World Premier International Research Center Initiative (WPI)
Executive Summary (for Final Evaluation)

Host Institution	Osaka University	Host Institution Head	Shojiro Nishio
Research Center	Immunology Frontier Research Center	Center Director	Shizuo Akira

About filling out this form:
This summary is to be based on the Center's Progress Report and Progress Plan, with reference to the following items, prepare the summary within a space of **up to 6 pages.**

A. Progress Report of the WPI Center

I. Summary

IFReC was started as a sustainable innovative World Premier Institute of immunology in Osaka University. Our mission as a WPI is to accelerate immunology research as well as develop interdisciplinary studies with other fields, globalization of the university and our society, and system reform of the host institute. Headed by Director Shizuo Akira, an eminent immunologist, IFReC convenes approximately 30 of the world's top-class principal investigators from Japan and overseas in the fields of immunology, live imaging and bioinformatics to conduct innovative immunological research. In March 2011, a new research building was completed on Osaka University's Suita Campus providing superior research facilities and an international environment in which to focus on research.

Immunology is definitely important in human health and social welfare. The researchers of IFReC have published over one thousand papers during 2007 to 2015. Almost 10% of them were published in high-impact journals such as Science, Cell, Nature, and their journal families. The production of Top 1% and Top 10% articles are much higher than average. The amount of competitive research funds obtained by IFReC researchers well exceeds the WPI program subsidy. IFReC scientists have been awarded for their brilliant achievements and significant impact on society. In particular, Akira and S. Sakaguchi were given the Canada Gairdner International Award, known as one of world's most prestigious awards. Kishimoto and Hirano were the first Japanese winners of the Crafoord Prize for their contribution not only to basic research but also for application to medical care. These evaluations in publication and awards demonstrate that the quality of science of IFReC has reached "the world top level". IFReC research achievements have been disseminated to the general public through many PR and outreach activities.

IFReC is promoting interdisciplinary research by establishing a live immune-imaging facility in the IFReC research building with animal rooms and a high-performance MRI and a two-photon microscope, and through programs to promote fusion research to encourage IFReC young researchers under the "Research Support Program for Combined Research Fields" and "Dual Mentor Program". IFReC expanded collaboration with external organizations such as Quantitative Biology Center (QBiC) of RIKEN and the Center for Information and Neural Networks (CiNet) of the National Institute of Information and Communications Technology (NICT). These collaborations have had a great effect on creating new interdisciplinary domains in IFReC.

The high level of research activities at IFReC continues to attract many capable young researchers at home and from overseas. IFReC has employed a total of 49 postdocs out of 318 applicants through international open recruitment. The percentage of overseas researchers at all levels has satisfied the WPI target level of 30% during the WPI program except in the most recent two years. The research planning and management office together with the general affairs section in the administration office provides overseas researchers with a variety of support for research and daily life to comfortably devote themselves to their research. IFReC exchanged cooperative research agreements with four overseas institutions or organizations. In particular, one of the most successful cooperative activities with overseas institutes has been the "NIF Winter School on Advanced Immunology" jointly organized with Singapore Immunology Network. The School has been organized every winter since 2012 and has succeeded in globally fostering young researchers in the next generation, in raising the international visibility of IFReC and in promoting its internationalization.

IFReC was given highest priority in the university's strategy, and the university

positioned "Immunology being promoted mainly by the leading role of the world premier research center" as one project for emphasis in the 2nd Medium-Term Plan. 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. To ensure the independence of IFReC management and research beyond the end of the WPI grant, IFReC and the host university have been taking measures including strengthening collaboration with industry.

II. Items

1. Overall Image of Your Center

The principal mission of IFReC is world-leading basic immunology to strongly impact the medical sciences. Our institute provides a highly-equipped research platform for young next generation researchers and world premier scientists who have contributed greatly in studies of cytokines, molecular mechanisms of innate immunity, cell death, and regulation of immune system. PI composition is maintained at the highest level through the retention of world-prominent scientists and recruiting of young and energetic scientists from all over the world. The center director, the vice directors and the administrative office continuously search for investigators and encourage them to study in the center.

At the same time, we offer an excellent research environment that attracts prominent scientists to work and develop at IFReC. IFReC has implemented strategic measures to foster young researchers and to raise international visibility, such as IFReC colloquium, research support programs for interdisciplinary research and Winter School. Under these strategic measures, IFReC researchers lively conducted their research contributing to top level immunology.

In over nine years since its launch, IFReC has implemented various activities to accomplish WPI four objectives. The WPI Program Committee concluded that IFReC achieved a "World Premier Status", fully meeting the goal of the WPI program. Measures to sustain the center as a world premier international research center after program funding ends (including measures of support by the host institution and the government) are recognized as important issues, since about 60 percent of WPI grant is assigned for personnel costs. Through achieving WPI objectives, IFReC has been exerting utmost efforts to be a pinnacle of Osaka University. The University and IFReC are seeking to become a next-generation innovative institute for collaboration with various industries and organizations exceeding the boundaries of the campus.

2. Research Activities

The research at IFReC has been maintained at a very high level in both quantitative and qualitative aspects ever since its establishment. The total number of papers by authors affiliated with IFReC during the period of 2007 to 2015 is 1090. In 2015 the average number of citations of these papers was 38.4 and the h-index of IFReC as a whole was 84 (WEB OF SCIENCETM by Thomson Reuters ©). The considerable increase in these factors since 2013 (total papers 809, citations 29.2, and h-index 65) demonstrates that IFReC has secured steady progress in immunology researches. The numbers for Top 1% Papers and Top 10% Papers (Percentage of highly cited papers published in the same research fields, publication years, and document type) were 58 and 290, respectively (InCites by Thomson Reuters ©). The productivity rate for Top 1% and Top 10% are 5.3 and 2.7 times higher than average values, which proves that the quality of science papers by IFReC scientists has reached the world top level.

The laboratories in the IFReC research complex are designed for the specialties of the 17 research groups including live animal experiments, cell and molecular biology, as well as advanced imaging. The animal facility manages a specific pathogen-free (SPF) environment for animals that is indispensable for immunological research. This facility, with its impressive capacity to hold animals, provides researchers with the space for various animal experiments such as infectious experiments, cell transplantation and imaging experiments. The live-imaging facility contains a high performance 11.7T Magnetic Resonance Imaging (MRI) instrument and an animal room to rear 700 mice in SPF environment, which enables the observation of immune phenomena in the same animals over a few weeks. One feature of the IFReC research support system is the Research Planning and Management Office (RPMO) in administration, which provides varied and intensive support for IFReC researchers.

The amount of competitive research funds obtained by IFReC researchers well exceeds the WPI program subsidy. IFReC researchers have successfully raised funds for their own research. The total amount of competitive funds obtained by IFReC researchers is 9,215 million yen since FY2007. IFReC also has received a large sum of donations from the private sector including Kishimoto Foundation (650 million yen from FY2010 to FY2015) and pharmaceutical companies. These donations have supported overseas researchers to stay at IFReC, or have enabled the invitation of talented researchers to IFReC.

IFReC has been promoting collaborative research with many institutes including Osaka University Hospital, RIKEN QBiC and CiNet. Of the papers published since IFReC establishment, 60% and 40% are joint papers respectively originating from collaborations with international and domestic research institutes.

IFReC scientists have been awarded for their brilliant achievements and significant impacts on society (Appendix 2-3-1). In particular, Akira (2011) and S. Sakaguchi (2015) were given the Canada Gairdner International Award, known as one of world's most prestigious awards. Four IFReC researchers, Kishimoto (1991), Akira (2009), S. Sakaguchi (2013) and Nagata (2015) have become foreign associates of the National Academy of Sciences (NAS) of USA, an honor for which a mere 46 scientists researching in Japan have ever been nominated.

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

IFReC has executed many PR and outreach activities to disseminate IFReC research achievements to the general public in various ways such as lectures, science cafes, press releases and publishing.

3. Interdisciplinary Research Activities

IFReC has implemented top-down and bottom-up strategic measures such as IFReC colloquia, Research Support Programs, Fusion research units and Study Session. The recent trend for papers produced at IFReC is an increase in the number of interdisciplinary research papers. The interdisciplinary researches between immunology, bioimaging, and bioinformatics have already joined the mainstream in IFReC.

4. International Research Environment

IFReC recruited active, talented, young researchers from overseas as PIs. A number of researchers of world-top class have taken the opportunity to visit IFReC on the occasion of seminars and international symposia. The high level of research activities at IFReC continues to attract many capable young researchers. Their research accomplishments and experiences in IFReC were highly appreciated, eleven postdocs who left IFReC have found assistant professor positions, and two overseas postdocs took the position of associate professor in their country of origin.

IFReC exchanged cooperative research agreements with four institutions or organizations. Above all, one of the most successful cooperative activities with overseas institutes has been "NIF Winter School on Advanced Immunology" (WS) jointly organized with Singapore Immunology Network (SIgN). The School has been organized every winter since 2012 and has succeeded in globally fostering young researchers of the world, who are expected to be leaders in the next generation in the field of immunology. WS has also been raising the international visibility of IFReC and in promoting its internationalization. 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 has organized a large number of international symposia including annual international symposia and workshops. Topics of these events covered diverse research fields including immunology, imaging, bioinformatics, and parasitology. Active communication among participants is expected to enhance their collaborations including interdisciplinary studies. Young researchers are encouraged to present posters, providing good opportunities to discuss their research with top scientists.

RPMO together with the general affairs section in the administration office provides overseas researchers with various support for research and daily life. The staff also responds to inquiries on family matters like children's education. IFReC webpages provide information necessary for life in Japan. 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.

5. Organizational Reforms

Authorized by Osaka University, IFReC director makes major decisions regarding personnel and budget allocation as well as other administrative matters, to which the administrative director gives full support. This top-down decision-making process is a unique management system in comparison with that of other faculties and institutions within the university. Newly recruited young IFReC PIs are provided with financial support. Programs to enhance interdisciplinary research at IFReC were established 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. IFReC implemented three strategies to increase the number of female researchers. Almost all administrative support staff are able to communicate in English with non-Japanese members. Some staff members have research experience as Ph.D. and can really understand IFReC researchers' needs. Also use of English in the center is enhanced by positioning a native English translator in the RPMO.

To achieve world premier status, IFReC was given highest priority in the university's strategy. In the 2nd Medium-Term Plan (FY2010-2015), the university positioned "Immunology being promoted mainly by the leading role of the world premier research center" as one project for emphasis. The host university provides IFReC with many supports including tenure positions for IFReC members. The existing support system of the host university did not cover issues that arose when accomplishing WPI missions. The measures taken were pioneering in the university and have been distributed as ripple effects.

6. Others

In addition to the activities mentioned above 1-5, IFReC conducted research promotion or staff development activities such as retreat and lecture series. Measures have been in progress to solidify the foundation for IFReC's continued development beyond the end of the WPI grant in 2017.

B. Progress Plan

1. Mid- to Long-term Research Objectives and Strategies Based on the Center's Research Results to Date

IFReC was established as a WPI center in recognition of the advanced research achievements produced in immunology. IFReC's mission is to combine the fields of immunology, imaging and informatics to comprehensively understand the dynamics of the immune systems. IFReC has produced research outcomes in medicine and basic immunology that are recognized by the Program Committee to be of a world-top-class standard and worthy of the World Premier Status. However, our role as a WPI center in Japan is not yet complete. IFReC has a potential to reach a higher state in research, which no one has ever reached. The development of IFReC should be seen over the long term. The first 10 years are the major first step, next is maintaining that momentum. In the next 10 year phase, emphasis is on the support of world-leading researchers and the precise setting of new goals to encourage proactive investment into new horizons. IFReC decided to set the goals for the next 10 years as follows;

1-1. "IFReC, a cradle for innovative immunologists"

Researchers to develop IFReC and immunology in the future, especially those who promote fusion studies and those who are expected to succeed internationally will be fostered and utilized through the strengthening technology of bioinformatics and imaging during the period of preparation for the next stage after the WPI grant. IFReC will serve as a hub for international brain circulation based on active recruiting and mobility of young researchers. Also, the internationalization system nurtured in the WPI program will be dispersed in the university to encourage the globalization of OU. International visibility as a WPI in Japan will be further increased and the ability to trust in Japanese science will be encouraged.

1-2. Generation of innovative immunotherapeutics

Because IFReC recognizes that development, deployment and transfer of new insights into immune-regulating mechanisms attained at IFReC, are crucial to address intractable

diseases, IFReC will accelerate the application of research outcomes to medical/clinical immunology.

(1) Development of innovative immune-regulating techniques: The innate immune system takes part in a wide range of diseases and/or their symptoms such as cancer metastasis and infiltration, allergies, metabolic syndromes, heart diseases, autoimmune diseases, even psychiatric disorders and so on. IFReC has elucidated the affect and influence on diseases by post-transcriptional regulation of cytokine mRNA. Based on achievements, IFReC will develop novel techniques regulating innate immune responses, leading to prevention and/or cure of the diseases described above.

(2) Development of innovative cancer immunotherapy: The aim of cancer immunotherapy is to evoke and enhance effective anti-tumor immune responses by targeting various immune responses. Recent clinical studies have shown that several immunotherapeutic agents are of significant help in treatment of advanced cancers via control of regulatory T (Treg) cells and resulting activation of effector T cells. Small molecules that selectively target Treg cells and stimulate innate immunity have been discovered. Application of these small molecules for therapy is planned.

(3) Development of novel diagnostic and therapeutic strategies for autoimmune diseases: Approximately one third of the diseases designated as of concern by the Ministry of Health, Labor and Welfare are immune-related diseases. Information on these pathological conditions collected by medical scientists in the clinic will be analyzed based on bioinformatics methodology, and a framework to develop novel antibody-based medicine will be established through diagnosis of symptoms of autoimmune diseases and evaluation of therapy effects via collaboration between basic immunologists and researchers developing medicines.

(4) Promotion of new drug development with innovative PET/MR and PET/CT imaging: PET/MR facility for small animals is established based on the Good Laboratory Practice in Osaka University to enable selection of the most suitable compound as a new drug at the preclinical stage. Preclinical PET imaging studies with this facility will facilitate drug development for immunotherapy and improve safety.

(5) Forefront vaccine development: IFReC will promote research and development studies of vaccines against a broad range of diseases from infectious diseases and cancer to many other lifestyle-related diseases through implementation of industry-academia-government joint cooperation through active exchanges of researchers at the Research Institute for Microbial Diseases, Osaka University, the National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN), and the Research Foundation for Microbial Diseases of Osaka University.

2. Management System of the Research Organization

To systematically conduct research in the mid- to long-term, IFReC will form a system for seamless progress from basic research to medical/ clinical immunology. In addition, researcher involvement in drug and diagnostic development will ensure researchers have a greater awareness of and commitment to social contribution. The center will also form its own system to acquire the funding to achieve these goals.

(1) PI organization with strong potential: New PIs will encourage the seamless development of basic research toward application to medial and clinical immunology and will further promote interdisciplinary research. Three new PIs will be added in FY2017.

(2) Use of outstanding researchers: It is vital to maintain a high research standard across generations. IFReC will not simply cease research when a researcher reaches a certain age. At IFReC, if researchers are able to continue to achieve outstanding research outcomes as well as acquiring external funding of 100 million yen per year, they will be provided with a research environment.

(3) Introduction of a tenure track to train young PIs: A tenure track system will be introduced to enable the employment of young PIs, including women and foreigners with the aim of training the next generation of IFReC core researchers.

