	2013-2014
		Saitoh	218	2012-2016
		Hatazawa	157	2012-2016

		Kurosaki	210	2009-2013
		Kikutani	210	2008-2012
		Saitoh	108	2007-2011
		Kikuchi	106	2008-2012
		Takeda	115	2007-2011
JST	Strategic Basic Research Programs (CREST)	Arase	230	2009-2014
		Kurosaki	160	2009-2014
		Sakaguchi	370	2012-2016
		Takeda	341	2010-2016
		Ishii M.	240	2011-2015
		Ishii K.	112	2008-2013
		Kumanogoh	246	2012-2017
MEXT	Grants-in-Aid for Scientific Research, Specific Area Research	Saitoh	126	2007-2011
		Takeda	110	2007-2011
MEXT	Platform for Drug Discovery, Informatics, and Structural Life Science	Standley	98	2012-2016
MEXT	Project for Development of Innovative Research on Cancer Therapeutics	Ishii M.	44	2011-2015
MEXT	Regional Innovation Cluster Program	Ishii K.	123	2007-2011
MEXT	Targeted Proteins Research Program	Ishii K.	88	2007-2011
MHLW	Grants-in-Aid for Scientific Research	Ishii K.	888	2012-2016
		Standley	46	2012-2016
		Ishii K.	50	2010-2012
NEDO	Translational Research Promotion Project	Ishii K.	63	2009-2011
Cabinet Office	Funding Program for Next Generation World-Leading Researchers (NEXT)	Kumanogoh	166	2010-2012
JST	Strategic Basic Research	Hanayama	52	2012-2014

	Programs (PRESTO)	Suzuki	52	2011-2013
		Smith	52	2009-2012
HFSP	Carrier Development Award	Hanayama	30	2011-2014
HFSP	Carrier Development Award	Ishii M.	27	2009-2011
HFSP	Program Grant (Young Investigator's Grant)	Ishii M.	36	2011-2013
Private	Takeda Pharmaceutical Co., Ltd.	Murakami	60	2011-2016
Private	Takeda Science Foundation	Ishii M.	30	2013
Private	Bill & Melinda Gates Foundation	Coban	11	2008-2009
Private	Shionogi Co., Ltd.	Ishii K.	12	2010-2011
Private	Daiichi Sankyo Healthcare Co.,Ltd.	Ishii K.	80	2011-2014
Overseas	National Institute of Health (USA)	Akira	215	2012-2017

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

3-1. Major Awards

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

1. Toshio Yanagida, Persons of Cultural Merit, Japan (2013).
2. Yuki Mori, Masaaki Murakami, Yasunobu Arima, Dasong Zhu, Yoshichika Yoshioka, Bayer International Publication Award (2013).
3. Shimon Sakaguchi, Foreign Associate of the National Academy of Sciences USA (2012).
4. Tadamitsu Kishimoto, The Royal Decoration from Thai Kingdom (2012).
5. Toshio Yanagida, Fellow of the US Biophysical Society (2011).
6. Shimon Sakaguchi, Asahi prize (2011).
7. Shimon Sakaguchi, Japan Academy Award (2011).
8. Shizuo Akira, Jules Hoffmann, The Keio Medical Science Prize (2010).
9. Shizuo Akira, Jules Hoffmann, The Canada Gairdner International Award (2010).
10. Tadamitsu Kishimoto, Clinical Immunology Society President's Award (2010).
11. Tadamitsu Kishimoto, Toshio Hirano, The Japan Prize (2010).
12. Toshio Yanagida, US Genomics Award for Outstanding Investigator in the Field of Single Molecule Biology (2010).
13. Shizuo Akira, Persons of Cultural Merit, Japan (2009).
14. Shizuo Akira, Foreign Associate of the National Academy of Sciences USA (2009).

15. Tadamitsu Kishimoto, Toshio Hirano, Charles Dinarello, The Crafoord Prize in Polyarthritis (2009).
16. Shimon Sakaguchi, Fred Gage, The Keio Medical Science Prize (2008).

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

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

1. Ken Ishii, Understanding vaccine developments and opportunities in Japan, The World Vaccine Congress & Expo, Mar. 24, 2014.
2. Tomohiro Kurosaki, Calcium signaling in B lymphocytes, Keystone Symposia: Biology of B Cell Reponses, Feb. 11, 2014.
3. Masaru Ishii, S1P-mediated control of bone cell dynamics visualized by intra-vital microscopy, Gordon Research Conferences, Jan. 12, 2014.
4. Hisashi Arase, Misfolded proteins complexed with MHC class II molecules are targeted by autoantibodies, Germany-Japan Immunology Seminar, Dec. 5, 2013.
5. Atsushi Kumanogoh, Immune regulation by semaphorins and their receptors, EMBO Workshop, Oct. 31, 2013.
6. Tadamitsu, Kishimoto, IL-6: A new era comes for the treatment of inflammatory autoimmune diseases, 15th International Congress of Immunology, Aug. 22, 2013.
7. Shimon Sakaguchi, Plenary lecture: Control of immune responses by regulatory T cells, 15th International Congress of Immunology, Aug. 22, 2013.
8. Taroh Kinoshita, Remodeling and function of GPI anchors in protein sorting, trafficking, and dynamics, FASEB SRC-Protein Lipidation, Signaling, and Membrane Domains, July 15, 2013.
9. Jun Hatazawa, Molecular Stroke: another insight on evolving brain infarct based on astrocytic energy metabolism, BRAIN & Brain PET 2013, May 20, 2013.
10. Kiyoshi Takeda, Regulation of gut homeostasis by innate immunity, Immunology 2013, May 3, 2013.
11. Shizuo Akira, The role of mRNA stability in the immune response, Harvard Medical School Committee on Immunology Seminar, Apr. 17, 2013.
12. Shimon Sakaguchi, Regulatory T cells for immune tolerance and homeostasis, Karolinska Research Lectures at Nobel Forum, Apr. 4, 2013.
13. Toshio Yanagida, Single molecules in vitro and vivo, Gordon Research Conferences -Single Molecule Approaches to Biology, Jul. 18, 2012.
14. Cevayir Coban, Innate immunity and malaria parasites, Molecular Immunology & Immunogenetics Congress, Apr. 28, 2012.
15. Shizuo Akira, The Awardee Lecture for the Canada Gairdner International Award, Oct. 27, 2011.
16. Tadamitsu Kishimoto, Memorial Lecture for the Gairdner Symposium, Oct. 28, 2011.
17. Shizuo Akira, Innate Immune Responses: Pathogen Recognition and Signaling, The Nobel Forum 2010, Nov. 23, 2010.
18. Shizuo Akira, Innate Immunity and vaccines, The Royal Society in London, UK, Nov. 15, 2010.
19. Tadamitsu Kishimoto and Toshio Hirano, The commemorative lectures for the Crafoord Prize in Polyarthritis, May 11, 2009.
20. Shizuo Akira, Pathogen recognition and signaling in innate immunity, Dyer lecture at National Institute of Health, USA, May 7, 2008.

4. List of Achievements of Center's outreach activities

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

Activities	FY2011 (number of activities, times held)	FY2012 (number of activities, times held)	FY2013 (number of activities, times held)
PR brochure, pamphlet	4	4	4
Lectures, seminars for general public	2	3	17
Teaching, experiments, training for elementary and secondary school students	4	2	0
Science cafe	4	7	3
Open houses	3	5	2
Participating, exhibiting in events	3	4	4
Press releases	17	13	10

5. List of Media Coverage of Projects carried out between FY 2011 – 2013 (within 2 pages)

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

1) Japan

No.	Date	Type media (e.g., newspaper, magazine, television)	Description
1	Apr.1, 2013	Yomiuri Shimbun	Progress of immunity lengthens our life-span (Prof. Akira)
2	Apr.8, 2013	Yomiuri Shimbun	A great variety of roles of macrophages (Prof Akira, Prof. Kumanogoh, and Dr. Satoh)
3	Apr.9, 2013	Nikkei Shimbun Yomiuri Shimbun Asahi Shimbun	How does Vitamin D protect bones? (Prof. M. Ishii)
4	Apr.18, 2013	Asahi Shimbun	Revealing the mechanism for degradation of gout (Prof. Akira)

5	May 9, May 16 May 23, 2013	Asahi Shimbun	Special issues for Prof. Toshio Yanagida (part 1-3)
6	May 14, 2013	Nikkei Shimbun Yomiuri Shimbun	Discovering a protein involving rheumatism (Prof. Kishimoto)
7	May 24, 2013	Asahi Shimbun Nikkei Shimbun	A protein braking on runaway immunity (Prof Akira)
8	May 25, 2013	Mainichi Shimbun	Expecting for new therapy for rheumatoid arthritis (Prof. Kishimoto)
9	Jun.25, 2013	Asahi Shimbun	Osaka University established “Distinguished Professors”; New high-income position (Prof Akira & Prof. Sakaguchi)
10	Jul.9, 2013	Nikkei Shimbun	Early detection of cancer by MRI (Prof. Kikuchi)
11	Aug.15, 2013	Nikkei Shimbun	A protein giving the signal “Defend against virus!” (Prof. Akira)
12	Aug.15, 2013	Yomiuri Shimbun	Fluctuation is universal principle (Prof. Yanagida)
13	Sep.2, 2013	Yomiuri Shimbun	Immune regulation; a perfect balance (Prof. Kishimoto)
14	Oct.25, 2013	Nikkei Shimbun Mainichi Shimbun	Person for cultural merit; personal history and achievements (Prof. Yanagida)
15	Oct.26, 2013	Asahi Shimbun	15 persons for cultural merit in 2013 (Prof. Yanagida)
16	Nov.10, 2013	Yomiuri Shimbun	New treatment for leukemia (Prof. Sakaguchi)
17	Nov.25, 2013	Asahi Shimbun	A world leading immunologist (Prof. Kishimoto)
18	Nov.25, 2013	Asahi Shimbun	Microcosms in our bodies (Prof. Akira and prof. M. Ishii)
19	Dec.5, 2013	Asahi Shimbun	Immune suppression; research against headwind (Prof. Sakaguchi)
20	Dec.12, 2013	Asahi Shimbun	Someone pays attention to interesting studies (Prof. Sakaguchi)