(4) Use of corporate vitality toward medical and clinical immunology development: To ensure the independence of IFReC management and research, a new contract between academia and industry in the form of a comprehensive collaboration contract was concluded with Chugai Pharmaceutical Co., Ltd. for one billion yen a year for 10 years (2017-2026). This contract solidifies the foundation for IFReC's continued development after the WPI grant. The benefits gained by the company via this contract are preferential disclosure of research outcomes and first right of refusal to apply for joint research, intellectual property or right to work. These rights are restricted to the comparative percentage of IFReC's total expenses supplied by the company thereby guaranteeing the independence of researchers. In

addition, other companies are free to apply for joint research on topics other than those selected by the pharmaceutical company. IFReC's policy is to proactively seek collaboration and joint research with other industry entities by introducing Open Innovation Laboratory.

(5) Enhanced function as a hub for international brain circulation: To maintain a research level that is world top level, it is vital to ensure a diversity of ideas by proactively employing researchers from overseas or having researchers in Japan gain overseas experience. To function as an international brain circulation hub, IFReC is investigating the potential for cooperative research centers with overseas institutions to encourage IFReC researchers through mutual training via exchange of young researchers.

(6) Preservation of the research support system: Greater cooperation with a wider range of researchers both overseas and in Japan will increase competitiveness and support the formation of a dynamic hub for brain circulation. To achieve these measures, it is important to train staff who support research within the organization such as administration and technical staff, and promote their activities.

3. Center's Position within the Host Institution, and Measures Taken by Host Institution to Provide Resources to the Center

Osaka University has created the "OU Vision 2021" for the third six-year mid-term goal period—considered the "period of evolution"—to guide continuous efforts for self-reform. Osaka University aims to create and deepen diverse knowledge from world-top-level basic research and interdisciplinary research. Due to a new strategy of establishing an International Advanced Research Institute (provisional name), the university will sustain IFReC, which is recognized as an institute with outstanding research capability and sophisticated research facilities, and will create world top-level research centers that emulate IFReC. Osaka University is expected to approve the transition of IFReC as a 10 year provisional position in the university (by the end of WPI support; March 2017) to a permanent research organization, and will support IFReC with its exceptional research capability, as well as its global visibility, as a leading research center of Osaka University. Osaka University has provided IFReC with seven research support administrative staff, enabled researchers to join on cross-appointments for diversity, and in FY2015, provided tenure positions for overseas researchers (one professor and two associate professors). Further, the university plans to offer five further tenure positions (including two professors) for three laboratories.

World Premier International Research Center Initiative (WPI)
Progress Report of the WPI Center (for Final Evaluation)

Host Institution	Osaka University	Host Institution Head	Shojiro Nishio
Research Center	Immunology Frontier Research Center	Center Director	Shizuo Akira

* 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 2016) 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 1-1~7], 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, project funding, project expenditures, and WPI grant expenditures.

IFReC was started as a sustainable innovative world premier institute of immunology in Osaka University. The principal mission is world-leading basic immunology to strongly impact the medical sciences. Our institute provides a highly-equipped research platform for young next generation researchers and world premier scientists who have contributed greatly in studies of cytokines, molecular mechanisms of innate immunity, cell death, and regulation of immune system. PI composition is maintained at the highest level through the retention of world-prominent scientists and recruiting of young and energetic scientists from all over the world. The center director, the vice directors and the administrative office continuously search for investigators and encourage them to study in the center. At the same time, we offer an excellent research environment that attracts prominent scientists to work and develop at IFReC. IFReC has implemented strategic measures to foster young researchers and to raise international visibility, such as IFReC colloquium, research support programs for interdisciplinary research and Winter School. Under these strategic measures, IFReC researchers lively conducted their research contributing to top level immunology.

Our mission in WPI is to accelerate immunology research as well as develop interdisciplinary studies with other fields, globalization of the university and our society, and system reform of the host institute. In over nine years since its launch, IFReC has implemented various activities to accomplish these four missions. The WPI Program Committee concluded that IFReC achieved a "World Premier Status", fully meeting the goal of the WPI program. Measures to sustain the center as a world premier international research center after program funding ends (including measures of support by the host institution and the government) are recognized as important issues, since about 60 percent of the WPI grant is assigned for personnel costs. Through achieving WPI objectives, IFReC has been exerting utmost efforts to be a pinnacle of Osaka University. The University and IFReC are seeking to become a next-generation innovative institute for collaboration with various industries and organizations exceeding the boundaries of the campus.

Research of the highest world level: As shown in the list of WPI-Articles, the researchers of IFReC have published over 1,000 papers during 2007 to 2015. Almost 10% of them were published

in "High-impact journals" such as Science, Cell, Nature, and their journal families. The average number of citations of these papers and the h-index of IFReC as a whole were comparable to those of the world top level institutes in immunology such as La Jolla Institute for Allergy and Immunology in USA. The production of Top 1% and Top 10% articles is much higher than average. These objective analysis results demonstrate that the quality of science at IFReC has reached "the world top level". Highly acclaimed prizes including Crafoord Prize to Kishimoto and Hirano, and the Canada Gairdner International Award to Akira and S. Sakaguchi were awarded to IFReC researchers. As of 2015, four IFReC scientists (Kishimoto, Akira, S. Sakaguchi, and Nagata) have been elected as members of the Foreign Associates of National Academy of Sciences of USA, placing IFReC as a rare research institute worldwide.

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

Globalization of university and our society: IFReC recruited active, talented, young researchers from overseas. In particular, the Kishimoto Foundation Fellowship has greatly contributed to the recruitment of young overseas researchers to IFReC. The research accomplishments and experiences in IFReC of the overseas researchers were highly appreciated and they were promoted to take higher positions after IFReC. The Research Planning and Management Office together with the general affairs section in the administration office provides overseas researchers with a variety support not only for research but also for their daily life. Since its foundation, IFReC has organized a large number of international symposia and workshops. Active communication among participants is expected to enhance their collaborations including interdisciplinary studies. A number of world-top class researchers have taken the opportunity to join. Young researchers are encouraged to discuss their research with their international colleagues and top scientists.

Systems reform of the host institute: Based on the regulations established for 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. The existing support system of the host university did not cover issues that arose when accomplishing WPI missions. The measures taken were pioneering in the university and have been distributed as ripple effects. IFReC was given highest priority in the university's strategy, and the university positioned "Immunology being promoted mainly by the leading role of the world premier research center" as one project for emphasis in the 2nd Medium-Term Plan. IFReC strategy for collaboration with industries is incorporated in a new form of university-industry cooperation at Osaka University.

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 2016. 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 2-1, list the papers underscoring each research achievement (up to 40 papers) and provide a description of each of their significance.

Researchers with diverse expertise at IFReC have been studying a wide variety of research fields including autoimmune diseases, infectious disease, metabolic syndrome, and many others. These researches will lead to new and more efficient development strategies for vaccines and immune therapies when combating infectious diseases, cancers and autoimmune diseases.

The research at IFReC has been maintained at a very high level in both quantitative and qualitative aspects ever since its establishment. The total number of papers by authors affiliated with IFReC during the period of 2007 to 2015 is 1090 (See the list of WPI-Articles). In 2015 the average number of citations of these papers was 38.4 and the h-index of IFReC as a whole was 84 (WEB OF SCIENCE™ by Thomson Reuters ©). The considerable increase in these factors since 2013 (total papers 809, citations 29.2, and h-index 65) demonstrates that IFReC has secured steady progress in immunology researches. The numbers for Top 1% Papers and Top 10% Papers (Percentage of highly cited papers published in the same research fields, publication years, and document type) were 58 and 290, respectively (InCites by Thomson Reuters ©). The productivity rate for Top 1% and Top 10% are 5.3 and 2.7 times higher than average values, which proves that the quality of science papers by IFReC scientists has reached the world top level.

IFReC continues to explore novel research topics and obtain results after the WPI Extension Application Screening in 2014. The group headed by Suzuki is fascinated with the interactive regulation between the nervous system and immune system and revealed a molecular mechanism by which adrenergic nerves control lymphocyte dynamics. The result was featured in general magazines, and widely attracted the interest of general citizens.

*[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] 1-1).

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] 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 directly observing NETs-HIV complex using super-resolution structured illumination microscopy ([Appendix 2-1] 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 responses ([Appendix 2-1] 2-4). They showed that activation of NLRP3 inflammasome is promoted by microtubule-driven spatial arrangement of mitochondria. The findings explain the functional mechanism of classical gout medication ([Appendix 2-1] 2-5).

*[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 Jumonji domain containing-3 (Jmjd3)-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection ([Appendix 2-1] 3-6). 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] 3-7).

*[4] Toward the development of effective vaccines

For developing optimal vaccines for clinical applications, it is important to understand the mechanisms by which the vaccines affect the 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 the immunogenicity in mice ([Appendix 2-1] 4-8).

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] 4-9).

*[5] New findings about 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] 5-10).

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] 5-11). They also revealed the role of the caecal patch as a major site for generation of IgA-secreting cells.

*[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). Advanced nations are responsible for developing countermeasures against malaria.

Coban group found 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. yoeliiNL parasitemia, anemia, and host survival. They concluded Lipocalin 2 has multiple roles in immunity against malaria ([Appendix 2-1] 6-12).

Coban, K. Ishii, and Yoshioka groups showed with ultra-high-field MRI and multiphoton microscopy that the olfactory bulb is physically and functionally damaged (loss of smell) by Plasmodium parasites during Experimental Cerebral Malaria (ECM). The trabecular small capillaries comprising the olfactory bulb show parasite accumulation and cell occlusion followed by microbleeding, events associated with high fever and cytokine storm. Thus, early detection of olfaction loss and blockade of pathological cell recruitment may offer potential therapeutic strategies for ECM ([Appendix 2-1] 6-13).

*[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] 7-14).

Takeda and Yamamoto groups showed that ATF6β is a host cellular target of the T. gondii virulence factor ROP18 ([Appendix 2-1] 7-15).

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] 7-16).

*[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] 8-17). The group also demonstrated that neutrophil recruitment in inflammatory responses is regulated by PILRα via modulation of integrin activation ([Appendix 2-1] 8-18).

*[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. Investigation of these TLR-inducible genes is important for clarifying the control mechanisms of immune reactions. Akira group has tried to reveal a new concept of post transcriptional immune regulation by mRNA decay. They, together with Standley groups, identified the TLR-inducible gene Zc3h12a as an immune response modifier that has an essential role in preventing immune disorders by regulating IL-6 mRNA degradation ([Appendix 2-1] 9-19), and Zc3h12a was renamed regulatory RNase-1 (Regnase-1) thereafter.

Akira group also 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] 9-20). 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] 9-21).

*[10] Immune regulation and mRNA stabilizing by Arid5a

IL-6 is a key molecule in various autoimmune diseases. Its post-transcriptional regulation has recently been characterized, such as the function of Regnase-1 (see [9]), 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 through binding on its 3' untranslated region, and showed that Arid5a inhibited the destabilizing effect of Regnase-1 on IL-6 mRNA ([Appendix 2-1] 10-22).

*[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.

S. 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 diseases, and presumably microbial immunity, by driving Th17 development ([Appendix 2-1] 11-23).

Kishimoto group demonstrated that Aryl hydrocarbon receptor (Ahr) deficiency in T cells, but not macrophages, suppresses collagen-induced arthritis development as 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] 11-24).

*[12] New finding about immune regulation by the nervous system

As the proverb "Illness starts in the mind" says, it has long been proposed that some aspects of immune responses are affected by activities of the nervous system.

Suzuki group revealed that β2-adrenergic receptors (β2ARs) expressed on lymphocytes regulate their egress from lymph nodes by altering the responsiveness of chemokine receptors CCR7 and CXCR4. In mouse models of inflammation, signals through β2ARs were shown to inhibit trafficking of pathogenic lymphocytes and reduce their numbers recruited into inflamed tissues ([Appendix 2-1] 12-25).

*[13] New findings about regulatory T cells

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

As a pioneer in this field, S. Sakaguchi and his colleagues have achieved important results with Treg developments and functions. They showed Treg-specific cytotoxic T lymphocyte antigen 4 (CTLA-4)　deficiency impairs in vivo and in vitro suppressive function of Tregs. CTLA-4 is a key molecular target for controlling Treg-suppressive function in both physiological and pathological immune responses including autoimmunity, allergy, and tumor immunity ([Appendix 2-1] 13-26). They also found that T cell receptor stimulation-induced epigenetic changes and Foxp3 expression are independent and complementary events required for Treg cell development ([Appendix 2-1] 13-27). Further, they showed Treg cells can render self-reactive human CD8+ T cells anergic in vitro, likely by controlling the costimulatory function of antigen-presenting cells. Their results suggest that Treg cell–mediated induction of anergy in autoimmune T cells is important for maintaining self-tolerance ([Appendix 2-1] 13-28).

*[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 some other IFReC researchers have discovered various immunological and physiological functions of molecules in semaphorin groups.

Kumanogoh group showed the importance of Semaphorin 3A (Sema3A)-mediated signals in dendritic cell trafficking, particularly for passage through the lymphatics, and also identified a previously unknown mechanism that promotes actomyosin contraction at the trailing edge of migrating cells ([Appendix 2-1] 14-29).

Kumanogoh and others also showed that 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] 14-30).

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. Sema4A

gene transfer successfully prevents photoreceptor degeneration in Sema4AF350C/F350C and Sema4A−/− mice. Their findings provide a novel therapeutic target for retinal degenerative diseases ([Appendix 2-1] 14-31).

*[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 for 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] 32).

[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] 33). They also showed the dynamic mechanism of CTLA-4-mediated T cell suppression at the cSMAC by employing the latest bioimaging technique ([Appendix 2-1] 16-34).

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

During an immune response, antigen specific B cells create memory cells, which 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 leads to predisposition of IgG1 memory B cells toward plasma cell differentiation ([Appendix 2-1] 17-35).

*[18] Calcium sensors controlling B cell regulatory function

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 Stromal Interaction Molecules (STIMs) control B cell regulatory function through IL-10 production. Their results from a mouse model of multiple sclerosis established STIM-dependent Store-Operated Calcium (SOC) - influx as a key signal for B cell regulatory function required to limit autoimmunity ([Appendix 2-1] 18-36).

*[19] Analysis for the protein functions in cell biology

Various kinds of proteins including glycoprotein are indispensable elements for the maintenance of homeostasis in mammalian cells. Kinoshita group described a novel molecular 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] 19-37). 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] 19-38).

*[20] Regulation of osteoclast

Osteoporosis, which means 'porous bone' is characterized by too little bone formation, excessive bone loss, or a combination of both, leading to bone fragility (NIH - National Institute of Arthritis and Skin Diseases). Prevention and developing therapeutic approaches 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] 20-39).

During osteoclast differentiation, a shift toward more oxidative metabolic processes occurs. M. Ishii group identified the de novo DNA methyltransferase 3a (Dnmt3a) as a transcription factor that couples these metabolic changes to osteoclast differentiation. They also found that receptor activator of nuclear factor-κB ligand (RANKL), an essential cytokine for osteoclastogenesis, induces this metabolic shift towards oxidative metabolism, which is accompanied by an increase in S-adenosylmethionine (SAM) production ([Appendix 2-1] 20-40).

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.