21	Jan.10, 2014	Mainichi Shimbun	Symposium for General Audience "Future Medical Treatment Created by Immunology" (Prof Akira and Prof. Kurosaki)
22	Jan.24, 2014	Asahi Shimbun	Vaccination using antibodies (Prof. Saito)
23	Jan.25, 2014	Asahi Shimbun	Discovering “main culprit” for Rheumatoid arthritis (Prof. Arase)
24	Feb.17, 2014	Asahi Shimbun	For new cancer immunotherapy (Dr. Nishikawa)
25	Feb.25, 2014	Asahi Shimbun	Discovering “main culprit” for Rheumatoid arthritis (Prof. Arase)
26	Mar.11, 2014	Nikkei Shimbun	Identifying a contributory factor for rheumatoid arthritis (Prof. Arase)
27	Mar.13, 2014	Asahi Shimbun	Prevention of hay fever and rheumatism? (Prof. Sakaguchi)
28	Mar.18, 2014	Yomiuri Shimbun	My Osaka-logy; Get publicity for its scholarship and culture (Prof. Kishimoto)
29	Mar.25, 2014 Mar.30, 2014	Asahi Shimbun Nikkei Shimbun	Big funded project by Lotte foundation (Dr. Saitoh)

2) Overseas

No.	Date	Type media (e.g., newspaper, magazine, television)	Description
1	Feb.25, 2014	“Editors' Choice” in Science	Rheumatoid Rescue? (Prof. Arase)
2	May 14, 2013	HOT Articles in Analyst; web Journal	Early malaria diagnosis (Dr. Coban & Dr. Smith)
3	May 13, 2013	chemistry world; web Journal	Early malaria diagnosis just one day after infection (Dr. Coban & Dr. Smith)

World Premier International Research Center Initiative (WPI)

List of papers of representative of interdisciplinary research activities

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

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

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

1. Uehata, Takuya; Iwasaki, Hidenori; Vandenbon, Alexis; Kuniyoshi, Kanako; Satoh, Takashi; Mino, Takashi; Standley, Daron M.; Takeuchi, Osamu; Akira, Shizuo. Malt1-induced cleavage of Regnase-1 in CD4(+) Helper T cells regulates immune activation. Cell 153:1036-1049, 2013.

   Akira's group showed that Regnase-1 (also known as Zc3h12a) is essential for preventing aberrant effector CD4+ T cell generation cell autonomously. Moreover, in T cells, Regnase-1 regulates the mRNAs of a set of genes, including c-Rel, Ox40, and Il2, through cleavage of their 3′ UTRs. Interestingly, T cell receptor (TCR) stimulation leads to cleavage of Regnase-1 at R111 by Malt1/paracaspase, freeing T cells from Regnase-1-mediated suppression. Furthermore, Malt1 protease activity is critical for controlling the mRNA stability of T cell effector genes. Collectively, these results indicate that dynamic control of Regnase-1 expression in T cells is critical for controlling T cell activation. Standley and his bioinformatics group used University of California Santa Cruz (UCSC) annotations of transcripts for the initial mapping of tags to the transcriptome.

2. Misawa, Takuma; Takahama, Michihiro; Kozaki, Tatsuya; Lee, Hanna; Zou, Jian; Saitoh, Tatsuya; Akira, Shizuo. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. Nature Immunology 14:454-460, 2013.

   Akira's group showed that microtubules mediated assembly of the NLRP3 inflammasome. Inducers of the NLRP3 inflammasome caused aberrant mitochondrial homeostasis to diminish the concentration of the coenzyme NAD+, which in turn inactivated the NAD+-dependent α-tubulin deacetylase sirtuin 2; this resulted in the accumulation of acetylated α-tubulin. Acetylated α-tubulin mediated the dynein-dependent transport of mitochondria and subsequent apposition of ASC on mitochondria to NLRP3 on the endoplasmic reticulum. Therefore, in addition to direct activation of NLRP3, the creation of optimal sites for signal transduction by microtubules is required for activation of the entire NLRP3 inflammasome. They succeeded direct observation of microtubules that mediate the approximation of ASC on mitochondria to NLRP3 on the endoplasmic reticulum in response to inducers of the NLRP3 inflammasome using SR-SIM (Carl Zeiss).

3. Kikuta, Junichi; Kawamura, Shunsuke; Okiji, Fumie; Shirazaki, Mai; Sakai, Sadaoki; Saito, Hitoshi; Ishii, Masaru. Sphingosine-1-phosphate-mediated osteoclast precursor monocyte migration is a critical point of control in antibone-resorptive action of active vitamin D. Proceedings of National Academy of Sciences USA 110:7009-7013, 2013.

Masaru Ishii's group showed that calcitriol, the hormonally active form of vitamin D, and its therapeutically used analog, eldecalcitol, inhibit bone resorption by modulating this mechanism. They found active vitamin D reduced the expression of S1PR2, a chemorepulsive receptor for blood S1P, on circulating osteoclast precursor monocytes both in vitro and in vivo. Calcitriol- or eldecalcitol-treated monocytoid RAW264.7 cells, which display osteoclast precursor-like properties, migrated readily to S1P. Concordantly, the mobility of circulating CX3CR1(+) osteoclast precursor monocytes was significantly increased on systemic administration of active vitamin D. In vivo S1PR2-mediated control of migration of osteoclast precursor monocytes was visualized using intravital multiphoton imaging method developed by themselves.

4. Satoh, Takashi; Yamamoto, Masahiro; Takemura, Naoki; Yoshioka, Yoshichika; Takeuchi, Osamu; Akira, Shizuo. Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. Nature 495:524-528, 2013.

   Akira's group showed Trib1, an adaptor protein involved in protein degradation is critical for the differentiation of F4/80+MR+ tissue-resident macrophages (M2-like macrophages), and eosinophils but not for the differentiation of M1 myeloid cells. Trib1 deficiency causes a severe reduction of M2-like macrophages in various organs, including bone marrow, lung and adipose tissues. Mice lacking Trib1 in haematopoietic cells show diminished adipose tissue mass accompanied by evidence of increased lipolysis, even when fed a normal diet. Supplementation of M2-like macrophages rescues the pathophysiology. In response to a high-fat diet, mice lacking Trib1 in haematopoietic cells develop hypertriglyceridaemia and insulin resistance, together with increased proinflammatory cytokine gene induction. The epididymal adipose tissues from normal and Trib1(-/-) mice fed a normal diet were analyzed using MRI by Yoshioka's group.

5. Kikuta, Junichi; Wada, Yoh; Kowada, Toshiyuki; Nishiyama, Issei; Mizukami, Shin; Maiya, Nobuhiko; Yasuda, Hisataka; Kumanogoh, Atsushi; Kikuchi, Kazuya; Germain, Ronald N.; Ishii, Masaru. Dynamic visualization of RANKL and Th17-mediated osteoclast function. Journal of Clinical Investigation 123:866-873, 2013.

   Masaru Ishii's group 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. They also found that rapid application of the osteoclast-activation factor RANKL converted many N osteoclasts to R, suggesting a novel point of action in RANKL-mediated control of mature osteoclast function. Furthermore, they showed that Th17 cells, a subset of RANKL-expressing CD4+ T cells, could induce rapid N-to-R conversion of mature osteoclasts via cell-cell contact. These findings provide new insights into the activities of mature osteoclasts in situ and identify actions of RANKL-expressing Th17 cells in inflammatory bone destruction.

6. Hobro, Alison J.; Konishi, Aki; Coban, Cevayir; Smith, Nicholas I. Raman spectroscopic analysis of malaria disease progression via blood and plasma samples. Analyst 138:3927-3933, 2013.

In this study featured on the cover of the Analyst journal, Raman spectroscopy has been used to monitor the changes in erythrocytes and plasma during Plasmodium infection in mice, following malaria disease progression over the course of 7 days. The Raman spectra of both samples are dominated by the spectra of hemoglobin and hemozoin, due to their resonant enhancement. In plasma samples, due to the inherently low heme background, heme-based changes in the Raman spectra could be detected in the very early stages of infection, as little as one day after Plasmodium infection, where parasitemia levels were low, on the order of 0.2%, and typically difficult to detect by existing methods. Their results show that plasma analysis has significant potential for early, quantitative and automated detection of malaria, and to quantify heme levels in serum which modulate malarial effects on the immune system.

7. Maruyama, Kenta; Fukasaka, Masahiro; Vandenbon, Alexis; Saitoh, Tatsuya; Kawasaki, Takumi; Kondo, Takeshi; Standley, Daron; Takeuchi, Osamu; Akira, Shizuo. The transcription factor Jdp2 controls bone homeostasis and antibacterial immunity by regulating osteoclast and neutrophil differentiation. Immunity 37:1024-1036, 2012.