The IFReC research complex consists of two research buildings, the core instrumentation facility and the animal facility in the same proximate area. The two buildings are connected by covered walkways that allow IFReC members to move freely, and laboratories are designed for the specialties of the 17 research groups including live animal experiments, cell and molecular biology, as well as advanced imaging. The core instrumentation facility and animal facility are run together with the Research Institute for Microbial Diseases, Osaka University. Highly advanced instruments of the core instrumentation facility, maintained in good condition, are available 24 hours for use by the researchers. Also in-house services such as cell sorting, DNA sequencing, electron microscopy and mass spectrometry are provided by skilled technicians of the facility. The animal facility manages a specific pathogen-free (SPF) environment for animals which is indispensable for immunological research. This facility, with its impressive capacity to hold animals, provides researchers with the space for various animal experiments such as infectious experiments, cell transplantation and imaging experiments.

New servers and network system were installed in the IFReC Research Building in 2011 to facilitate the fusion between immunology and informatics. The host university covered the cost to set up the servers. They have been updated a few times and capable of working as a data hub to promote interdisciplinary researches.

The construction in 2012 of the live-imaging facility in the IFReC Research Building is outstanding. The facility contains a high performance 11.7T Magnetic Resonance Imaging (MRI) instrument, a two-photon microscope and an animal room to rear 700 mice in SPF environment. The facility enables the observation of immune phenomena in the same animals over a few weeks. This new experimental system has opened up a whole new perspective in immunology research.

One feature of the IFReC research support system is the Research Planning and Management

Office (RPMO) in administration. In the RPMO five PhD holders with research experience provide various and intensive support for IFReC researchers (See 4-3 and 5-2). When setting up a new laboratory for a newcomer, RPMO helps with layout, installation of equipment, securing animal rooms and chemical administration etc. RPMO also backs up research arrangements. PhD holders in RPMO provide support on procedures of material transfer agreement (MTA), ethical guidelines, possession of pathogens, submitting experiment protocols and others. Since these procedures are often linked, this comprehensive support is vital to promote efficient and effective world-leading research.

In addition, IFReC emphasizes compliance with regulations pertaining to safety measures, use of research funds, and so on. RPMO organizes annual orientations for the researchers both in Japanese and in English and provides information regarding compliance.

As a result, IFReC has succeeded in the establishment of a research complex to guarantee world-leading research where researchers are able to smoothly and effectively promote their research.

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 2-2, 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 well exceeds the WPI program subsidy. IFReC researchers have successfully raised funds for their own research. The total amount of research funds obtained by IFReC researchers is 9,215 million yen since FY2007 including 3,140 million yen for Grants-in-Aid for Scientific Research (KAKENHI), 5,682 million yen for sponsored research, and 455 million yen for others. In addition, Akira obtained a grant from the Funding Program for World-Leading Innovative R&D on Science and Technology (Cabinet Office-sponsored FIRST Program, FY2009-FY2013, 2,520 million yen) as one of the 30 selected core researchers. The grant contributed to the instalment of advanced core instruments in IFReC such as a very high performance MRI instrument (see section 2-2). Other IFReC researchers also acquired large-scale grants as listed in Appendix 2-2. Young, talented PIs also obtained prestigious research grants including from the Funding Program for Next Generation World Leading Researchers (Kumanogoh) and Strategic Basic Research Programs of JST (PRESTO, Smith, Hanayama, and Suzuki).

IFReC also has received a large sum of donations from the private sector including Kishimoto Foundation (650 million yen from FY2010 to FY2015) and pharmaceutical companies. The annual donation from the Kishimoto foundation has greatly contributed to the internationalization of IFReC by supporting overseas researchers to stay at IFReC for the short or long term. It has also enhanced the research capability of IFReC by inviting Kaisho from RIKEN to take an endowed chair as a new PI in 2011. The donation from Chugai Pharmaceutical Co., Ltd. enabled IFReC to install a new laboratory for Nagata, who was invited from Kyoto University in 2015. In order to promote medical/ clinical immunology, as proposed in our application for the WPI support extension in 2014, IFReC has made efforts to develop collaboration with the pharmaceutical industry. IFReC researchers successfully obtained 335 million yen for 54 collaborative researches with industry

including publicly offered grants based on an open-innovation strategy.

2-4. State of Joint Research

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

Published joint papers: Since the establishment of IFReC, 1,090 papers have been published, of which 658 (60%) and 438 papers (40%) are joint papers respectively originating from collaborations with international and domestic research institutes. Most of the collaborations are independently organized by researchers.

CiNet and QBiC: Osaka University concluded cooperative agreements with the National Institute of Information and Communications Technology (NICT) in 2009 and with RIKEN in 2010. Based on these agreements, two research centers, the Center for Information and Neural Networks (CiNet) of NICT and Quantitative Biology Center (QBiC) of RIKEN were opened on or in the vicinity of 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, as such, our collaborations with CiNet and QBiC have been actively advanced. The Yanagida Laboratory was installed at QBiC, and Seymour of CiNet was jointly appointed as a PI of IFReC in April 2014 to develop psychoneuroimmunology.

Domestic Satellites: IFReC has established strong collaborative relationships with the following four domestic research institutions under satellite agreements. Researchers from each of these institutions have been invited as IFReC PIs.

(1) National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN) K. Ishii, Project Leader of Adjuvant Innovation Laboratory of NIBIOHN develops safe and effective vaccines and adjuvants. He has been playing a central role in The Consortium for Innovative Cancer Immunotherapy, in which IFReC promotes immunotherapy research against cancer together with NIBIOHN, Osaka University Hospital and the National Cancer Center Hospital East.

(2) RIKEN Center for Integrative Medical Sciences (RIKEN-IMS) Kurosaki and Saito, group directors of RIKEN-IMS, are concurrently appointed as PIs of IFReC. Kurosaki conducts research mainly at IFReC and Saito at RIKEN-IMS.

(3) Kyoto University S. Sakaguchi, a former director of the Institute of Frontier Medical Sciences of Kyoto University, joined IFReC as a PI in April 2011. His main focus is research at IFReC but he also develops medical applications in collaboration with industry in his laboratory in Kyoto University.

(4) University of Hyogo Hata develops novel technologies for imaging and analysis in collaboration with researchers of University of Hyogo.

Osaka University Hospital: IFReC also has a close collaborative relationship with the School of Medicine and the University Hospital. A sample collection center is jointly operated to stock patients' serum provided through clinics in the Osaka area and to supply them for orphan disease research. Furthermore, the University Hospital has been playing a critical role in translational research

development at IFReC by providing human biological specimens to IFReC researchers and conducting joint clinical trials.

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 2-3, list the awards received and invitational lectures given by the Center's researchers.

IFReC scientists have been awarded for their brilliant achievements and significant impacts on society (Appendix 2-3-1). In particular, Akira (2011) and S. Sakaguchi (2015) were given the Canada Gairdner International Award, 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 for their contribution not only to basic research but also for application to medical care.

Four IFReC researchers, Kishimoto (1991), Akira (2009), S. Sakaguchi (2013) and Nagata (2015) have become foreign associates of the National Academy of Sciences (NAS) of USA, an honor for which a mere 46 scientists researching in Japan have ever been nominated. It explicitly demonstrates that distinguished researchers are gathered at IFReC. Thomson Reuter selected Akira (2008) and S. Sakaguchi (2015) for Citation Laureates, and regularly selects researchers from Akira, S. Sakaguchi and Takeda groups for Most Cited Researchers.

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 contributions to science. Adding them to Kishimoto who was elected as early as 1990, IFReC has three researchers with this very high honor.

The high quality of IFReC is well recognized as written in an article of the Nikkei, "Immunology at Osaka University, a gathering of Nobel Prize-worthy scientists" (March 9, 2016).

Osaka University provided a tenure position to S. Sakaguchi as professor in 2011, and nominated S. Sakaguchi and Akira as Osaka University's Distinguished Professors in 2013.

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.

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

Translational research

(1) Clinical Trial: DNA adjuvant (K. Ishi) As Akira elucidated, adjuvants enhanced effects of vaccines, 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. He successfully completed a phase-I clinical trial in collaboration with Kumanogoh in March 2015, which is the first investigator-driven clinical trial at Osaka University. A phase-II clinical trial in Africa (Burkina Faso) is now in the preparation stage.

Furthermore, the Institutional Review Board (IRB) approved initiation of a trial of the CpG adjuvant

to be used with cancer peptide vaccine for acute leukemia.

The second generation of CpG adjuvants developed by K. Ishii's group has been provided to industry. Translational and reverse-translational researches in clinical trials with various vaccines are conducted by academic institutions and private enterprise.

(2) Clinical Trial: Treg targeted cancer immunotherapy (S. Sakaguchi) S. Sakaguchi found that tumor-infiltrating T cells in a variety of cancers contained a higher frequency of effector regulatory T cells (Tregs) compared with peripheral blood. These effector Tregs dominantly expressed CCR4 and were depressed by anti-CCR4 monoclonal antibody treatment in vitro. An investigator-driven phase II/III clinical trial of a cancer immunotherapy with Treg depression started in February 2016, in which an existing cancer vaccine is used in combination with anti-CCR4 monoclonal antibody. The first trial for an adult T-cell lymphoma patient is in operation at Osaka University Hospital as of March 2016.

(3) Clinical Trial: HVJ adjuvant (Kumonogoh) An investigator-driven clinical trial of Hemagglutinating Virus of Japan (HVJ, Sendai virus) adjuvant to malignant pleural mesothelioma has been in operation since 2016 in collaboration with Prof. Kaneda of Osaka University.

(4) Clinical Trial: Expanded indications for Tocilizumab (Kishimoto and Kumonogoh) Tocilizumab, a human anti-IL-6 receptor antibody, was first developed by Kishimoto as a rheumatoid arthritis therapeutic agent (trade name "Actemura") and known as a blockbuster for Roche-Chugai Pharmaceutical Group (more than 100 million USD a year sold) and is the first antibody drug developed in Japan to be approved for use by the rest of the world. Indications for Tocilizumab have recently been expanded. It has been shown that Tocilizumab is effective for many other refractory autoimmune diseases. Kumanogoh has conducted clinical trials of Tocilizumab in adult onset Still's disease since 2014, and in systemic sclerosis since 2015. Clinical trials of Tocilizumab for diseases such as diabetes, cardiac infarction, Takayasu arteritis, neuromyelitis optica, polymyalgia rheumatica, infection of human immunodeficiency (HIV) virus and others are in progress around the world. Tocilizumab is extending its applicability to other diseases.

Collaboration with Industry

IFReC has conducted collaborative research with industry in order to develop medical/clinical immunology (See 2-3).

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 2-4, list and describe media coverage, press releases, and reporting.

IFReC has executed many PR and outreach activities in various ways such as lectures, science cafes, press releases and publishing. Since the establishment of WPI outreach policy in 2010, IFReC has become more aware of various types of stakeholders, including tax payers and students, to be accountable for IFReC research outcomes and to enhance citizen's understandings. Our unique activities bulletized below have also contributed to improve IFReC visibility and people's science literacy.

Publishing

- IFReC has put out media releases to the Japanese press club 10-15 times per year, resulting in a high rate of publication in major newspapers.
- IFReC published the original leaflets for introducing IFReC and WPI program (both in English and Japanese), and more than 10,000 copies were distributed to school students. These leaflets reflect the latest research information, and have been revised every year.
- Books authored by IFReC PIs or staff for general public were published and have placed highly on the bestselling ranking in the life science field.
- An IFReC RPMO staff published an article describing the science communication in the IFReC administrative office, and it has been downloaded more than 1400 times.

To general citizens

- IFReC has organized/co-organized "Café on the Edge", a science café series introducing the latest researches in IFReC, and has welcomed over 1000 participants in total.
- A 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.
- IFReC has a home page and Facebook page, and transmits various information enhancing IFReC visibility.

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. "The mystery of life visualized by advanced live imaging technique", an open school for high school students was held in August, 2010.
- Director Akira gave a memorial lecture to "Super Science High Schools (SSH)" students at "The Congress of SSH" in Kobe in August, 2011. Other IFReC researchers joined the mini seminars as lecturers.
- IFReC researchers delivered talks in junior high schools, high schools and a college. Some talks included the topic regarding career development to of researchers.
- IFReC was featured as "World Leading Institute in Japan" in a popular supplementary reader for high school students. Moreover, IFReC has decided to cooperate in producing a TV program for high school students on NHK educational TV after 2013.
- Osaka University joined edX, one of the major Massive Open Online Course (MOOC) platforms. IFReC researchers provided lectures as the first course of OsakaUx (edX courses by Osaka University) with the help from the Teaching and Learning Support Center of Osaka University. Over 12,000 people enrolled in and enjoyed the course.

3. Interdisciplinary Research Activities **(within 3 pages)**

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

IFReC is aiming at creating interdisciplinary domains between immunology and imaging and also immunology and informatics for comprehensive understanding of immune dynamism. Therefore, IFReC has implemented several strategic measures as follows.

IFReC colloquia: A series of colloquium has been held bimonthly. Open only to IFReC members, speakers from 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 is organized for participants including young scientists and Ph.D. students to exchange their ideas and discuss future collaborations in an informal setting.

Research Support Programs: IFReC established two programs to facilitate the fusion of different research fields by providing financial support for three years. One program is the "Research Support Program for Combined Research Fields" and the other is the "Dual Mentor Program". The former program encourages IFReC researchers with different specialties or research backgrounds to collaborate on new projects. The latter program supports graduate students or young post-doctoral fellows to engage in interdisciplinary projects under the supervision of two PIs from different disciplines. The projects were selected by open application system and are evaluated every year by IFReC PIs based on a presentation. Since 2009, a total of 26 research projects 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 by providing semi-independent positions. 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 from IFReC and share research facilities with the parent laboratories. Three units were set up in total.

Live immune-imaging facility: (See 2-2) was constructed to promote fusion of immunology and imaging, and has made it possible to observe and track 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. Having this new experimental setup in close proximity, IFReC researchers enjoy opening up new vistas in immunological research. The number of fusion research projects using this facility is steadily increasing and some of the projects have successfully reached the publication stage.

Collaboration with external institutions: As detailed in 2-4, IFReC has promoted collaboration with the Center for Information and Neural Networks (CiNet) of NICT and the Quantitative Biology Center (QBiC) of RIKEN. Some IFReC researchers are concurrently affiliated with CiNet and some established a research activity base at QBiC. These collaborations have had a great effect on creating new interdisciplinary domains in IFReC.

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

"Study Session on Mathematical Modeling in Biology and Related Topics" has been

voluntarily organized by a member of a fusion research unit. It is a series of seminars to share knowledge of mathematical and theoretical biology among researchers from a wide range of fields, not only immunology, such as theoretical biology, mathematics, physics, and robot science from both inside and outside of the University. The participants, including Director Akira, frankly discuss the topic and deepen understanding. It has been held 45 times and is gaining an impressive reputation among the researchers in interdisciplinary fields. The English version of the session is now creating a new network among international researchers on campus.

The Osaka Immunology School was initiated by Kumanogoh and Takeda with the cooperation of a pharmaceutical company to promote interaction between clinical and basic researchers. It was held seven times by the end of FY2015.

A seminar series titled **"Immunology Frontier: From Bench to Bed and from Bed to Bench"** has also been started due to the initiative taken by S. Sakaguchi.

Proposed by IFReC overseas researchers, regular gatherings called **Happy Hour** were voluntarily organized in 2012, with support from RPMO, for interaction among IFReC researchers. It provided a good opportunity to deepen communication with each other in an informal setting. In fact chatting at Happy Hour triggered a new interdisciplinary research project. After five Happy Hour gatherings this was transformed into a center-wide gathering held after the IFReC colloquium.

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.