   Akira's group generated an AP-1 family transcription factor Jdp2(-/-) mice and discovered its crucial roles not only in bone metabolism but also in differentiation of neutrophils. Jdp2(-/-) mice exhibited osteopetrosis resulting from impaired osteoclastogenesis. Jdp2(-/-) neutrophils were morphologically normal but had impaired surface expression of Ly6G, bactericidal function, and apoptosis. They also found that ATF3 was an inhibitor of neutrophil differentiation and that Jdp2 directly suppresses its expression via inhibition of histone acetylation. Strikingly, Jdp2(-/-) mice were highly susceptible to Staphylococcus aureus and Candida albicans infection. Thus, Jdp2 plays pivotal roles in in vivo bone homeostasis and host defense by regulating osteoclast and neutrophil differentiation. ChIP-seq enrichment profiles in wild-type and Jdp2(-/-) peritoneal neutrophils were analyzed by Standley's group.

8. Ohkura, Naganari; Hamaguchi, Masahide; Morikawa, Hiromasa; Tanaka, Atsushi; Nakai, Kenta; Sakaguchi, Shimon. T cell receptor stimulation-induced epigenetic changes and Foxp3 expression are independent and complementary events required for Treg cell development. Immunity 37:785-799, 2012.

   Sakaguchi's group showed that Treg cell development was 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. The Treg cell-type CpG hypomethylation began in the thymus and continued to proceed in the periphery and could be fully established without Foxp3. The hypomethylation was required for Foxp3(+) T cells to acquire Treg cell-type gene expression, lineage stability, and full suppressive activity. Thus, those T cells in which the two events have concurrently occurred are developmentally set into the Treg cell lineage. This model explains how Treg cell fate and plasticity is controlled and can be exploited to generate functionally stable Treg cells. The calculation for DNA methylation was done by bioinformatics methods using the super computer system at the University of Tokyo.

9. Matsushita, Hisashi; Mizukami, Shin; Mori, Yuki; Sugihara, Fuminori; Shirakawa, Masashiro; Yoshioka, Yoshichika; Kikuchi, Kazuya. F-19 MRI Monitoring of Gene Expression in Living Cells through Cell-Surface beta-Lactamase Activity. Chembiochem 13:1579-1583, 2012.

   Magnetic resonance imaging provides important intravital information on deep tissues that cannot be visualized by other methods. Although Yoshioka and Kikuchi's groups had previously developed an off/on switching (19)F MRI probe to monitor reporter enzyme activity on the basis of the paramagnetic relaxation enhancement effect, it was difficult to monitor biological events in living cells because the (19)F MRI probe did not permeate living cell membrane. They have developed a new (19)F MRI system for monitoring gene expression in living cells by exploiting cell-surface-displayed β-lactamase and the specifically designed (19)F MRI probe. By using this system, cellular gene expression was successfully detected by (19)F MRI without cell fixation. This imaging strategy shows promise for monitoring in vivo gene expression, and therefore it could lead to useful technologies for the diagnosis and therapy of various diseases.

10. Saitoh, Tatsuya; Komano, Jun; Saitoh, Yasunori; Misawa, Takuma; Takahama, Michihiro; Kozaki, Tatsuya; Uehata, Takuya; Iwasaki, Hidenori; Omori, Hiroko; Akira, Shizuo. Neutrophil Extracellular Traps mediate a host defense response to Human Immunodeficiency Virus-1. Cell Host & Microbe 12:109-116, 2012.

    Akira's group showed that neutrophil extracellular traps (NETs) capture human immunodeficiency virus (HIV)-1 and promote HIV-1 elimination through myeloperoxidase and α-defensin. Neutrophils detect HIV-1 by TLR7 and TLR8, which recognize viral nucleic acids. Engagement of TLR7 and TLR8 induces the generation of reactive oxygen species that trigger NET formation, leading to NET-dependent HIV-1 elimination. However, HIV-1 counteracts this response by inducing C-type lectin CD209-dependent production of interleukin (IL)-10 by dendritic cells to inhibit NET formation. IL-10 suppresses the reactive oxygen species-dependent generation of NETs induced upon TLR7 and TLR8 engagement, resulting in disrupted NET-dependent HIV-1 elimination. The samples containing DNA and HIV-1 virions were subjected to SR-SIM (Zeiss), and NETs were directly observed.

11. Hutchins, Andrew Paul; Poulain, Stephane; Miranda-Saavedra, Diego. Genome-wide analysis of STAT3 binding in vivo predicts effectors of the anti-inflammatory response in macrophages. Blood 119:110-119, 2012.

    In macrophages, the anti-inflammatory response (AIR) is driven by STAT3 upon IL-10 signaling. Miranda-Saavedra's group described a systematic approach to identify the elusive STAT3-controlled effectors of the AIR. In vivo STAT3-binding sites were identified by ChIP-seq, coupled to expression analysis by RNA-seq, both in resting and IL-10-treated peritoneal macrophages. They report the genomic targets of STAT3 and show that STAT3's transcriptional program during the AIR is highly specific to IL-10-stimulated macrophages, that STAT3 is a positive transcriptional regulator, and they predict severalputative AIR factors that merit further investigation. This is the first in-depth study of the AIR by next-generation sequencing and provides an unprecedented degree of detail into this fundamental physiologic response.

12. Teraguchi, Shunsuke; Kumagai, Yutaro; Vandenbon, Alexis; Akira, Shizuo; Standley, Daron M.. Stochastic binary modeling of cells in continuous time as an alternative to biochemical reaction equations. Physical Review E 84:62903, 2011.

    Akira and Standley's groups have developed a coarse-grained formulation for modeling the dynamic behavior of cells quantitatively, based on stochasticity and heterogeneity, rather than on biochemical reactions. They treat each reaction as a continuous-time stochastic process, while reducing each biochemical quantity to a binary value at the level of individual cells. The system can be analytically represented by a finite set of ordinary linear differential equations, which provides a continuous time course prediction of each molecular state. They introduce the formalism and demonstrate it with several examples.

13. Iwasaki, Hidenori; Takeuchi, Osamu; Teraguchi, Shunsuke; Uehata, Takuya; Kuniyoshi, Kanako; Satoh, Takashi; Saitoh, Tatsuya; Standley, Daron M.; Akira, Shizuo. The I kappa B kinase complex regulates the stability of cytokine-encoding mRNA induced by TLR-IL-1R by controlling degradation of regnase-1. Nature Immunology 12:1167-1175, 2011.

    Akira's group showed that the inhibitor of transcription factor NF-κB (IκB) kinase (IKK) complex controlled the stability of mRNA for IL-6 by phosphorylating regnase-1 in response to stimulation via the IL-1 receptor or TLR. Phosphorylated regnase-1 underwent ubiquitination and degradation. Regnase-1 was reexpressed in IL-1R- or TLR-activated cells after a period of lower expression. Regnase-1 mRNA was negatively regulated by regnase-1 itself via a stem-loop region present in the regnase-1 3′ untranslated region. Their data demonstrate that the IKK complex phosphorylates not only IκBα, thereby activating transcription, but also regnase-1, thereby releasing a 'brake' on IL-6 mRNA expression. Mathematical model that captured the activity of regnase-1 and IL-6 mRNA based on biochemical equations was constructed by Standley's group.

14. Ishii, Masaru; Kikuta, Junichi; Shimazu, Yutaka; Meier-Schellersheim, Martin; Germain, Ronald N. Chemorepulsion by blood S1P regulates osteoclast precursor mobilization and bone remodeling in vivo. Journal of Experimental Medicine 207:2793-2798, 2010.

    Masaru Ishii's group showed that Osteoclast precursors (Ops) also express S1PR2, an S1P receptor which mediates negative chemotaxis (or chemorepulsion). OP-positive chemotaxis is prominent in gradients with low maximal concentrations of S1P, whereas such behavior is minimal in fields with high maximal S1P concentrations. This reverse-directional behavior is caused by S1PR2-mediated chemorepulsion acting to override S1PR1 upgradient motion. Inhibition of S1PR2 function by the antagonist JTE013 changed the migratory behavior of monocytoid cells, including OPs, and relieved osteoporosis in a mouse model by limiting OP localization and reducing the number of mature OCs attached to the bone surface. The reciprocal regulation of S1P-dependent chemotaxis controls bone remodeling by finely regulating OP localization. This regulatory axis may be promising as a therapeutic target in diseases affecting OC-dependent bone remodeling.

15. Satoh, Takashi; Takeuchi, Osamu; Vandenbon, Alexis; Kumagai, Yutaro; Miyake, Tohru; Saitoh, Tatsuya; Standley, Daron M.; Akira, Shizuo. The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. Nature Immunology 11:936-944, 2010.

Jumonji domain containing-3 (Jmjd3), a histone 3 Lys27 (H3K27) demethylase, has been implicated in the activation of macrophages. Akira's group showed that Jmjd3 is essential for M2 macrophage polarization in response to helminth infection and chitin, though Jmjd3 is dispensable for M1 responses. Furthermore, Jmjd3 (also known as Kdm6b) is essential for proper bone marrow macrophage differentiation, and this function depends on demethylase activity of Jmjd3. Jmjd3 deficiency affected trimethylation of H3K27 in only a limited number of genes. Among them, they identified Irf4 as encoding a key transcription factor that controls M2 macrophage polarization. Collectively, these results show that Jmjd3-mediated H3K27 demethylation is crucial for regulating M2 macrophage development leading to anti-helminth host responses. Standley's group analyzed ChIP-Seq data including genome-wide distribution of H3K27me3.