The recent trend for papers produced at IFReC is an increase in the number of interdisciplinary research papers, as indicated in Appendix 3. The 40 papers described in Appendix 2-1 include the 15 papers in interdisciplinary research fields in Appendix 3. The interdisciplinary researches ("Fusion Researches") between immunology, bioimaging, and bioinformatics have already joined the mainstream in IFReC. The representative results are described below.

Multi-photon microscopy for observation of immune reactions: Using two-photon microscope, M. Ishii group studied osteoclast dynamics and bone homeostasis (Appendix 3-6, 14, 20). The method was used for the observation of the olfactory bulb, which was physically and functionally damaged (loss of smell) by Plasmodium parasites during Experimental Cerebral Malaria (ECM) (Appendix 3-2).

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 (Appendix 3-5). Yoshioka and Kikuchi groups successfully detected cellular gene expression by 19F-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 3-10). Yoshioka and Coban groups observed the olfactory bulb damaged by Plasmodium parasites during ECM (Appendix 3-2).

Laser Raman Microscopy for immune cell: Smith group demonstrated spatial control by scanning a laser beam to write characters in gold inside a cell. Such light-based control of the

intracellular particle generation reaction also offers avenues for in-situ plasmonic device creation in organic targets (Appendix 3-1). Using a system elaborated by Smith group, Coban group monitored changes in erythrocytes and plasma during Plasmodium infection in mice (Appendix 3-7).

Immunology studies using other imaging technologies: Using super-resolution structured illumination microscopy, Akira group showed that neutrophil extracellular traps capture HIV-1 (Appendix 3-11). They also succeeded in observing NLRP3 inflammasome formation (Appendix 3-4).

Using confocal time-lapse video-microscopy, Kumanogoh group showed plexin-A1 is crucially involved in the entry of dendritic cells into the lymphatics (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 (Appendix 3-16).

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 paper from Standley lab (Katoh & Standley, Mol Biol & Evol 30:772-780, 2013) has the best citation score through the nine years' achievements of IFReC, and was ranked Top 0.01% Paper (InCites by Thomson Reuters ©).

Standley group covers a wide range of aspects of structure/function relationship of important molecules in immune system, which is most beneficial to many findings by Akira group. 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 plays crucial roles not only in bone metabolism but also in differentiation of neutrophils (Appendix 3-8). Regnase-1 is essential for preventing aberrant effector CD4+ T cell generation cell autonomously (Appendix 3-3). Akira and Standley 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 (Appendix 3-12). Collaborating with Standley group, Yamamoto and Takeda groups generated highly polymorphic parasite-derived kinase ROP16-deficient type I parasites, and found a severe defect in parasite-induced Stat3 activation, resulting in enhanced production of IL-6 and IL-12 p40 in the infected macrophages (Appendix 3-18).

S. Sakaguchi group showed that Treg cell development was achieved by the combination of two independent processes, the expression of Foxp3 and the establishment of Treg cell-specific CpG hypomethylation pattern. The calculation for DNA methylation was done by bioinformatics methods using the super computer system (Appendix 3-9).

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 4-1, give the number of overseas researchers among all the Center's researchers, and the yearly transition in their numbers.

IFReC recruited active, talented, young researchers from overseas as PIs. A number of researchers of world-top class have taken the opportunity to visit IFReC on the occasion of seminars, international symposia and the Winter School (see 4-4), which is co-organized by IFReC and Singapore Immunology Network (SIgN). Furthermore IFReC has accepted many renowned researchers for the short or long term to promote collaborative research with IFReC researchers.

Participation as PIs: Diego Miranda-Saavedra, a bioinformatics specialist, joined IFReC as a junior PI (led Bioinformatics and Genomics group) in 2010. His group published 19 papers in three years until he was promoted to take up a post of reader at Institute of Cellular Medicine, Newcastle University, UK in 2013. **Daron Standley**, a bioinformatics specialist, joined IFReC as a junior PI (led Systems Immunology group) in 2008, was promoted to a PI in 2014 and took up a joint appointed post of professor at Kyoto University by a cross-appointment agreement between Kyoto University and Osaka University in 2015. As a senior PI, **Fritz Melchers**, a world-famous immunologist and the former director of the Basel Institute of Immunology, participated in IFReC as an overseas PI of IFReC. He has stayed at IFReC four times to participate to IFReC international symposia or other meetings to exchange views on various aspects of immunological research with Akira and other PIs.

Resident Research by joint researchers: Michel C. Nussenzweig, who is a professor of The Rockefeller University Howard Hughes Medical Institute (USA), a member of National Academy of Sciences of USA, and a famous researcher on molecular aspects of the immune system's innate and adaptive responses stayed for collaboration with Kurosaki for 10 days in 2012. IFReC accepted a biochemist, **Michel L. Tremblay** (professor and center director, McGill University Rosalind and Morris Godman Cancer Research Center, Canada) during his sabbatical leave mainly for collaboration with Kurosaki and Miranda-Saavedra for 10 months in 2011. **Florent Ginhoux** (Senior Principal Investigator, Singapore Immunology Network (SIgN), Singapore) stayed for collaboration with Kaisho for a month in 2014. He also exchanged views on the Winter School with IFReC, which IFReC jointly organizes with SIgN. **Khromykh Alexander**, a current vice director of Australian Infectious Diseases Research Centre of the University of Queensland, Australia stayed to study virus-host interaction with Akira for 5 months in 2008.

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 4-2~4, 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 continues to attract many capable young researchers

as indicated by the fact that IFReC has received 113 postdocs (42 Japanese and 71 other nationals). IFReC has employed 49 postdocs out of 318 applicants through international open recruitment in total. Overseas researchers made up 94% of the applicants and 39 of the employed postdocs (Appendix 4-2). The Kishimoto Foundation Fellowship has greatly contributed to the recruitment of overseas researchers to IFReC. Since the establishment of the Fellowship in 2009, 25 overseas researchers from 12 countries have been employed and 19 from 12 countries have been accepted to stay at IFReC for the short term.

In principle, the employment term for postdoctoral researchers in IFReC is limited to three years, and can be extended only when IFReC promotes them to an assistant professor or a higher position. Sixteen postdocs including 6 overseas postdocs have been promoted to assistant professors in IFReC and then one further to an associate professor. As listed in Appendix 4-4, suggesting that their research accomplishments and experiences in IFReC were highly appreciated, eleven postdocs who left IFReC have found assistant professor positions, and two overseas postdocs took a position of an associate professor in their country of origin. A good example is **Nam Trung Nguyen**, who joined IFReC as a post-doc in 2009 and was promoted to an assistant professor at IFReC in 2013. He moved to his country as a group leader at National Key Laboratory of Gene Technology, Institute of Biotechnology (IBT), Vietnam Academy of Science and Technology (VAST) of Vietnam in 2013. He continues to collaborate with Kishimoto and visited IFReC for 3 months in both 2013 and 2015. Twenty-two out of 57 overseas postdocs (39%) have found new positions in Japan after IFReC. It is notable that 15 associate professors in their early forties were promoted to professors or group leaders in their new institutions.

Active recruitment of young researchers as PIs such as Suzuki, Hanayama, Yamamoto, Smith, resulted in the average age of PI being maintained around 55.0 years as of March 2016.

The percentage of overseas researchers at all levels has satisfied the WPI target level of 30% during the WPI program except in two years (Appendix 3-1). The overseas researcher ratio has recently decreased because overseas researchers, including a PI, left IFReC for promotion in the previous years. It was, however, very difficult for IFReC to recruit overseas researchers because IFReC could only offer them positions with an employment term limited to the end of the WPI support. IFReC and Osaka University have been working out future strategies to sustain IFReC after WPI support and have started to prepare formalities, which will enable long term employment beyond the current limitation. IFReC will restart actively recruiting to increase the number of international researchers soon.

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

- In Appendix 4-5, describe the state of the Center's agreements concluded with overseas satellites and other cooperative organizations.

At the beginning of IFReC establishment (2007), IFReC formed contracts as satellites with six world famous bioimaging institutions in USA 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 (NIAID) and University of California, San Francisco (UCSF). The partnerships ended successfully with the publication of 20 collaborative papers. IFReC PIs, M. Ishii

and Suzuki were recruited from NIAID and UCSF, respectively.

As listed in Appendix 4, IFReC exchanged cooperative research agreements with four institutions or organizations. Above all, one of the most successful cooperative activities with overseas institutes has been "NIF Winter School on Advanced Immunology" jointly organized with Singapore Immunology Network (SIgN). The School has been organized every winter since 2012 and has succeeded in globally fostering young researchers in the next generation, in raising the international visibility of IFReC and in promoting its internationalization (details described in 4-4).

4-2. Center's Record of Holding International Symposia, Workshops, Research Meetings, Training Meetings and Others

・ In Appendix 4-6, 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 4-6. Topics of these events covered diverse research fields including immunology, imaging, bioinformatics, and parasitology. Active communication among participants is expected to enhance their collaborations 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 IFReC young researchers with guest speakers.
- IFReC co-organized five international joint symposia with overseas organizations (Singapore 1, Korea 2, China 1, New Zealand 1).
- IFReC also co-organized the international symposia "Towards Comprehensive Understanding of Immune Dynamism (TCUID)" with FIRST Program, AKIRA Project in 2011, 2012, and 2013. The participants from different research fields ranging from immunology to bioinformatics enjoyed lively discussion beyond individual fields of expertise.
- The Kishimoto Foundation Lectures by World Leading Scientists have been co-organized six times by IFReC and Research Institutes for Microbial Diseases at Osaka University.
- IFReC and Bristol-Myers Squibb co-organized "Cancer Immunotherapy Forum" in 2014 for the acceleration of cancer immunotherapy-one of IFReC's future goals.
- In FY2014 and FY2015, IFReC organized the international symposia "Immunology at the Forefront". Each symposium provided a forum for the newest developments in wide-ranging areas of immunology. In particular, the symposium in FY2015 was organized to follow the 5th NIF Winter School by IFReC and Singapore Immunology Network, providing an opportunity for young researchers to form a global research network.

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.

Research planning and management office (RPMO) together with the general affairs section in the

administration office provides overseas researchers with various support for research (details are shown 5-2) and daily life. For daily life, bilingual staff members help overseas researchers to settle in Japan by finding rooms to stay, opening bank accounts, obtaining cellular phones etc. The staff also responds to inquiries on family matters such as children's education, visa application, and emergencies. IFReC webpages provide information necessary for life in Japan, which is useful for overseas researchers who are already settled as well as those who have been newly accepted and are preparing for their new lives in Japan. IFReC offers two levels of weekly Japanese language classes by a qualified Japanese teacher to encourage communication among overseas and Japanese researchers, other staff and locals. The classes are held inside the IFReC building in the evening, which makes it easier for researchers to balance the classes with their work. Along with the classes, Japanese cultural exchange events are held to introduce Japanese culture. According to questionnaires, IFReC overseas researchers are quite satisfied with these approaches.

For research support, RPMO organizes annual orientation in English, which consists of compulsory lectures providing information on how to conduct experiments and use the facilities, and to ensure that overseas researchers also are aware of regulations and rules. Grant information, and application forms when requested, are translated by RPMO staff. PhD holders in RPMO are consulted for grant applications. Support is also provided for completing the experiment protocols or forms necessary to conduct experiments.

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. Twenty-two 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, to discuss ideas and forge 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 (from about 50 countries) ranging from PhD students to postdoctoral fellows within three years of receiving their PhD, and about 50 applicants are selected to participate. 251 young researchers have participated to date. The WS program lasts 4 to 5 days and consists of lectures by world top immunologists and presentations by participants. 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 have 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. This top-down decision-making system is a unique management system compared with that of 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.

N. Sakaguchi was appointed as new administrative director (specially appointed professor) after Kodama in April 2015. N. Sakaguchi (M.D., Ph.D.) is an immunologist, and has experience in university management as a former vice president of Kumamoto University. Under N. Sakaguchi, administrative staff provides effective support for researchers to devote themselves to their research. Almost all administrative support staff are able to communicate in English with non-Japanese members. Some staff members have a Ph.D. and research experience and can understand IFReC researchers' needs. The Research Planning and Management Office (RPMO) is organized as part of the administrative section. Its focus is on tasks related to WPI and provides essential support to accomplish the four WPI missions. RPMO manages seminars, symposia, outreach activities, intellectual property, safety and hygiene issues etc. Also use of English in the center is enhanced by positioning a native English translator in the RPMO.

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.)

The existing support system of the host university did not cover issues that arose when accomplishing WPI missions. The measures taken were pioneering in the university and have been distributed as ripple effects.

(1) To assist international researchers in the acquisition of MEXT grants-in-aid for scientific research (KAKENHI), IFReC initiated an annual orientation in English in 2011. Osaka University recognized its importance and effectiveness and started to host a similar version on a University level. Several international researchers at IFReC contributed to the orientation as lecturers to provide practical information for the application and acquisition of KAKENHI.

(2) RPMO in IFReC (see 5-2) edited "Manual for organizing Science Café" and provided it to departments of Osaka University and other universities to help with their outreach activities.

(3) Using RPMO as a role model, the University Support Office for Large-Scale Education and Research Projects launched its URA team to consolidate a university research support system.

(4) IFReC and the Research Institute for Microbial Diseases have co-organized the annual orientations for researchers who use genetically modified organisms, pathogens and animals.

Sessions on human genome analysis researches are open to all researchers at Osaka University by request from the research ethics committee of Osaka University.

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

(6) The Liaison Office (LO), which is a virtual office in administration, has bilingual staff that provides support for international researchers and their families on visa-related procedures, accommodation, and daily life. The experience and knowledge accumulated by LO has had a substantial influence on the Osaka University Support Office to improve the service for international staff and students of the university.

(7) In FY2014, IFReC used the cross-appointment system for an international PI at IFReC, by agreement between Osaka University and Kyoto University. This was one of the earliest cases. This system serves to establish a better international research environment and to accelerate interdisciplinary research at IFReC.

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 5-1, describe the concrete measures being taken by the host institution.

(1) Osaka University established CiNet and QBiC with NICT and RIKEN in and near Suita Campus, forming a remarkable complex of integrating imaging technologies in Japan. This greatly helps to advance imaging technologies of IFReC, which is necessary for interdisciplinary research.

(2) Osaka University respects the top-down decision making system of IFReC (see 5-1) on issues concerning IFReC management.

(3) Osaka University built the Integrated Life Science building (2009) and provided a site for an IFReC research building (2011). The buildings enable the assembly of IFReC's core researchers.

(4) When building the IFReC animal resource center for specific pathogen-free animals in 2009, the university created a new lending system to financially support the center.

(5) All the indirect expenses in the WPI budget during 2007-2010 were allocated to IFReC.

(6) Osaka University responded to a request from IFReC and other faculties and built a new international-standard accommodation facility (Kasugaoka House).

(7) 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 with visa applications. The Support Office has assisted IFReC to accept many researchers from abroad.

(8) Since the successes of capable international researchers are important to promote internationalization of the University, Osaka University provided tenure positions for one professor and two associate professors to IFReC international researchers in 2015. Osaka University President is preparing to provide tenure positions to IFReC core members after WPI support.

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

・ To Appendix 5-2, 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 a WPI research center and started operations during the latter half of the Osaka University Medium-term Plans for the 1st Period (FY2004 - FY2009). To achieve world premier status, IFReC was given highest priority in the university's strategy. As shown in Appendix 5-2, in the 2nd Medium-Term Plan (FY2010-2015), the university positioned "Immunology being promoted mainly by the leading role of the world premier research center" as one project for emphasis. Thus, IFReC is one of the top priorities for the development of the university.

(2) In 2011, the Osaka University Institute for Academic Initiatives (IAI FY2012-FY2015) was set up to promote interdisciplinary medium- and long-term education and research, and strategies for a comprehensive future. The IAI aims to cultivate research organizations that will become new WPI-like research centers, and regards IFReC as the role model (Appendix 5-2).

(3) In "Osaka University Vision 2021" announced in 2016, IFReC policy is clearly stated as "Osaka University firmly determined to sustain Immunology Frontier Research Center (IFReC) of World Premier Initiative (WPI)". Establishment of world top-class research centers based on strength and uniqueness of Osaka University and development of multidisciplinary and multi-direction research is indispensable for Osaka University to be one of the world's best research universities. It is also described in the vision as "the WPI center, which has prominent research ability and advanced equipment, and which Osaka University is proud of, take its leading role with usage/research centers".

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 5-3, give the transition in the number of female researchers.

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

(2) The original programs to enhance interdisciplinary research at IFReC (sections 3-1 and 3-2) were established 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:

a. Targeted recruitment advertising for a number of excellent female students who participated in annual Winter School in January;

b. Publicizing the university's support systems such as day care centers within the premises of Osaka University for child welfare;

c. A young, talented female researcher was employed as the leader of a fusion unit (section 3-1), and is expected to be a PI in the future.

(4) A series of seminars and lectures for staff development have been held since 2013. Female speakers with outstanding careers were invited to encourage women to become researchers.

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.

IFReC organized a retreat in Nov 2012. This event served as a great opportunity to get to know colleagues and their research projects. IFReC technicians and secretaries were also encouraged to participate and attend the workshop to introduce the WPI program. Through this approach, they were motivated to support world leading research center.

RPMO organizes "Immunology Lecture Series". It was initiated in 2013 as staff development to provide fundamental knowledge of immunology to IFReC research support staff such as technicians, secretaries and other administrative staff. A young researcher at IFReC is invited as a speaker to give a talk about the basics of their research up to cutting-edge research in an easy-to-understand manner. The lecture is also open to all Osaka University members. This event serves as effective measure to develop IFReC research support staff as members of a WPI center, to publicize IFReC in Osaka University, as well as to give educational value to the young speakers selected from IFReC researchers. This event was proposed for "Osaka University's Improvement Idea Awards Contest" as an activity model and was admirably selected for the award. Another activity for staff development is science communication seminars. Guest lecturers from the National Museum of Emerging Science (Miraikan) talked about helpful skills to interpret one's research effectively.

To solidify the foundation for IFReC's continued development and to ensure the independence of IFReC management and research beyond the end of the WPI grant in 2017, a new contract between academia and industry in the form of a comprehensive collaboration contract is planned to be concluded with Chugai Pharmaceutical Co., Ltd. for one billion yen a year for 10 years (2017-2026). The Open Innovation Laboratory is also planned to promote the establishment of a joint research department or cooperative laboratory based on joint research between IFReC researchers and industry in IFReC or within Osaka University.

7. Center's Response to Results of FY2015 Follow-up (including Site Visit Results)

* Describe the Center's Response to Results of FY2015 Follow-up. Note: If you have already provided this information, please indicate where in the report.

(Comment from the program committee)

1. For future challenge, IFReC should commit to leading translational and clinical research in immunology. This may require additional time, effort, and a substantial amount of financial support. IFReC will need to learn from the Osaka University's past successful experience in transitioning from bench to bedside to develop novel therapies.

2. Osaka University is expected to create a new system/rules including for (intellectual interest) IP, freedom of research, etc. before entering into close interaction with private enterprises.

(Reply from IFReC)

IFReC replies to the above two comments as follows;

Tocilizmab (Actemura), an interleukin-6 receptor inhibitor is an example of remarkable success for product development from outcomes of fundamental science at Osaka University. For this success, it was indispensable to have strong and close collaboration with a pharmaceutical company. In order to promote translational and medical/clinical research, IFReC needs to be supported financially and technologically by industry and to collaborate with them more tightly than ever before.

At the follow-up meeting in October 2015, Osaka University expressed a policy to maintain IFReC after WPI support, where IFReC will be further strengthened by a close collaboration with industry with their financial and technological support using a new framework of industry-university collaboration, called "Handai-Style", and revealed that IFReC and Osaka University had already begun negotiations for such collaboration with a certain company at the time. Osaka University signed a comprehensive collaborative agreement with Chugai Pharmaceutical Co., Ltd., and will be provided one billion yen per year for 10 years from FY2017 (see 2-2 in the Progress Plan).

Collaborative research based on outcomes of fundamental research have not been carried out with companies so far, even if they are excellent as fundamental research, because most projects are not matured as seeds for applied research. Companies provide researchers with costs only for specific research projects, and require outcomes of the specific projects in return for the provided grants.

In the agreement, IFReC provides the company with the first right of refusal in return for the provided grants. It enables the disclosure of research achievements preferentially to the industry as permitted and to give priority for application to do collaborative research with IFReC researchers, patent application and licensing. In this framework, it became possible to carry out collaboration with industry beyond the range of the conventional university-industry collaboration, and to realize collaboration seamlessly from fundamental research with a long-term perspective, in which seeds for applied research are created, to applied research covered by the conventional collaborations. Because the number of collaborations to be made with the company within the limits of the proportion of the provided grants to the total expenses for IFReC's activities, IFReC will willingly accept collaboration with other companies for research achievements at IFReC that are not selected by the company. In addition, it should be mentioned that Osaka University and IFReC gave sufficient consideration to, and concluded with the industry, the handling of intellectual property in the collaborations.

World Premier International Research Center Initiative (WPI)

Appendix 1-1. FY 2015 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 Appendix1-1a, "Biographical Sketch of a New Principal Investigator".

<Results at the end of FY2015>

Principal Investigators Total:27

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* (63)	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* (76)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	70%	0%	30%	0%	01/11/2007	Usually stays at IFReC	
Hitoshi Kikutani* (65)	Professor, Research Institute for Microbial Diseases, Osaka University	MD, PhD (Immunology)	70%	10%	20%	0%	01/10/2007	Usually stays at IFReC	
Taroh Kinoshita* (64)	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* (49)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	50%	0%	0%	50%	01/10/2007	Usually stays at IFReC	
Kiyoshi Takeda* (49)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	70%	0%	0%	30%	01/11/2007	Usually stays at IFReC	
Hisashi Arase* (50)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	95%	0%	0%	5%	01/10/2007	Usually stays at IFReC	
Shimon Sakaguchi* (65)	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	50%	10%	17%	23%	01/12/2007	Usually stays at IFReC	
Takashi Saito* (65)	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* (60)	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	

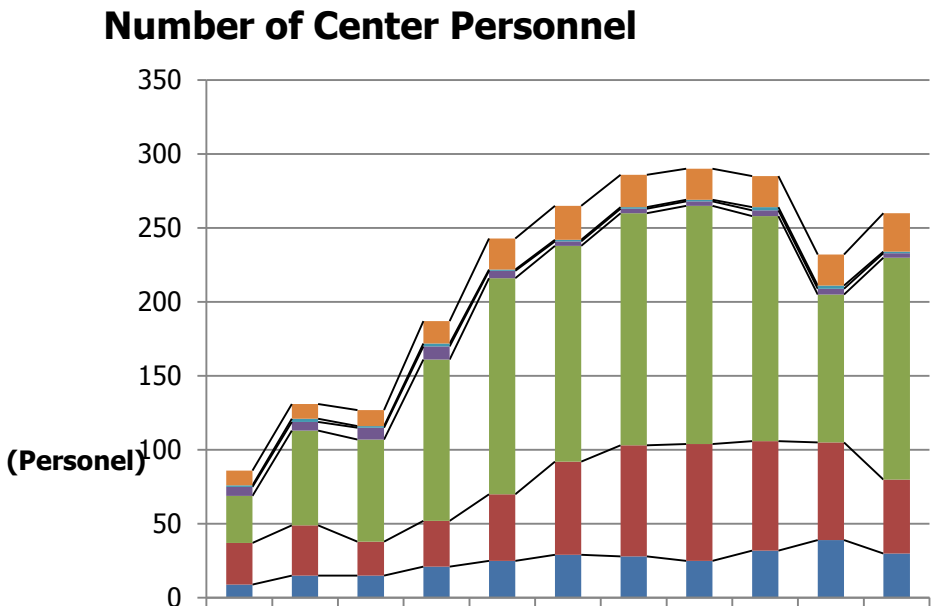
Fritz Melchers* (79)	Max Planck Fellow	PhD (Immunology)	10%	0%	10%	80%	01/10/2007	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	
Toshio Yanagida* (69)	Professor, Graduate School of Frontier Biosciences, Osaka University	PhD (Molecular imaging)	25%	0%	65%	10%	01/11/2007	Usually stays at IFReC	
Yoshichika Yoshioka* (62)	Professor, WPI Immunology Frontier Research Center, Osaka University	DSc (Biophysics)	100%	0%	0%	0%	01/02/2008	Usually stays at IFReC	
Yutaka Hata* (54)	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 (48)	Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Chemistry)	20%	0%	80%	0%	01/10/2008	He visits his laboratory at IFReC once a week.	
Jun Hatazawa* (62)	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Nuclear Medicine)	5%	5%	45%	45%	16/01/2009	Usually stays at IFReC	

Masaru Ishii (42)	Professor, Graduate School of Frontier Biosciences, Osaka University	MD, PhD (Bioimaging)	30%	0%	70%	0%	01/12/2008	Usually stays at IFReC	
Kazuya Kikuchi (50)	Professor, Graduate School of Engineering, Osaka University	PhD (Chemical Biology)	28%	2%	50%	20%	01/08/2009	Usually stays at IFReC	
Cevayir Coban (43)	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 (41)	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* (47)	Project Leader, National Institute of Biomedical Innovation (NIBIO)	MD, PhD (Immunology, Vaccine Science)	5%	5%	85%	5%	01/11/2007	He visits his laboratory at IFReC once a week.	
Tsuneyasu Kaisho* (56)	Professor, Department of Immunology Institute of Advanced Medicine Wakayama Medical University	MD, PhD (Immunology)	5%	5%	70%	20%	01/03/2011	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	

Kazuhiro Suzuki (40)	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 (41)	Professor, Department of Immunology Kanazawa University Graduate School of Medicine	MD, PhD (Cell Biology)	5%	5%	70%	20%	01/10/2011	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	
Masahiro Yamamoto (37)	Professor, Research Institute for Microbial Diseases, Osaka University	PhD (Immunology)	90%	10%	0%	0%	01/04/2012	Usually stays at IFReC	
Nagata Shigekazu* (66)	Professor, WPI Immunology Frontier Research Center	PhD (Science)	100%	0%	0%	0%	01/04/2014	Usually stays at IFReC	
Seymour Benjamin John (43)	NICT Invited Executive Researcher and Wellcome Trust Intermediate Clinical Fellow (Cambridge University)	PhD (Neurological Science)	20%	5%	65%	10%	01/04/2014	He visits IFReC several times/year to attend symposia, etc. to contribute to research at IFReC. He regularly communicates with us by emails.	

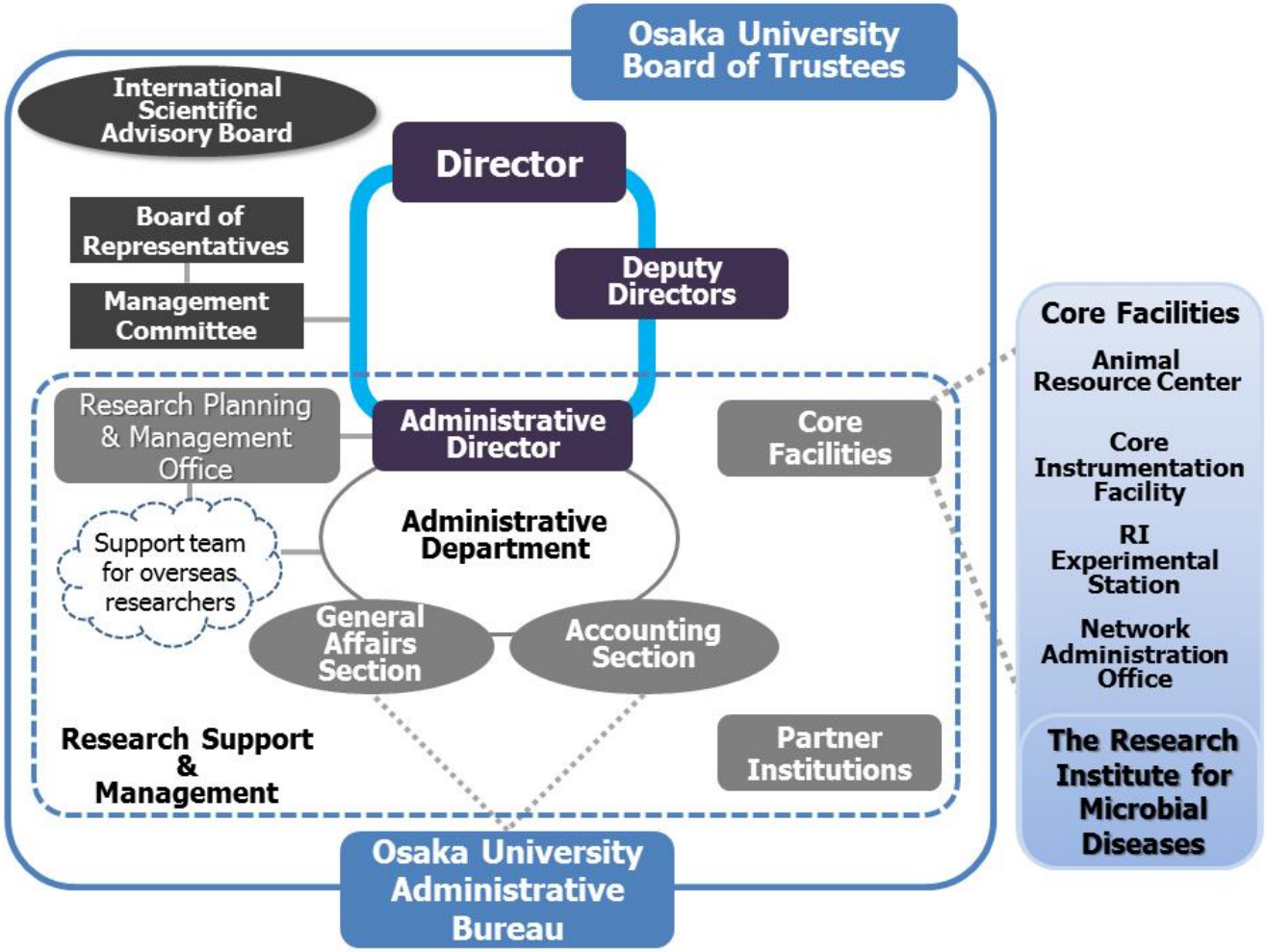
World Premier International Research Center Initiative (WPI)
Appendix 1-2. Annual Transition in the Number of Center Personnel