16. Yokosuka, Tadashi; Kobayashi, Wakana; Takamatsu, Masako; Sakata-Sogawa, Kumiko; Zeng, Hu; Hashimoto-Tane, Akiko; Yagita, Hideo; Tokunaga, Makio; Saito, Takashi. Spatiotemporal basis of CTLA-4 costimulatory molecule-mediated negative regulation of T cell activation. Immunity 33:326-339, 2010.

Saito's group demonstrate the dynamic behavior of CTLA-4 in its real-time competition with CD28 at the central-supramolecular activation cluster (cSMAC), resulting in the dislocalization of protein kinase C-θ and CARMA1 scaffolding protein. CTLA-4 translocation to the T cell receptor microclusters and the cSMAC is tightly regulated by its ectodomain size, and its accumulation at the cSMAC is required for its inhibitory function. The CTLA-4-mediated suppression was demonstrated by the in vitro anergy induction in regulatory T cells constitutively expressing CTLA-4. These results show the dynamic mechanism of CTLA-4-mediated T cell suppression at the cSMAC. Real-time imaging of single fluorescent molecules was achieved by total internal reflection fluorescence microscopy (TIRF) that had been developed by them.

17. Takamatsu, Hyota; Takegahara, Noriko; Friedel, Roland H.; Rayburn, Helen; Tessier-Lavigne, Marc; Okuno, Tatsusada; Mizui, Masayuki; Kang, Sujin; Nojima, Satoshi; Toyofuku, Toshihiko; Kikutani, Hitoshi; Kumanogoh, Atsushi. Semaphorins guide the entry of dendritic cells into the lymphatics by activating myosin II. Nature Immunology 11:594-600, 2010.

Kumanogoh's group shows that plexin-A1, a principal receptor component for class III and class VI semaphorins, was crucially involved in the entry of dendritic cells (DCs) into the lymphatics. Additionally, they show that the semaphorin Sema3A, but not Sema6C or Sema6D, was required for DC transmigration and that Sema3A produced by the lymphatics promoted actomyosin contraction at the trailing edge of migrating DCs. Their findings not only demonstrate that semaphorin signals are involved in DC trafficking but also identify a previously unknown mechanism that induces actomyosin contraction as these cells pass through narrow gaps. In their experiments, two-dimensional migration of bone marrow–derived DCs (BMDC) was observed in three-dimensional collagen matrices using confocal time-lapse video microscopy.

18. Yamamoto, Masahiro; Standley, Daron M.; Kayama, Hisako; Matsuda, Tadashi; Soldati-Favre, Dominique; Takeda, Kiyoshi. A single polymorphic amino acid on Toxoplasma gondii kinase ROP16 determines the direct and strain-specific activation of Stat3. Journal of Experimental Medicine

206:2747-2760, 2009.

Takeda, Yamamoto, and Standley's groups generated a highly polymorphic parasite-derived kinase ROP16-deficient type I parasites, and found a severe defect in parasite-induced Stat3 activation, culminating in enhanced production of interleukin (IL) 6 and IL-12 p40 in the infected macrophages. Furthermore, overexpression of ROP16 but not ROP18 in mammalian cells resulted in Stat3 phosphorylation and strong activation of Stat3-dependent promoters. In addition, kinase-inactive ROP16 failed to activate Stat3. ROP16 bound Stat3 and directly induced phosphorylation of this transcription factor. These results formally establish an essential and direct requirement of ROP16 in parasite-induced Stat3 activation and the significance of a single amino acid replacement in the function of type II ROP16. Structural modeling of the ROP16 kinase domain by in silico, in vitro, and in vivo was constructed by Standley's group.

19. Matsushita, Kazufumi; Takeuchi, Osamu; Standley, Daron M.; Kumagai, Yutaro; Kawagoe, Tatsukata; Miyake, Tohru; Satoh, Takashi; Nakamura, Haruki; Akira, Shizuo. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Nature 458:1185-1190, 2009.

Akira's groups showed that the TLR-inducible gene Zc3h12a-deficient mice suffered from severe anaemia, and most died within 12 weeks. Zc3h12a-/- mice also showed augmented serum immunoglobulin levels and autoantibody production, together with a greatly increased number of plasma cells, as well as infiltration of plasma cells to the lung. Macrophages from Zc3h12a-/- mice showed highly increased production of interleukin (IL)-6 and IL-12p40, in response to TLR ligands. Although the activation of TLR signaling pathways was normal, Il6 messenger RNA decay was severely impaired in Zc3h12a-/- macrophages. Zc3h12a is an essential RNase that prevents immune disorders by directly controlling the stability of inflammatory genes. The structural modeling of the Zc3h12a N-terminal domain was carried out by Standley's group.

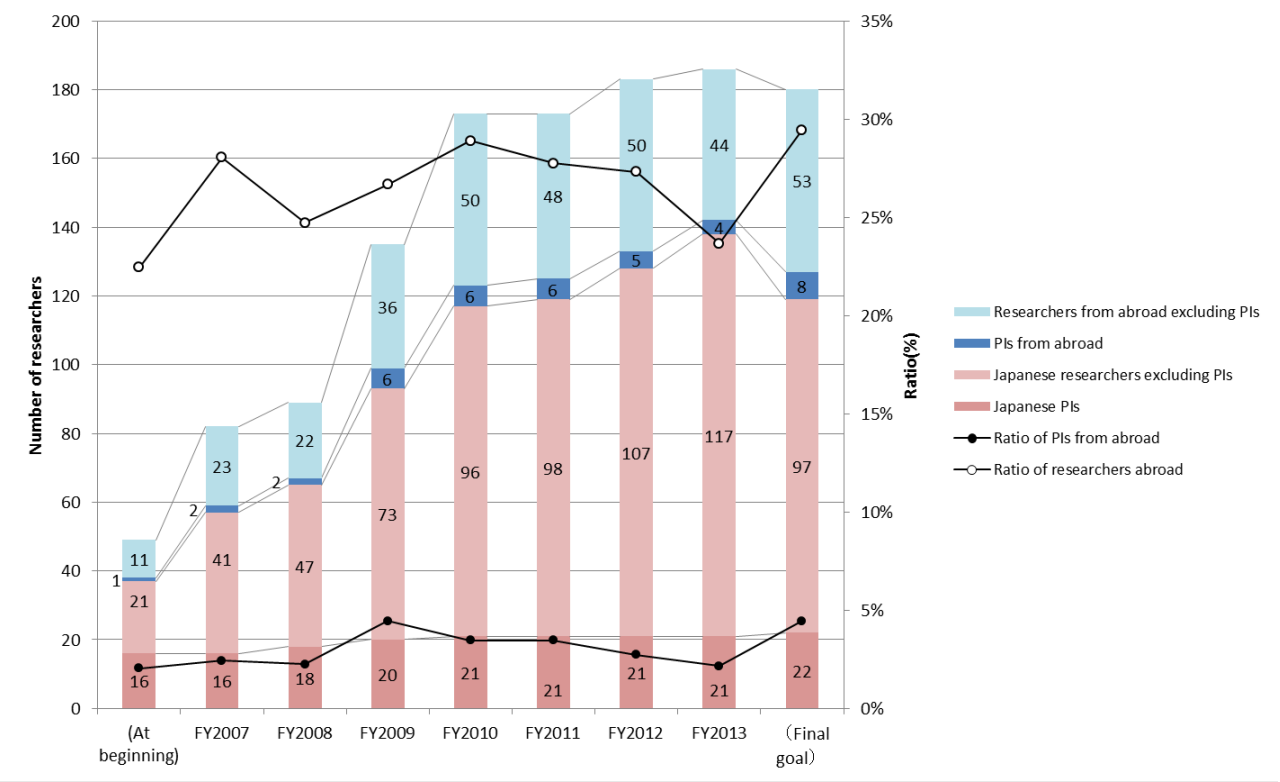
20. Ishii, Masaru; Egen, Jackson G.; Klauschen, Frederick; Meier-Schellersheim, Martin; Saeki, Yukihiko; Vacher, Jean; Proia, Richard L.; Germain, Ronald N. Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. Nature 458:524-528, 2009.

Masaru Ishii's group reported sphingosine-1-phosphate (S1P), a lipid mediator enriched in blood, induces chemotaxis and regulates the migration of osteoclast precursors not only in culture but also in vivo, contributing to the dynamic control of bone mineral homeostasis. Intravital two-photon imaging of bone tissues showed that a potent S1P(1) agonist, SEW2871, stimulated motility of osteoclast precursor-containing monocytoid populations in vivo. Osteoclast/monocyte (CD11b) lineage-specific conditional S1P(1) knockout mice showed osteoporotic changes due to increased osteoclast attachment to the bone surface. Their data showed that S1P controls the migratory behavior of osteoclast precursors, dynamically regulating bone homeostasis, and identifies a critical control point in osteoclastogenesis having potential as a therapeutic target. For their experiments, two-photon intravital bone tissue imaging had been developed by themselves.