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



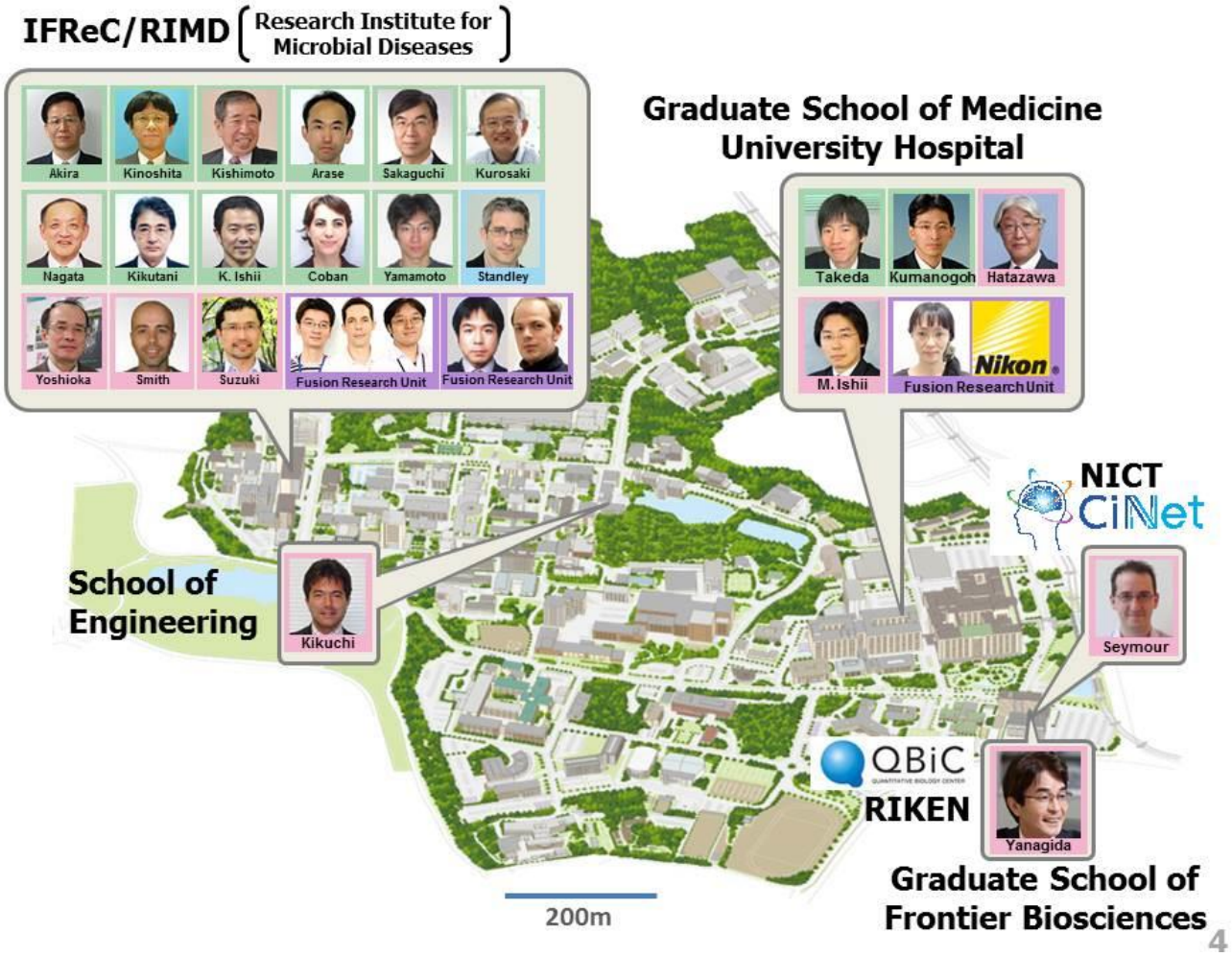
	(At beginning)	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	(Final goal)
PI : Researchers from within host institution	10	10	11	15	21	23	22	21	21	21	26
PI : Foreign researchers invited from abroad	1	2	1	2	1	1	1	1	2	2	1
PI : Researchers invited from other Japanese institutions	6	6	8	9	5	3	3	3	4	4	3
Other researchers	32	64	69	109	146	146	157	161	152	100	150
Research support staffs	28	34	23	31	45	63	75	79	74	66	50
Administrative staffs	9	15	15	21	25	29	28	25	32	39	30

World Premier International Research Center Initiative (WPI)
Appendix 1-3. Diagram of Management System



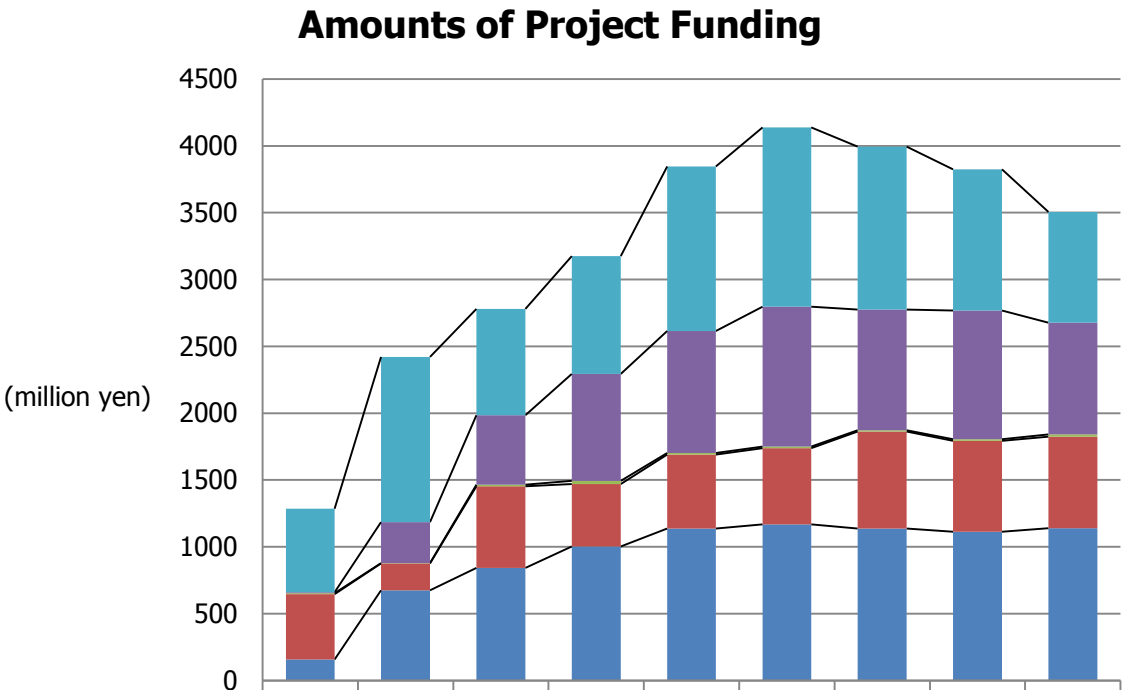
World Premier International Research Center Initiative (WPI)
Appendix 1-4. Campus Map

Osaka University Suita campus



World Premier International Research Center Initiative (WPI)
Appendix 1-5. 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	FY2014	FY2015
Research projects	625	1237	794	882	1230	1342	1219	1057	829
Equipment	8	305	521	800	912	1046	903	962	837
Travel	7	4	12	23	14	12	9	11	15
Project activities	489	201	609	467	553	572	727	680	686
Personnel	157	674	843	1004	1136	1167	1136	1114	1139

Appendix 1-6. FY2015 Project Expenditures (the exchange rate used: 1USD=110 JPY)

i) Overall Project Funding

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	28.2
	Principal investigators (no. of persons):22	140.9
	Other researchers (no. of persons):165	566.4
	Research support staffs (no. of persons):66	213.6
	Administrative staffs (no. of persons):18	86.4
	Total	1035.5
Project activities	Gratuities and honoraria paid to invited principal investigators	0.0
	Cost of dispatching scientists (no. of persons):12	27.3
	Research startup cost (no. of persons):1	9.1
	Cost of satellite organizations (no. of satellite organizations):	0.0
	Cost of international symposiums (no. of symposiums):1	22.7
	Rental fees for facilities	12.7
	Cost of consumables	1.8
	Cost of utilities	59.1
	Other costs	490.9
	Total	623.6
Travel	Domestic travel costs	2.7
	Overseas travel costs	3.6
	Travel and accommodations cost for invited scientists (no. of domestic scientists): (no. of overseas scientists):7	4.5
	Travel cost for scientists on secondment (no. of domestic scientists):5 (no. of overseas scientists):3	2.7
	Total	13.5
Equipment	Depreciation of buildings	143.6
	Depreciation of equipment	617.3
	Total	760.9
Other research projects	Projects supported by other government subsidies, etc.	56.4
	Commissioned research projects, etc.	374.5
	Grants-in-Aid for Scientific Research, etc.	322.7
	Total	753.6
Total		3187.2

Ten thousand dollars

WPI grant	1190
Costs of establishing and maintaining facilities	
Establishing new facilities (Number of facilities: , m²) Costs paid:	
Repairing facilities (Number of facilities: , m²) Costs paid:	
Others	
Cost of equipment procured	57.3
Individual Ventilation Cage System: Number of units: 15 Costs paid:	50
NanoDrop One microvolume Spectrophotometer Number of units: 1 Costs paid:	1.8
All-in-one anesthesia apparatus for small animals (combined with recovery unit): Number of units: 2 Costs paid:	0.9
Beads based cell smasher: Number of units: 1 Costs paid:	0.9
Central experiment bench: Number of units: 3 Costs paid:	1.8
Cell Counter: Number of units: 1 Costs paid:	0.9
Others	0.9

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):5	
	Research support staffs (no. of persons):2	
	Administrative staffs (no. of persons):0	
	Total	22.7
Project activities		0.0
Travel		0.0
Equipment		0.0
Other research projects		5.5
Total		28.2

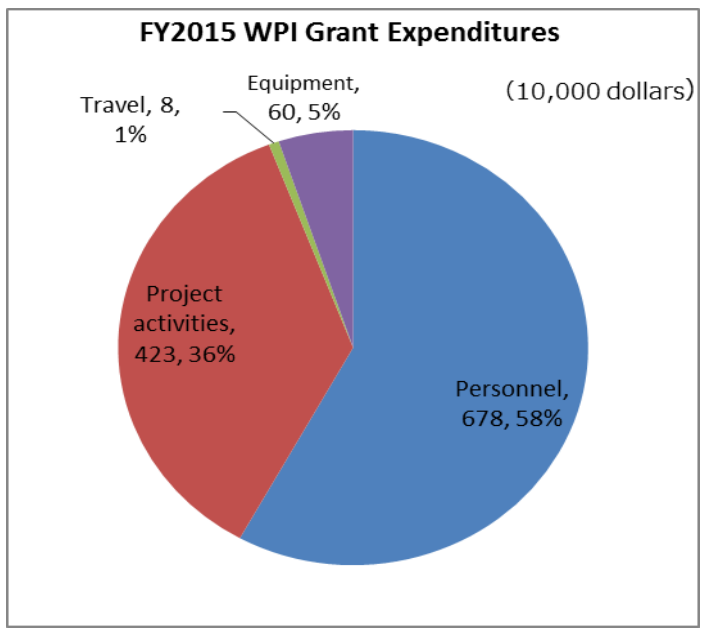
World Premier International Research Center Initiative (WPI)

Appendix 1-7. FY2015 WPI Grant Expenditures (the exchange rate used: 1USD= 110 JPY)

i) Overall Expenditures

* Describe a circle graph for cost items.

Cost Items	Details	Costs (10,000 dollars)
Personnel	Center director and Administrative director	28.2
	Principal investigators (no. of person)	67.3
	Other researchers (no. of person)	331.8
	Research support staffs (no. of person)	200.0
	Administrative staffs (no. of person)	50.9
	Total	678.2
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of person)	0.0
	Cost of dispatching scientists (no. of person)	27.3
	Research startup cost (no. of person)	0.0
	Cost of satellite organizations (no. of satellite organization)	0.0
	Cost of international symposiums (no. of symposiums)	22.7
	Rental fees for facilities	12.7
	Cost of consumables	1.8
	Cost of utilities	59.1
	Other costs	299.1
	Total	422.7
Travel	Domestic travel costs	1.8
	Overseas travel costs	3.6
	Travel and accommodations cost for invited scientists (no. of domestic scientists) (no. of overseas scientists)	0.0
	Travel cost for scientists on secondment (no. of domestic scientists) (no. of overseas scientists)	2.7
	Total	8.2
Equipment	Cost of equipment procured	60.0
	Total	60.0
Total		1169.1



ii) Costs of Satellites and Partner Institutions

Cost Items	Details	Costs (10,000 dollars)
Personnel	Principal investigators (no. of person)	
	Other researchers (no. of person)	
	Research support staffs (no. of person)	
	Administrative staffs (no. of person)	
	Total	2.7
Project activities		0
Travel		0
Equipment		0
Total		2.7

World Premier International Research Center Initiative (WPI)
Appendix 2-1. 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.

***Research result 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 groups 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 ribonucleoprotein, 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. The results suggest that Mincle is a receptor that senses non-homeostatic 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 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 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.

***Research result 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 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) conjugations 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. The 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 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.

***Research result 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 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 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 hematopoietic 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 hematopoietic cells develop hypertriglyceridemia and insulin resistance, together with increased proinflammatory cytokine gene induction. The results demonstrate Trib1 is critical for adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue-resident M2-like macrophages.

***Research result 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 groups 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 hematopoietic cells was critical for the induction of antigen-specific B and CD4(+) T cells, whereas in non-hematopoietic 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 hematopoietic and non-hematopoietic 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 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 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.

***Research result 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 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. The 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 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.

***Research result 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 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.

*13. Zhao, Hong; Aoshi, Taiki et al. Olfactory Plays a Key Role in Spatiotemporal Pathogenesis of Cerebral Malaria. Cell Host & Microbe 15:551-563, 2014.

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

Research Result 7: Immune responses to Toxoplasma

*14. 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 groups generated 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.

*15. 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 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.

*16. 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 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. The results suggest that Gbpchr3 play a pivotal role in anti-T. gondii host defense by controlling IFN-γ-mediated Irgb6-dependent cellular innate immunity.

Research Result 8: Roles of PILR in immune responses

*17. 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 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. The 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.

*18. 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 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. Pilrα−/− mice had increased neutrophil recruitment to inflammatory sites and were highly susceptible to endotoxin shock. Pilrα−/− 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.

***Research Result 9: Immune regulation and mRNA decay by Regnase-1**

*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 and Standley 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.

*20. 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 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 re-expressed 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. The 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.

*21. 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 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.

***Research Result 10: Immune regulation and mRNA stabilizing by Arid5a**

*22. 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 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.

***Research Result 11: Autoimmune diseases and Th17 cells**

*23. 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 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.

*24. 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 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 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.

***Research Result 12: New finding about immune regulation by the nervous system**

*25. Nakai, Akiko; Hayano, Yuki; Furuta, Fumika; Noda, Masaki; Kazuhiro, Suzuki. Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors. Journal of Experimental Medicine 211:2583-2598, 2014.

As the proverb "Illness starts in mind." says, it has long been proposed that some aspects of immune responses are affected by activities of the nervous system. Kazuhiro Suzuki group revealed that β2-adrenergic receptors (β2ARs) expressed on lymphocytes regulate their egress from lymph nodes by altering the responsiveness of chemokine receptors CCR7 and CXCR4. In mouse models of inflammation, signals though β2ARs were shown to inhibit trafficking of pathogenic lymphocytes and reduce their numbers recruited into inflamed tissues.

***Research Result 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 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-induced 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 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.

*28. Maeda, Yuka; Nishikawa, Hiroyoshi et al. Detection of self-reactive CD8+ T cells with an anergic phenotype in healthy individuals. Science 346:1536-1540, 2014.