World Premier International Research Center Initiative (WPI)

1. Number of overseas researchers and annual transition

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



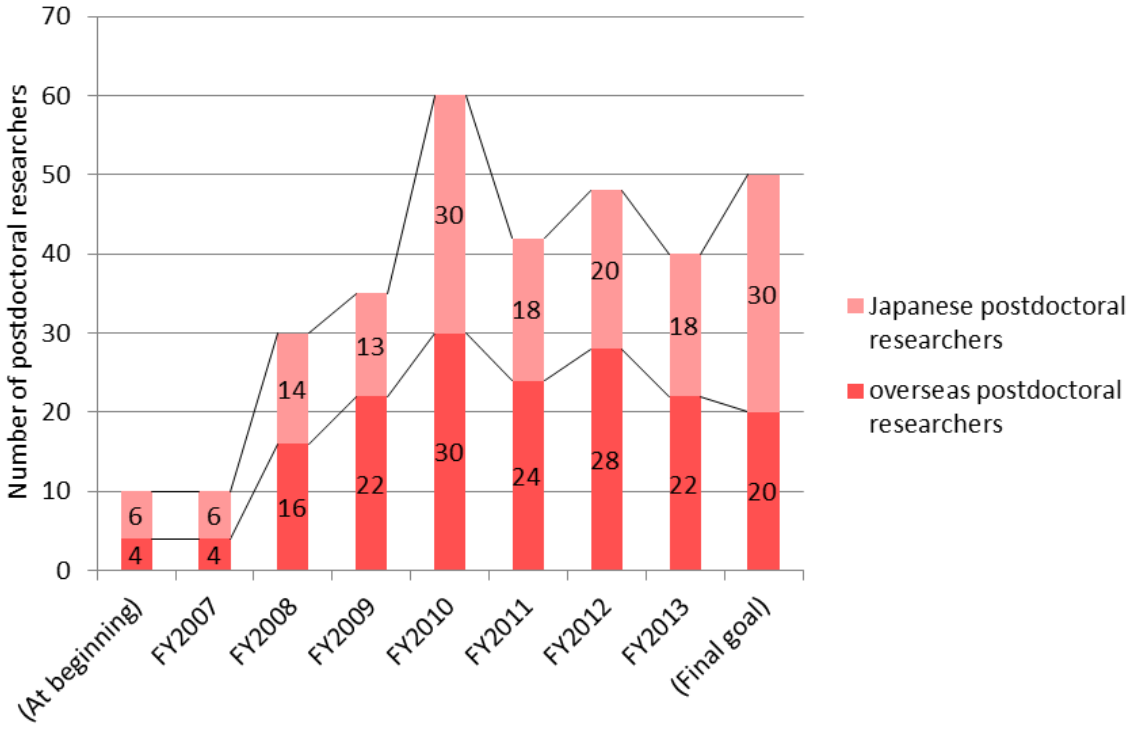
2. Postdoctoral positions through open international solicitations

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

FY	number of applications	number of selection
FY2007	29 <29, 100 %>	3 <3, 100%>
FY2008	42 <42, 100%>	0 <0, 0 %>
FY2009	61 <61, 100%>	5 <5, 100%>
FY2010	7 <7, 100%>	5 <5, 100%>
FY2011	37 <32, 86%>	9 <6, 66.7%>
FY2012	37 <24, 65%>	14 <7, 50%>
FY2013	83 <83, 100%>	3 <3, 100%>

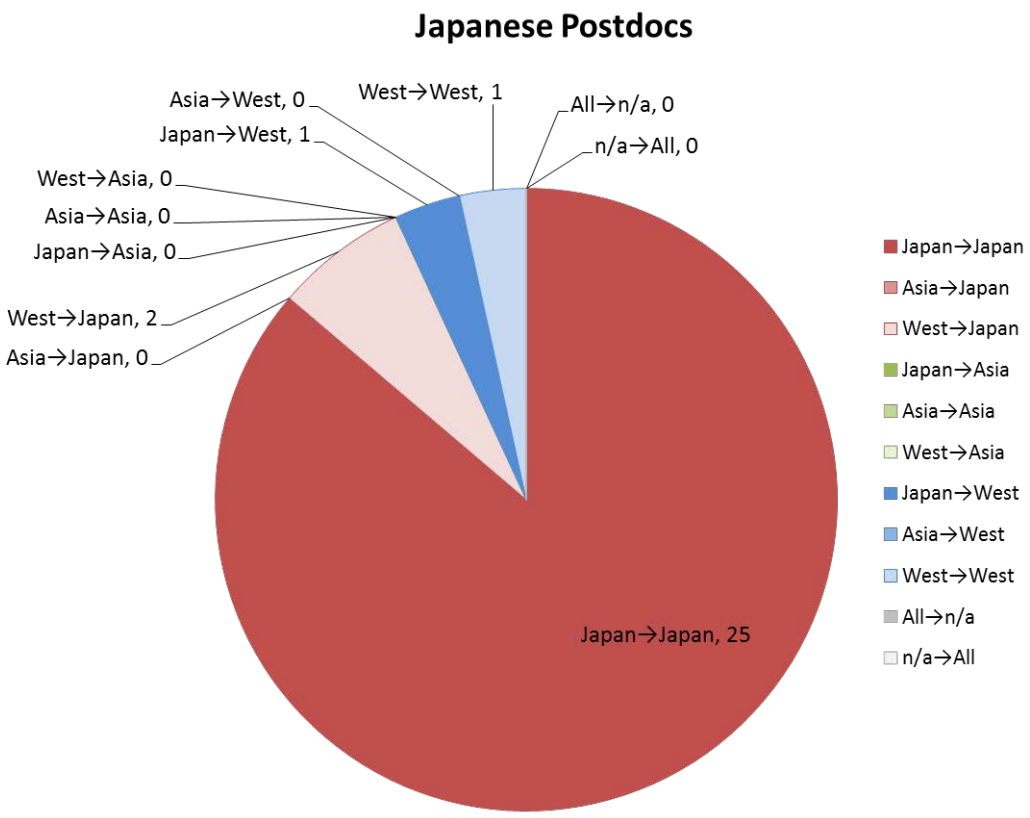
3. Number of overseas postdoctoral researchers and annual transition

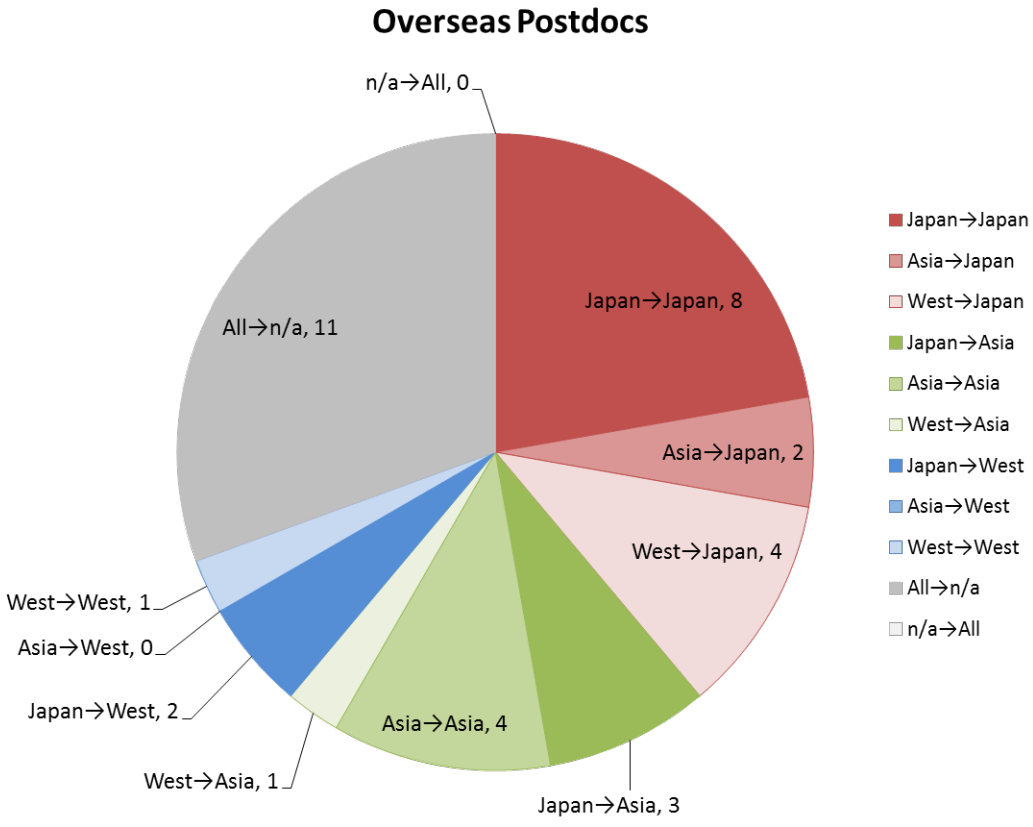
*Make a graph of the transition in the number of overseas postdoctoral researchers since the application.



4. Status of postdoc employment at institutions of postdoctoral researchers

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





5. List of the cooperative research agreements outside Japan

1. Counterpart of an Agreement: Pohang University of Science and Technology(POSTECH)
   Department of Life Science, Division of Integrative Biosciences and Biotechnology
   Name of an Agreement: Agreement on Academic Exchange between WPI Immunology Frontier Research Center, Osaka University and Department of Life Science and Division of Integrative Biosciences and Biotechnology, Pohang University of Science and Technology
   Dates of an Agreement: 11/November/2009
   Summary of an Agreement: IFReC and POSTECH concluded an academic exchange agreement to encourage joint research activities on immunology with the objective of promoting cooperation in the fields of education and academic research.

2. Counterpart of an Agreement: Indian Institute of Science Education and Research(IISER), Bhopal
   Name of an Agreement: Agreement on Academic Exchange between Indian Institute of Science Education and Research (IISER), BHOPAL and WPI Immunology Frontier Research Center, Osaka University
   Dates of an Agreement: 3/February/2010
   Summary of an Agreement: IFReC and IISER concluded an academic exchange agreement to encourage joint research activities with the objective of promoting cooperation in the fields of education and academic research.