Sakaguchi group showed that Treg cells can render self-reactive human CD8+ T cells anergic (i.e., hypoproliferative and cytokine hypoproducing upon antigen restimulation) in vitro, likely by controlling the costimulatory function of antigen-presenting cells. Anergic T cells were naïve in phenotype, lower than activated T cells in T cell receptor affinity for cognate antigen, and expressed several coinhibitory molecules, including cytotoxic T lymphocyte–associated antigen-4 (CTLA-4). Using these criteria, they detected in healthy individuals anergic T cells reactive with a skin antigen targeted in the autoimmune disease vitiligo. Collectively, the results suggest that Treg cell–mediated induction of anergy in autoimmune T cells is important for maintaining self-tolerance.

***Research Result 14: New findings about semaphorins**

*29. 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 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. The 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.

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

Kumanogoh 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.

*31. 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 group generated a series

of knock-in mouse lines with corresponding mutations (D345H, F350C or R713Q) in the Sema4A gene and found 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, the 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.

***Research Result 15: Discovery of a gateway of immune cells to nerve system**

*32. 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 groups showed 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.

Research Result 16: T cell activation and its visualization

33. 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 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.

34. 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 group demonstrated 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.

***Research Result 17: Factor of memory B cells toward plasma cell differentiation**

*35. 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 group have generated a mouse containing IgG1 B cells that have never encountered antigens. They found that, upon challenge, antigen-experienced IgG1 memory B cells rapidly differentiated into plasma cells, whereas non-experienced IgG1 B cells did not, suggesting the importance of the stimulation history. In addition, The 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.

***Research Result 18: Calcium sensors controlling B cell regulatory function**

*36. 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 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. The data establish STIM-dependent SOC influx as a key signal for B cell regulatory function required to limit autoimmunity.

***Research Result 19: Analysis for the protein functions in cell biology**

*37. 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 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 counter-ion conductance. Thus, GPHR modulates Golgi functions through regulation of acidification.

*38. 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 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. The 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.

***Research Result 20: Regulation of osteoclast**

39. 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 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. The 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.

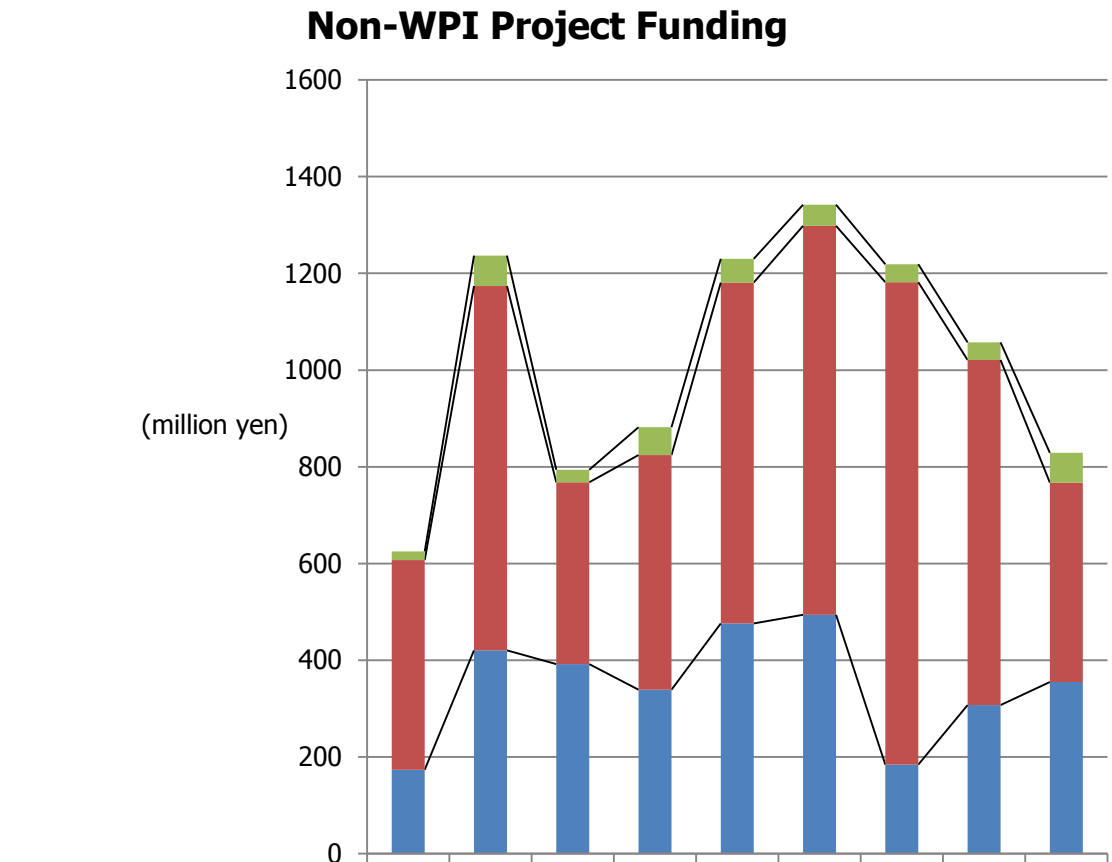
*40. Nishikawa, Keizo et al. DNA methyltransferase 3a regulates osteoclast differentiation by coupling to an S-adenosylmethionine–producing metabolic pathway. Nature Medicine 21:281-287, 2015.

Masaru Ishii group identified the de novo DNA methyltransferase 3a (Dnmt3a) as a transcription factor that couples these metabolic changes to osteoclast differentiation. They also found that receptor activator

of nuclear factor-κB ligand (RANKL), an essential cytokine for osteoclastogenesis, induces this metabolic shift towards oxidative metabolism, which is accompanied by an increase in S-adenosylmethionine (SAM) production. They found that SAM-mediated DNA methylation by Dnmt3a regulates osteoclastogenesis via epigenetic repression of anti-osteoclastogenic genes. The importance of Dnmt3a in bone homeostasis was underscored by the observations that Dnmt3a-deficient osteoclast precursor cells do not differentiate efficiently into osteoclasts and that mice with an osteoclast-specific deficiency in Dnmt3a have elevated bone mass due to a smaller number of osteoclasts. Furthermore, inhibition of DNA methylation by theaflavin-3, 3'-digallate abrogated bone loss in models of osteoporosis.

World Premier International Research Center Initiative (WPI)
Appendix 2-2. 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.



	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015
Projects supported by other government subsidies, etc.	18	63	26	58	49	44	37	36	62
Commissioned research projects, etc.	434	754	376	485	705	804	998	714	412
Grants-in-Aid for Scientific Research, etc.	173	420	392	339	476	494	184	307	355

[External funding warranting special mention]

Agency	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
HFSP	Carrier Development Award	Hanayama	30	2011-2014
HFSP	Carrier Development Award	M. Ishii	27	2009-2011

HFSP	Carrier Development Award	Hanayama	30	2011-2014
HFSP	Program Grant (Young Investigator's Grant)	M. Ishii	36	2011-2013
JSPS	Grant-in-Aid for Specially Promoted Research	Akira	873	2008-2012
JSPS	Grant-in-Aid for Specially Promoted Research	Sakaguchi	460	2008-2012
JSPS	Grant-in-Aid for Specially Promoted Research	Nagata	318	2010-2014
JSPS	Grant-in-Aid for Specially Promoted Research	Akira	564	2015-2019
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kurosaki	210	2009-2013
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Saito	218	2012-2016
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Hatazawa	157	2012-2016
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kikutani	210	2008-2012
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Saito	108	2007-2011
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Nagata	169	2015-2019
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kikuchi	219	2013-2017
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kurosaki	195	2014-2018
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Kikuchi	106	2008-2012
JSPS	Grants-in-Aid for Scientific Research, Scientific Research (S)	Takeda	115	2007-2011
JSPS	Funding Program for Next Generation World-Leading Researchers (NEXT)	Kumanogoh	166	2010-2012
JST	Strategic Basic Research Programs (CREST)	K. Ishii	112	2008-2013
JST	Strategic Basic Research Programs (CREST)	Nagata	255	2014-2018
JST	Strategic Basic Research Programs (CREST)	M. Ishii	320	2015-2020
JST	Strategic Basic Research Programs (PRESTO)	Hanayama	52	2012-2014
JST	Strategic Basic Research Programs (PRESTO)	Suzuki	52	2011-2013
JST	Strategic Basic Research Programs (PRESTO)	Smith	52	2009-2012
AMED	Development of Medical Devices and Systems for Advanced Medical Services	M. Ishii	360	2015-2018
AMED	Advanced Research & Development Programs for Medical Innovation	Arase	230	2009-2014
AMED	Advanced Research & Development Programs for Medical Innovation	Kurosaki	160	2009-2014
AMED	Advanced Research & Development Programs for Medical Innovation	Sakaguchi	370	2012-2016
AMED	Advanced Research & Development Programs for Medical Innovation	Takeda	341	2010-2014
AMED	Advanced Research & Development Programs for Medical Innovation	M. Ishii	240	2010-2014

AMED	Advanced Research & Development Programs for Medical Innovation	Kumanogoh	246	2012-2017
AMED	Project for Development of Innovative Research on Cancer Therapeutics	M. Ishii	44	2011-2015
AMED	Project for Development of Innovative Research on Cancer Therapeutics	Sakaguchi	110	2014-2015
MEXT	Grants-in-Aid for Scientific Research, Specific Area Research	Saito	126	2007-2011
MEXT	Grants-in-Aid for Scientific Research, Specific Area Research	Takeda	110	2007-2011
MEXT	Platform for Drug Discovery, Informatics, and Structural Life Science	Standley	98	2012-2016
MEXT	Regional Innovation Cluster Program	K. Ishii	123	2007-2011
MEXT	Targeted Proteins Research Program	K. Ishii	88	2007-2011
MHLW	Grants-in-Aid for Scientific Research	K. Ishii	888	2012-2016
MHLW	Grants-in-Aid for Scientific Research	Coban	106	2012-2016
MHLW	Grants-in-Aid for Scientific Research	Standley	46	2012-2016
MHLW	Contracted Scientific Research	Sakaguchi	110	2014-2016
NEDO	Translational Research Promotion Project	K. Ishii	63	2009-2011
Overseas	National Institute of Health (USA)	Akira	215	2012-2017
Private	Takeda Science Foundation	M. Ishii	30	2013
Private	Bill & Melinda Gates Foundation	Coban	11	2008-2009

AMED: Japan Agency for Medical Research and Development
HFSP: Human Frontier Science Program
JSPS: Japan Society for the Promotion of Science
JST: Japan Science and Technology Agency
MEXT: Ministry of Education, Culture, Sports, Science and Technology
MHLW: Ministry of Health, Labor and Welfare
NEDO: New Energy and Industrial Technology Development Organization

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

1. Major Awards

*List main internationally-acclaimed awards received/unofficially 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) Taroh Kinoshita, International Glycoconjugate Organization Award (2015).
2) Shimon Sakaguchi, Thomson Reuters Citation Laureate (2015).
3) Shizuo Akira, Shimon Sakaguchi, Ken Ishii, Kiyoshi Takeda, Hiroaki Hemmi, Masahiro Yamamoto, The World's Most Highly Cited Researchers (2015).
4) Shigekazu Nagata, Foreign Associate of the National Academy of Sciences USA (2015).
5) Shimon Sakaguchi, The Canada Gairdner International Award (2015).
6) Shizuo Akira, The Member of the Japan Academy (2014).
7) Toshio Yanagida, Honorary Member of the Physical Society of Japan (2014).
8) Toshio Yanagida, Persons of Cultural Merit, Japan (2013).
9) Shimon Sakaguchi, Foreign Associate of the National Academy of Sciences USA (2012).
10) Tadamitsu Kishimoto, The Royal Decoration from Thai Kingdom (2012).
11) Toshio Yanagida, Fellow of the US Biophysical Society (2011).
12) Shimon Sakaguchi, Asahi Prize (2011).
13) Shimon Sakaguchi, Japan Academy Award (2011).
14) Shizuo Akira, Jules Hoffmann, The Keio Medical Science Prize (2010).
15) Shizuo Akira, Jules Hoffmann, The Canada Gairdner International Award (2010).
16) Tadamitsu Kishimoto, Clinical Immunology Society President's Award (2010).
17) Tadamitsu Kishimoto, Toshio Hirano, The Japan Prize (2010).
18) Toshio Yanagida, US Genomics Award for Outstanding Investigator in the Field of Single Molecule Biology (2010).
19) Shizuo Akira, Persons of Cultural Merit, Japan (2009).
20) Shizuo Akira, Foreign Associate of the National Academy of Sciences USA (2009).
21) Tadamitsu Kishimoto, Toshio Hirano, Charles Dinarello, The Crafoord Prize in Polyarthritis (2009).
22) Shimon Sakaguchi, Fred Gage, The Keio Medical Science Prize (2008).

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) Taroh Kinoshita, Award Lecture at XXIII International Symposium on Glycoconjugates "Glycosylphosphatidylinositol-anchored proteins: biosynthesis, transport, shedding and deficiencies", Croatia, September 15, 2015.
2) Shimon Sakaguchi, The Awardee Lecture for the Canada Gairdner International Award, Oct. 27, 2015.
3) Taroh Kinoshita, Gordon Research Conference on Glycobiology, "Shedding of Cripto-1 by PGAP6, a membrane-bound, GPI-specific phospholipase A2", Italy, March 4, 2015.
4) Kiyoshi Takeda, 2nd Hengstberger Symposium on Microbial sensors in the B lymphocyte response "Regulation of antibody responses in the appendix", Heidelberg, Germany, January 7, 2015.
5) Hisashi Arase, France-Japan Immunology Meeting 2014, "Cellular misfolded proteins complexed with MHC class II molecules are targets for autoantibodies in autoimmune diseases Cassis", France, October

23, 2014.

6) Tomohiro Kurosaki, The 2nd Symposium of International Immunological Memory and Vaccine Forum, "Mechanisms underlying rapid memory IgG responses", USA, August 26, 2014.
7) Takashi Saito, FASEB Science Research Conference, "Direct sensing of nucleotides by T cells induces Th2 differentiation", Snowmass, USA, June 30, 2014.
8) Shizuo Akira/The 1st KI-OU Joint Symposium, "Regnase-1, an endoribonuclease regulating", Sweden, June 10, 2014.
9) Ken Ishii, WHO Meetings of Stakeholders for Selected Health R&D Demonstration Project, "Experience of clinical development of CpG ODN in vaccine", Geneva, Switzerland, May 7, 2014.
10) Cevayir Coban, The 2nd International Molecular Immunology & Immunogenetics Congress, "Host-Pathogen Interactions in the Context of Malaria", Antalya, Turkey, April 27, 2014.
11) Shizuo Akira, Distinguished Ludwig Lecture Series, "Regnase-1, a ribonuclease involved in the immune regulation", Switzerland, April 24, 2014.
12) Shigekazu Nagata, The Henry Kunkel Lecture 2014, "Human Immunology in Health and Disease", New York, April 3, 2014.Ken Ishii, Understanding vaccine developments and opportunities in Japan, The World Vaccine Congress & Expo, Mar. 24, 2014.
13) Tomohiro Kurosaki, Calcium signaling in B lymphocytes, Keystone Symposia: Biology of B Cell Reponses, Feb. 11, 2014.
14) Masaru Ishii, S1P-mediated control of bone cell dynamics visualized by intra-vital microscopy, Gordon Research Conferences, Jan. 12, 2014.
15) Hisashi Arase, Misfolded proteins complexed with MHC class II molecules are targeted by autoantibodies, Germany-Japan Immunology Seminar, Dec. 5, 2013.
16) Atsushi Kumanogoh, Immune regulation by semaphorins and their receptors, EMBO Workshop, Oct. 31, 2013.
17) Tadamitsu, Kishimoto, IL-6: A new era comes for the treatment of inflammatory autoimmune diseases, 15th International Congress of Immunology, Aug. 22, 2013.
18) Shimon Sakaguchi, Plenary lecture: Control of immune responses by regulatory T cells, 15th International Congress of Immunology, Aug. 22, 2013.
19) 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.
20) Jun Hatazawa, Molecular Stroke: another insight on evolving brain infarct based on astrocytic energy metabolism, BRAIN & Brain PET 2013, May 20, 2013.
21) Kiyoshi Takeda, Regulation of gut homeostasis by innate immunity, Immunology 2013, May 3, 2013.
22) Shizuo Akira, The role of mRNA stability in the immune response, Harvard Medical School Committee on Immunology Seminar, Apr. 17, 2013.
23) Shimon Sakaguchi, Regulatory T cells for immune tolerance and homeostasis, Karolinska Research Lectures at Nobel Forum, Apr. 4, 2013.
24) Toshio Yanagida, Single molecules in vitro and vivo, Gordon Research Conferences -Single Molecule Approaches to Biology, Jul. 18, 2012.
25) Shizuo Akira, The Awardee Lecture for the Canada Gairdner International Award, Oct. 27, 2011.
26) Tadamitsu Kishimoto, Memorial Lecture for the Gairdner Symposium, Oct. 28, 2011.
27) Shizuo Akira, Innate Immune Responses: Pathogen Recognition and Signaling, The Nobel Forum 2010, Nov. 23, 2010.
28) Shizuo Akira, Innate Immunity and vaccines, The Royal Society in London, UK, Nov. 15, 2010.
29) Tadamitsu Kishimoto and Toshio Hirano, The commemorative lectures for the Crafoord Prize in Polyarthritis, May 11, 2009.
30) Shizuo Akira, Pathogen recognition and signaling in innate immunity, Dyer lecture at National Institute of Health, USA, May 7, 2008.