3. Counterpart of an Agreement: Maurice Wilkins Center, the University of Auckland,
   Name of an Agreement: Agreement on Academic Exchange between Immunology Frontier Research Center, Osaka University and Maurice Wilkins Centre, the University of Auckland
   Dates of an Agreement: 22/December/2011
   Summary of an Agreement: IFReC and Maurice Wilkins Center of the University of Auckland concluded an academic exchange agreement to encourage joint research activities on immunology.

4. Counterpart of an Agreement: Seoul St.Mary's Hospital Catholic University of Korea,
   Convergent Research Consortium for Immunologic Disease Seoul St Mary's Hospital Catholic University of Korea
   Name of an Agreement: Agreement on Academic Exchange between the Catholic University of Korea Seoul St. Mary's Hospital and Convergent Research Consortium for Immunologic Disease, the Catholic University of Korea Seoul St. Mary's Hospital and WPI Immunology Frontier Research Center, Osaka University
   Dates of an Agreement: 19/December/2011
   Summary of an Agreement: IFReC, the Catholic University of Korea Seoul St.Mary's Hospital and CRCiD concluded an academic exchange agreement to encourage joint research activities on clinical immunology with the objective of promoting cooperation in the fields of education and academic research.

Reference material – the term expired agreements

1. Counterpart of an Agreement: Harvard Medical School
   Name of an Agreement: Contractual Agreement between Osaka University Immunology Frontier Research Center and President & Fellows of Harvard College, own behalf of Harvard Medical School for Research Exchange
   Dates of an Agreement: 1/April/2008
   Summary of an Agreement: The agreement aimed for joint research on imaging and immune cell. Based on the cooperative contract, the school employed a postdoctoral fellow financed by IFReC. They participated in the 4th IFReC international symposium and gave a presentation. The agreement terminated on 31/March/2011.
2. Counterpart of an Agreement: California Institute of Technology

Name of an Agreement: Contractual Agreement between Osaka University Immunology Frontier Research Center and California Institute of Technology for Research Exchange
Dates of an Agreement: 8/April/2008
Summary of an Agreement: The role of the agreement is for joint research on imaging the immune cell. Based on the contract, the institute employed a postdoctoral fellow financed by IFReC, who attended in the 4th IFReC international symposium and seminars of our laboratories. The agreement ended on 31/March/2011.

3. Counterpart of an Agreement: New York University of Medicine
Name of an Agreement: Contractual Agreement between Osaka University Immunology Frontier Research Center and New York University of Medicine, an Administrative Unit of New York University for Research Exchange
Dates of an Agreement: 6/May/2008
Summary of an Agreement: The agreement was contracted for joint research on imaging and intercellular interaction. Based on the contract, the university employed a postdoctoral fellow financed by IFReC. He attended the 4th IFReC international symposium and seminars of our laboratories. The agreement ended on 31/March/2011.

4. Counterpart of an Agreement: University of California, San Francisco
Name of an Agreement: Contractual Agreement between Osaka University Immunology Frontier Research Center and the Regents of the University of California, San Francisco for Research Exchange
Dates of an Agreement: 15/May/2008
Summary of an Agreement: The agreement was for joint research on imaging technique of intercellular interactions. Based on the contract, the university employed a postdoctoral fellow financed by IFReC. The agreement terminated on 31/March/2011.

5. Counterpart of an Agreement: Stanford University
Name of an Agreement: Contractual Agreement between Osaka University Immunology Frontier Research Center and Stanford University for Research Exchange
Dates of an Agreement: 16/May/2008
Summary of an Agreement: The role of the agreement is joint research on single molecular imaging. Base on the contract, the university employed a postdoctoral fellow financed by IFReC and he attended the 2nd IFReC international symposium to give a talk. The agreement terminated on 31/March/2011.

Researchers in the center and above institutions visited each other and exchanged information in order to improve imaging technique of the center. We offered employment expenses of US$ 50,000 to hire postdoctoral researchers to encourage the joint research activities.

6. Counterpart of an Agreement: National Institutes of Allergy and Infectious Diseases
Name of an Agreement: Contractual Agreement between Osaka University Immunology Frontier Research Center and National Institutes of Allergy and Infectious Diseases for Research Exchange
Dates of an Agreement: 18/June/2008
Summary of an Agreement: The role of the agreement is joint research on imaging data analysis and modeling immune responses. Base on the contract, the university employed a postdoctoral fellow financed by IFReC. He attended the 2nd IFReC international symposium to give a talk, visited laboratories and participated in seminars. The agreement terminated on 31/March/2011.

7. Counterpart of an Agreement: Systems Biology Institute
Name of an Agreement: Agreement on Academic Exchange between Osaka University Immunology Frontier Research Center and Institute for Systems Biology
Dates of an Agreement: 5/May/2008
Summary of an Agreement: IFReC and Systems Biology Institute concluded an academic exchange agreement to encourage joint research activities on bioinformatics with the objective of

promoting cooperation in academic research.
(Research theme: joint research on imaging data analysis and modeling of immune responses)

6. Holding international research meetings

* For each fiscal year, indicate the number of international research conferences or symposiums held and give up to two examples of the most representative ones using the table below.

Date	Meeting title and Place held	Number of participants
Mar. 27-28, 2008	Kick-off Symposium of WPI IFReC -Immunology and Imaging-	600
Feb. 12-13, 2009	The 2nd International Symposium of IFReC -Dynamics of Immune Responses-	400
May 11, 2009	International Symposium -Frontier Immuno-Imaging-	60
May 25-27, 2009	The International Symposium -Immune Regulation: Present and Future-	900
June 18-19, 2009	Joint Symposium by SIgN & IFReC -Integrating Immune Networks with Immuno-Imaging-	300
Sep. 18-19, 2009	The International Symposium by IFReC & International Vaccine Institute, Korea -Regulation of Innate Immunity-	150
Nov. 6, 2009	International Workshop -Bioinformatics in Immunology-	80
June 1-2, 2010	The 4th International Symposium of WPI IFReC -Immunology at the Forefront-	450
June 17-18, 2010	Joint Workshop by IFReC & New Zealand immunologists	70
Nov. 3-4, 2010	IFReC & Chinese Society of Immunology Joint Symposium	80
Mar. 1-2, 2011	The International Symposium "Towards Comprehensive Understanding of Immune Dynamism (TCUID 2011)"	200
Nov. 16-17, 2011	IFReC & Institute for protein Research (IPR) Joint Seminar -Multilevel Systems Biology: Genomes, Structures, and Networks-	80
Dec. 18-20, 2011	IFReC & Convergent Research Consortium for Immunologic Disease (CRCID), Korea Joint Symposium	300
Mar. 1-2, 2012	The Immunoparasitology Meeting	120
May 22-23, 2012	International Symposium "Dynamism of Immune Reactions & Regulation"	600
Jun. 22, 2012	"LICHT Leica Center" opening seminar	100
Oct. 29-31, 2012	The International Symposium "Towards Comprehensive Understanding of Immune Dynamism (TCUID 2012)"	200
Jun. 19, 2013	Live Immuno-Imaging Facility Opening Workshop	80
Nov. 18-20, 2013	The International Symposium "Towards Comprehensive Understanding of Immune Dynamism (TCUID 2013)"	200
Jan. 15, 2014	Mini Malaria Immunopathology Symposium	50

World Premier International Research Center Initiative (WPI)

1. Host institution's commitment

1-1. Contributions from host institution

(1) Fund, Personnel

(2007-2014)

<Fund> **(million yen)**

Fiscal Year	2007	2008	2009	2010	2011	2012	2013	2014	Total
Personnel	106.20	318.15	234.83	220.34	335.46	350.69	358.26	351.58	2275.51
- Faculty members (including researchers)	96.73	283.49	203.22	171.46	217.88	216.02	226.35	216.19	1631.34
Full-time	0	0	0	0	53.83	45.39	53.78	49.56	202.56
Concurrent	96.73	283.49	203.22	171.46	164.05	170.63	172.57	166.63	1428.78
- Postdocs	2.11	29.95	31.43	40.80	47.85	55.60	32.91	66.93	307.58
- RA etc.	0.17	0	0	0	0	11.41	21.86	10.08	43.52
- Research support staffs	0	0	0	0	10.64	10.45	10.99	9.97	42.05
- Administrative staffs	7.19	4.71	0.18	8.08	59.09	57.21	66.15	48.41	251.02
Project activities	253.64	143.03	600.05	268.12	177.22	200.53	312.56	138.60	2093.75
Travel	0.77	0.94	0.88	10.27	6.81	4.70	4.29	0	28.66
Equipment	987.63	691.90	2229.8	33.00	118.93	0.15	0.31	0	4061.72
Research projects	23.24	28.42	27.43	73.12	49.20	44.30	36.61	33.59	315.91
Total	1371.48	1182.44	3092.99	604.85	687.62	600.37	712.03	523.77	8775.55

<Personnel> **(person)**

Fiscal Year	2007	2008	2009	2010	2011	2012	2013	2014	Total
Personnel	34	36	42	49	66	119	131	114	591
- Faculty members (including researchers)	22	29	33	36	38	37	47	42	284
Full-time	0	0	0	0	5	4	5	4	18
Concurrent	22	29	33	36	33	33	42	38	266
- Postdocs	7	7	8	11	12	12	12	13	82
- RA etc.	4	0	0	0	0	51	51	46	152
- Research support staffs	0	0	0	0	5	8	7	3	23
- Administrative staffs	(1) 1	0	1	(2) 2	(11) 11	(11) 11	(12) 14	(8) 10	(45) 50

* Regarding "Fund" entry, describe with reference to the items in the Progress Report(実績報告書,Jisseki-hokoku-sho)based on Article 12 of the Grant Guidelines(交付要綱,Kofu-yoko).

* Don't include competitive funding obtained by researchers (used as research project funding)

* Under "Personnel", enter the number of full-time administrative staff within the parenthesis.

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

Land

Purpose	area or number of units
Building area ; Integrated Life Science Building, IFReC Research Building, Animal Resource Center	2,644㎡
Parking area（car）	70 units
Parking area（motorbike）	9 units

Building

Name	Construction	Total area (㎡)	Construction cost (million yen)	Start of operation
Integrated Life Science Building	S－10	9,258	2,544	2009.7.1
IFReC Animal Resource Center	R3－1	2,482	917	2009.7.16
IFReC Research Building	S—9	6,585	2,000	2011.4.1

Lab space

Name	Occupied Space (㎡)	Purpose	Start of operation	End of operation
Annex building	63	Laboratory, experimental room	2007.10.1	2012.3.31
Nano Biology building	36	experimental room	2012.4.1	2013.3.31
Open Laboratories for Advanced Bioscience and Biotechnology	85	Laboratory, experimental room	2012.7.1	2013.3.31
Open Laboratories for Advanced Bioscience and Biotechnology	145	Laboratory, experimental room	2013.4.1	In operation
Center for Information and Neural Networks (CiNet)	410	MRI Room	2013.4.1	In operation
Research Institute for the Dynamic Biological Systems (tentative name)	—	—	2014 autumn	—

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

Based on the regulations established for the WPI-IFReC, Osaka University has allocated part of its authority to IFReC, entitling the Director to manage and operate the center by making substantive decisions on personnel and budget allocation.

IFReC employs a top-down decision-making system, where the Director determines the employment and annual salaries of staff members, budget implementation (priority/ proportionate allocations) and budget for start-ups, while important matters such as the IFReC annual budget and the appointment of Principal Investigators and others at the same level are approved by the Center Management Committee or the Board of Representatives. As a result, IFReC has established a research environment where PIs can devote themselves to their researches.

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

When academic staff belonging to other departments participates in WPI program as full-time PIs at IFReC, Osaka University provides the departments with a supplemental budget for replacements.

In coordination with other departments, IFReC invites academic staff belonging to other departments as a PI with a concurrent position at IFReC.

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

- Osaka University preferentially positions at IFReC administrative staff who have a command of English in their work (administration, accounting, etc.). The university also employs new administrative staff with a high level of English skills.

- Osaka University established the following regulations and salary systems;

1) Regulations Pertaining to Special Measures Related to Human Resources at the World Premier International Research Center (Enacted on October 1, 2007)

-Enable IFReC to introduce a merit-based salary system in order to invite worldwide prominent researchers to the Center.

2) Cross-appointment system (January 1, 2014)

-Invite full-time researchers from other institutions and pay salary from both institutions.

3) Osaka University Distinguished Professor System (April 1, 2013)

-Award researchers who play leading roles by utilizing their outstanding achievements a special title of "Osaka University Distinguished Professors" and an allowance of up to six million yen a year.

4) Performance-related annual salary system (January 1, 2014)

-Pay bonus in accordance with academic staff's (professor level) performance

- Osaka University launched the Support Office for Large-Scale Education and Research Projects in July, 2009 to support government-sponsored large-scale programs such as

WPI-IFReC and Global COE program.

Osaka University set up the Support Office for International Students and Scholars in 2008 to provide one-stop service for researchers from overseas to assist their acquisition of Certificate of Eligibility for Status of Residence which is necessary to obtain visa. The Support office has been of great assistance for IFReC to be a world premier research institution

1-5. Accommodation of center's requirements for infrastructural support
Utilities and other infrastructure support provided by host institution.
(*In addition to listed in the item 1. Contributions from host institution)

① Long-term residence for international staff (Kasugaoka House)

Name	Total number of users
Kasugaoka House	39

② Short-term accommodations for international visitors (International House, International Student Dormitory, etc)

Name	Total number of users
International House	41
International Student Dormitory	4
Guest House of the Research Center for Nuclear Physics	41
Kasugaoka House	9

③ Apartments for university employees (University apartments)

Name	Total number of users
Tsukumodai Apartment	23
Momoyamadai Apartment	1
Sakuranotyou Apartment	1

④ Nursery school in university campus (Takenoko Child-care Center)

Name	Total number of users
Takenoko Child-care Center	2

⑤ Laboratory space for PIs with a concurrent position at another faculty

Affiliation	Number of laboratory	Name of laboratory			
Graduate School of Medicine	4	Kumanogoh	Takeda	Ishii	Hatazawa
Research Institute of Microbial Diseases	4	Kikutani	Yamamoto	Ikawa	Miki
Graduate School of Frontier Biosciences	2	Yanagida	Nanba		
Graduate School of Information Science and Technology	1	Matsuda			
Graduate School of Engineering	1	Kikuchi			

⑥ Research Institute of Microbial Diseases（Joint Operation）

Facility	Common area (㎡)
Core Instrumentation Facility	604
Animal Resource Center for Infectious Diseases, Building A	1391
Animal Resource Center for Infectious Diseases, Building B	1425
BIKEN Hall, Library, Meeting Room, etc.,	422

1-6. Support for other types of assistance

(Techno Alliance conception)
Osaka University constructed the Techno Alliance building in March, 2011, based on the conception of “Industry on Campus”. In the building, corporate research teams collaborate with the university’s researchers, providing the establishment of an environment to create technological innovation for the next generation in order to satisfy new industrial and social needs by utilizing seeds generated by the university’s fundamental researches. Under the Techno Alliance concept, Osaka University provides IFReC with a place to realize translational researches which enable the center to apply its results from fundamental researches to the development of new vaccines and treatment for immune-related diseases, the development of vaccines for infectious diseases and cancers, and treatment for immune-related intractable diseases such as autoimmune disorder.

3. Transition in the number of female researchers

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

(Person)

	FY2010	FY2011	FY2012	FY2013	Final goal
Researchers	35, 20.2%	35, 20.2%	39,21.3 %	35, 27.0 %	38, 21 %
	173	173	183	186	180
Principal investigators	1, 3.7%	1, 3.7%	1, 3.8 %	1, 4.0 %	3, 10 %
	27	27	26	25	30
Other researchers	34, 23.3%	34,23.3 %	38, 24.2 %	34, 21.1 %	35, 23 %
	146	146	157	161	150

Attachment (1)

国立大学法人大阪大学の達成すべき業務運営に関する目標（中期目標）

Management goals to be achieved by Osaka University (The Medium-term goals)

阪大企推第　３　号
平成２２年３月３０日

Mar 30, 2010

文部科学大臣　殿

To the Minister of the Ministry of Education, Culture, Sports, Science and Technology

国立大学法人大阪大学長
鷲田清一

President of Osaka University
Washida Seiichi

国立大学法人大阪大学の中期目標を達成するための計画（中期計画）の認可申請について

Application for approval of the plans to achieve the Medium-term goals of Osaka University (Medium-term plans)

標記の件について、国立大学法人法（平成１５年法律第１１２号）第３１条第１項の規定に基づき、当大学の中期計画を別部のとおり認可していただきたく申請します。なお、同条第２項第５号に関する資料を添えて提出します。

We hereby submit the application for approval of the plans to achieve Medium-term goals of Osaka University.

２１文科高第７９９号
平成２２年３月３１日

Mar 31, 2010

国立大学法人大阪大学長　殿

To the President of Osaka University

文部科学大臣
川端達夫

Minister of the Ministry of Education, Culture, Sports, Science and Technology
Kawabata Tatsuo

国立大学法人大阪大学の中期目標を達成するための計画（中期計画）について

Approval of the plans to achieve Medium-term goals of Osaka University (Medium-term plans)

平成２２年３月３０日付け阪大企推第３号をもって認可申請のあった標記の件については、別紙の留意点を付した上で認可します。

We hereby approve the application of the plans to achieve Medium-term goals of Osaka University.

抜粋：国立大学法人大阪大学の中期目標 Extract: The Medium-term goals of Osaka University

・平成 22 年 4 月 1 日から平成 28 年 3 月 31 日までの 6 年間とする。
The Medium-term goals will be implemented for the six year period from April 1, 2010 until March 31, 2016.

・（世界トップレベルの研究の推進）(Promoting world top class research)

8. 世界トップレベルの研究を推進するという理念のもと、研究科・附置研究所・センター等の組織の特徴を活かし、多様な研究形態の下で、知の創造を行うとともに、学際的・融合領域研究を促進し、基礎から応用までの幅広いイノベーション創出拠点の構築を目指す。
8. Under the University's principle to promote world top class research, our research objective has developed to advance knowledge in various research fields by fully utilizing the capacities of different research organizations of the university, and to promote interdisciplinary research by developing the University as a core for innovation that supports both basic and applied research.

抜粋：国立大学法人大阪大学の中期計画 Extract: The Medium-term plans of Osaka University

2 研究に関する目標を達成するための措置　2　Measures to achieve research goals

(1)　研究水準及び研究の成果等に関する目標を達成するための措置
Measures to achieve the goals in terms of the standard of research and the results from the research

（基盤的研究の充実）(Enhancement of the fundamental research)
8-1. 長期的な視野にたち、学問の発展に寄与する高度な基礎及び応用に関する基盤的研究を継続的に推進するとともに、学際的・融合的な学問分野の創出や、特色のある研究の推進などに取り組む。
8-1. In the long-term, we will continue to promote fundamental research involving sophisticated basic and applied researches that contribute to academic advancement. In addition, we will create interdisciplinary research fields and facilitate unique researches.

（重点プロジェクト研究の推進）(Promoting priority research projects)
8-2. 本学の重点的研究領域である生命科学・生命工学、先進医療、ナノサイエンス・ナノテクノロジー、環境・資源・エネルギー科学、光科学、物質と宇宙の起源、脳科学・ロボティックス、情報・コミュニケーション科学、サステイナビリティ学、社会の多様性と共生、人間行動の社会科学、世界トップレベル研究拠点を中心として推進している免疫学・感染症学など、２１世紀型の複合的諸課題や地球規模の諸問題の解決に必要な学問領域の開拓と発展に取り組むため、大型の重点プロジェクト研究を組織し、先端的な研究を推進する。
8-2. In order to cultivate and advance academic fields which are essential to solve challenges unique to the 21st century and various global scale problems, we will promote cutting-edge researches by initiating large-scale priority research projects. Thus, we will put more focus on our major fields; life science/engineering, advanced medicine, nanoscience/nanotechnology, environmental/energy sciences, photon science/robotics, information/communication science, sustainability science, social science on diversity, association and human behavior, and immunology and infectious diseases, the last two of which are actively conducted at the World Premier Research Center.

Attachment (2)　Excerpts from the Osaka University Institute for Academic Initiatives (2012 - 2015)

Osaka University Academic Initiatives for 2012-2015

"to be a university that shines forth even into the 22nd century"

Note

The part marked by yellow : consistent with the WPI's principle

The part marked by gray : Osaka University's intention to support IFReC

Preface

Based on the principle that providing scholarship and training that enables one to perceive the true essence of things is the mission of a university and that universities contribute to society by fulfilling this mission, Osaka University aims to become a world center for both scholarship and training under the motto of "Live Locally, Grow Globally," and to develop outstanding graduates with a high sense of ethics and international-mindedness.

～Partially omitted～

A condition in which each staff member can work with vigor and in which research and educational institutions of diversity cooperate with each other and at the same time enjoy their own uniqueness is essential for the development of a university. Under the leadership of the president, all members of management, administration, and education and research organizations must actively promote university reform in accordance with the requests of society.

Eight Principles of Academic Initiatives

1. The Institute for Academic Initiatives (IAI) was set up for the purpose of making flexible and swift decisions in strategic areas in order to (1) draft science policies and international strategies, (2) explore interdisciplinary research fields, (3) develop personnel with international-mindedness, expertise, and diversity, (4) promote fundamental research, and (5) nurture young researchers. The president assumes the position of director in order to display leadership and instill IAI in the heart of all university reform.
2. The Center for Education in Liberal Arts and Sciences will play a central role in implementing the globalization of OU education. The university will provide support for students wishing to study abroad and also work to actualize as early as possible campuses with a diversity of persons from all over the world — i.e., "Global Campuses."
3. In order to achieve Global Campuses, an international strategy must be devised, one that

reexamines the role of OU Overseas Centers in order to ensure a greater level of exchange with overseas universities.

4. Funds must be allocated effectively, a step that will encourage promotion of basic research and professional development, steps linked to our future growth. We will realize this end by making use of the perspectives of individuals and organizations and seeing the whole picture from a mid- and long-term perspective based on the ideas of the president, deans, and directors.
5. The university will continue to assume responsibility for the maintenance and management of facilities in accordance with the plan. To this end, we will create and implement measures to secure financial resources. Additionally, we will formulate measures on utilizing the university's facilities and lands, including disposal, from a mid- and long - term perspective.
6. Based on the Osaka University Academic Initiatives, we will draft and implement measures to increase Future Funds permanently in cooperation with the alumni union.
7. We will share Osaka University's fundamental attitude with society and the nation and aim to become a university more open to the public. We will further strengthen publicity and university-community collaboration activities at home and abroad in order to achieve this goal.
8. We aim to have healthy, comfortable, global campuses where there is reason to study and work not only because of renewed facilities, but because measures will be drafted and carried out in order to maintain an environment where one can immerse oneself in study and work while maintaining a healthy body and mind.

Hereunder are the detailed proposals to achieve these principles of the Institute for Academic Initiatives.

Establishing the Osaka University Institute for Academic Initiatives

～Partially omitted～

Setting up of the Research Groups

■ Establish research groups with full-time academic staff in order to explore new academic fields and show guidelines for Osaka University’s Academic Initiatives.

Carrying out graduate education such as “Leading Programs in Doctoral Education”

■ Promote innovative graduate education and produce superior graduates, possessing broad, unique, international perspectives.

Supporting the development of cutting-edge research groups

■ Support the construction of interdisciplinary programs, aiming for the realization of International Research Bases in order to advance and transform original research at OU into international cutting-edge research.

Finding a Path leading to the Future based on Research that sees the Truth of Things

Promoting fundamental research by strengthening the support system for research

■ Improve the **Adviser System** and **Challenge Support Program**.

■ Aim to establish company-sponsored programs to support revolutionary fundamental research from a long-term perspective.

■ Support all departments regarding provisions for opportunities for self-improvement and refreshment of researchers through overseas research and sabbaticals.

Supporting frontier research at Osaka University

■ Implement the **Exciting Leading-Edge Research Project** in order to support interdisciplinary research intensively.

■ Increase the number research administrators in order to support obtaining large-scale research funds by which frontier research projects can be stimulated and in order to promote a suitable research environment.

Improving the environment for promoting research

■ Encourage all departments to rethink the process for making decisions in order to securing sufficient time for research.

■ Improve and reorganize the system for centralizing data in order to secure time for research.

～Partially omitted～

International Strategy for attracting Students and Researchers from Overseas

Promoting the acceptance and dispatch of students and researchers

■ Improve current programs for the acceptance of students and researchers from overseas and develop new programs for the dispatch overseas of OU students and researchers.

■ In order to attract outstanding students from overseas, hold study-abroad fairs systematically and effectively. Also consider introducing a designated school system（指定校制度）in which OU accepts students from designated overseas high schools with which OU has signed agreements.

Implementation collaboration strategy with domestic and oversea universities and consortiums

■ Reexamine Osaka University basic policies for academic exchange agreements with foreign universities and promote practical and effective academic exchange and joint research.

■ Establish clear policies on participation in consortiums and our activities in such under the bilateral and multilateral network agreements so that related activities become more practical and effective.

～Partially omitted～

University-Industry Collaboration for Creating a Prosperous Society

Deepening and Enhancing University-Industry-Government Collaboration

■ Hand in hand with industries, Osaka University will promote “Industry on Campus” through

Research Alliance Laboratories and Joint Research Chairs. Additionally, by making use of these labs and chairs, we will facilitate human resource development and challenging research projects through university-industry collaboration.

- Assist in finding challenges and planning research projects for the successful launch of new projects through information and human exchange among the university, industry, and government.
- Try to set up university-industry collaboration involving both the humanities and sciences.

～Partially omitted～

University- Community Collaboration that Fosters Interaction among the university, citizens, and the local community

Centering on the university's scholarship, develop mutual education among citizens

- Continuously support outreach activities of researchers in order to introduce the university's scholarship and human assets to society.

～Partially omitted～

Osaka University Hospital-Quality and Ethics

～Partially omitted～

Contribution to local medical care and to the development and practice of advanced medical treatment

- Integrate "The Medical Center for Translational Research" and "Center for Clinical Investigation and Research" into "The Advanced Medical Center" to strengthen our clinical research framework and innovative drug-development base.

～Partially omitted～

Management of Finances that Focuses on the Future

Review the Distribution of Funds

- With the goal of promoting basic research, review the distribution of indirect research expenses, including the distribution of indirect research expenses for researchers.
- Secure the university's income through managerial efforts in the hospital and the promotion of cooperation between the university and industry. At the same time, review the distribution of funds within the university with an eye firmly on both maintaining and improving competitiveness, and develop a system for the realization of Osaka University Academic Initiatives.

～Partially omitted～

Flexible Overhaul of Systems and Organization

～Partially omitted～

Review of Education and Research Institutions

- Strategically decide upon the importance of the roles and functions that should be carried out by departments and address questions regarding the reorganization, elimination, consolidation, and/or establishment (essentially, in a “scrap-and-build” manner) of institutions.
- Using IAI, decide upon Osaka University’s own cross-sectional action plan from a medium- and long-term perspective and, along with this, carry out the overhaul of institutions necessary for the realization of the academic Initiatives.

Develop Flexible Personnel Systems

Securing young faculty, international faculty, researchers and medical technologists through more flexible personnel and employment systems.

- Introduce further flexibility into the university’s personnel and employment systems by means of instituting flexible employment systems for limited term staff, establishing a new employment system for faculty, and so on.
- Plan improvements in retirement severance pay packages in order to provide university personnel with more options in viewing their life plans following retirement from OU.
- Enrich the tenure tracking system and utilize the university’s reserve posts effectively. These will accelerate the employment and promotion of outstanding young and/or female faculty members.
- Continue to develop flexible personnel and salary systems able to accommodate specifics of the duties of medical staff members.

～Partially omitted～

Enhance Administrative Reform and Improvement

Building a flexible and dynamic organization

- Establish a flexible and dynamic administrative system to respond to requests from society, and to strengthen the support environment for education and research activities.
- Looking ahead to the future, systematically foster young administrative staff in the Project Management Team and Institute for Academic Initiatives.
- Enhance information sharing and awareness-raising among staff. Also, aim to improve communication between staff. Such measures will aid the construction of an even more comfortable work environment through the mutual effort and cooperation of faculty and staff.

～The rest is omitted～