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Appendix 2-4. List of Achievements of Center's Outreach Activities

* Using the table below, show the achievements of the Center's outreach activities from FY2007 through FY2015 (number of activities, times held).

Activities	FY2007 (number of activities, times held)	FY2008 (number of activities, times held)	FY2009 (number of activities, times held)
PR brochure, pamphlet	0	1	3
Lectures, seminars for general public	0	0	4
Teaching, experiments, training for elementary and secondary school students	0	0	0
Science cafe	0	0	0
Open houses	0	0	1
Participating, exhibiting in events	0	0	0
Press releases	1	32	26

Activities	FY2010 (number of activities, times held)	FY2011 (number of activities, times held)	FY2012 (number of activities, times held)
PR brochure, pamphlet	4	4	4
Lectures, seminars for general public	16	2	3
Teaching, experiments, training for elementary and secondary school students	0	4	2
Science cafe	3	4	7
Open houses	1	3	5
Participating, exhibiting in events	2	3	4
Press releases	20	17	13

Activities	FY2013 (number of activities, times held)	FY2014 (number of activities, times held)	FY2015 (number of activities, times held)
PR brochure, pamphlet	4	4	4
Lectures, seminars for general public	17	8	17
Teaching, experiments, training for elementary and secondary school students	0	0	0
Science cafe	3	2	2
Open houses	2	2	1
Participating, exhibiting in events	4	3	3
Press releases	10	17	10

List of Media Coverage of Projects carried out between FY 2007 – 2015

(within 2 pages)

* Select main items of press releases, media coverage, and reports for FY 2007-2015 (especially by overseas media)

1) Japan

No.	Date	Type media (e.g., Shimbun, magazine, television)	Description
1	2009.1.15	Asahi Shimbun, Mainichi Shimbun, Yomiuri Shimbun etc.	Tadamitsu Kishimoto & Toshio Hirano won The Crafoord Prize
2	2010.9.8	Yomiuri Shimbun	Osaka Science Prize was awarded to Atsushi Kumanogoh
3	2010.9.11	Nikkei Shimbun	Keio Medical Science Prize awarded to Shizuo Akira
5	2010.11.20	WEDGE magazine	Persons keeping changing mind do good jobs (Toshio Yanagida)
6	2010.12.24	Yomiuri Shimbun	Development of new therapy for osteoporosis (Masaru Ishii)
7	2011.1.26	Nikkei Shimbun, Mainichi Shimbun, Sankei Shimbun	The Japan Prize 2011 was awarded to Tadamitsu Kishimoto & Toshio Hirano
8	2011.3.26	Asahi Shimbun, Mainichi Shimbun, Yomiuri Shimbun etc.	Shizuo Akira of IFReC was awarded The Canada Gairdner International Award 2011
9	2011.10.4	Asahi Shimbun, Mainichi Shimbun, Yomiuri Shimbun etc.	Great achievements in immunology (Shizuo Akira)
10	2011.10.6	Asahi Shimbun	Nobel Prize for Groundbreaking discovery in innate immune system
11	2012.1.1	Asahi Shimbun	Recipients of the Asahi Prize (Shimon Sakaguchi)
12	2012. 3.13	Asahi Shimbun, Mainichi Shimbun, Nikkei Shimbun etc.	Japan Academy Prize (Shimon Sakaguchi)
13	2013.6.25	Asahi Shimbun,	Shizuo Akira & Shimon Sakaguchi elected Distinguished Professor of Osaka University

14	2013.10.26	Asahi Shimbun,	Toshio Yanagida named a Person of Cultural Merit
15	2014.9.13	Asahi Shimbun TV news etc.	Ken Ishii receiving Osaka Science Prize
16	2014.9.23	Nikkei Shimbun	Cancer therapy by immune regulation (Hiroyoshi Nishikawa)
17	2014.10.9	Mainichi Shimbun	Progressive technology for Nobel Prize in Chemistry (Toshio Yanagida)
18	2014.12.13	Nikkei Shimbun, Asahi Shimbun, Mainichi Shimbun Yomiuri Shimbun	Member of the Japan Academy (Shizuo Akira)
19	2015.3.26	Nikkei Shimbun Asahi Shimbun Mainichi Shimbun TV news etc.	Shimon Sakaguchi of IFReC was awarded The Canada Gairdner International Award 2015
20	2015.3.9	Nikkei Shimbun	Immunology at Osaka University, gathering institute for the leading scientists

2) Overseas

No.	Date	Type media (e.g., Shimbun, magazine, television)	Description
1	2009.9.9	Nature Spotlight	IFReC: Whole body imaging of the immune system
2	2010.11.16	Nature	Spotlight on Foreign Researchers in Japan (Cevayir Coban)
3	2011.11.1	Science OSAKA IN FOCUS	IFReC: World –Class Interdisciplinary Research on Imaging the Human Immune System
4	2014.2.25	Editors' Choice in Science	Rheumatoid Rescue? (Hisashi Arase)
5	2013.5.13	Chemistry World	Early malaria diagnosis just one day after infection (Cevayir Coban & Nicholas Smith)
6	2013.5.14	HOT Articles in Analyst	Early malaria diagnosis (Cevayir Coban & Nicholas Smith)
7	2014.10.3	Nature Spotlight	IFReC: A stimulating environment for immunology

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Appendix 3. 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. Smith, Nicholas I.; Mochizuki, Kentaro; Niioka, Hirohiko; Ichikawa, Satoshi; Pavillon, Nicolas; Hobro, Alison J.; Ando, Jun; Fujita, Katsumasa; Kumagai, Yutaro. Laser-targeted photofabrication of gold nanoparticles inside cells. Nature Communications 5:5144, 2014.

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

2. Zhao, Hong; Aoshi, Taiki; Kawai, Satoru; Mori, Yuki; Konishi, Aki; Ozkan, Muge; Fujita, Yukiko; Haseda, Yasunari; Shimizu, Mikiko; Kohyama, Masako; Kobiyama, Kouji; Eto, Kei; Nabekura, Junichi; Horii, Toshihiro; Ishino, Tomoko; Yuda, Masao; Hemmi, Hiroaki; Kaisho, Tsuneyasu; Akira, Shizuo; Kinoshita, Manabu; Tohyama, Koujiro; Yoshioka, Yoshichika; Ishii, Ken J.; Coban, Cevayir. Olfactory Plays a Key Role in Spatiotemporal Pathogenesis of Cerebral Malaria. Cell Host & Microbe 15:551-563, 2014.

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

3. 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 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.

4. 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 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).

5. 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 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.

6. 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 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.

7. 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.

8. 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 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.

9. 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 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.

10. 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 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.

11. 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 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.

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 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 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 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 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 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 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 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 group 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.

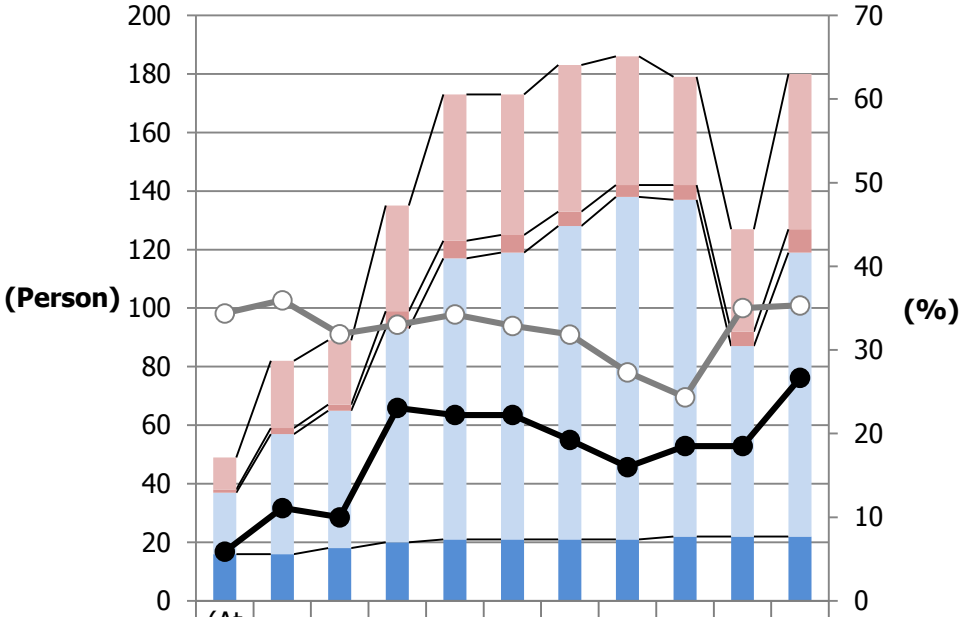
20. Ishii, Masaru; Egen, Jackson G.; Klauschen, Frederick; Meier-Schellersheim, Martin; Saeki, Yukihiko; Vacher, Jean; Proia, Richard L.; Germain, Ronald N. Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. Nature 458:524-528, 2009.

    Masaru Ishii 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)
Appendix 4-1. Number of Overseas Researchers and Annual Transition

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

Number of Overseas Researchers



	(At beginning)	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	(Final goal)
Researchers from abroad	11	23	22	36	50	48	50	44	37	35	53
PIs from abroad	1	2	2	6	6	6	5	4	5	5	8
Japanese researchers excluding PIs	21	41	47	73	96	98	107	117	115	65	97
Japanese PIs	16	16	18	20	21	21	21	21	22	22	22
Ratio of PIs from abroad	5.9	11.1	10.0	23.1	22.2	22.2	19.2	16.0	18.5	18.5	26.7
Ratio of researchers from abroad	34.4	35.9	31.9	33.0	34.2	32.9	31.8	27.3	24.3	35.0	35.3

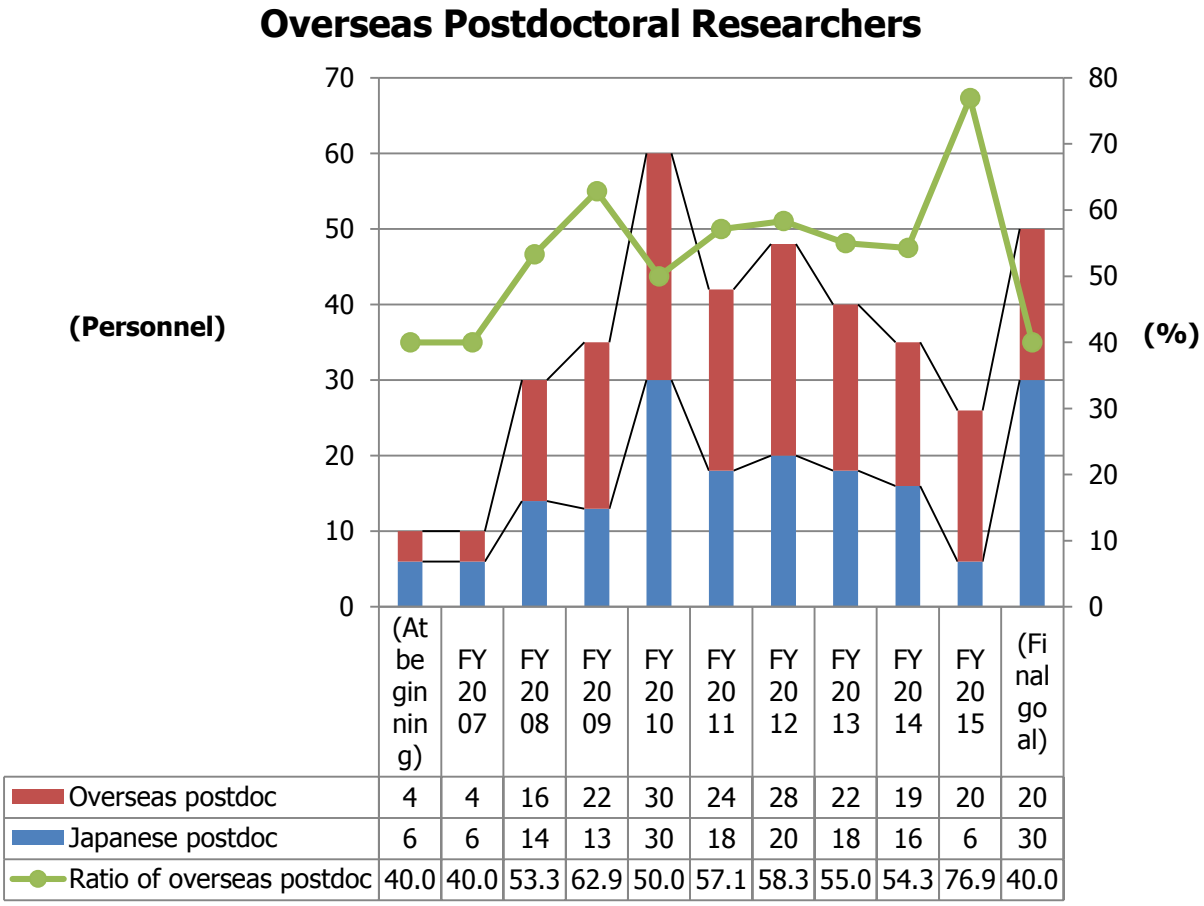
World Premier International Research Center Initiative (WPI)
Appendix 4-2. Postdoctoral Positions through Open International Solicitations

- 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%>
FY2014	10 <10, 100%>	5 <5,100%>
FY2015	12 < 11, 92%>	5 < 5, 100%>

World Premier International Research Center Initiative (WPI)
Appendix 4-3. Number of Overseas Postdoctoral Researchers and Annual Transition

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



	(At beginning)	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	(Final goal)
Overseas postdoc	4	4	16	22	30	24	28	22	19	20	20
Japanese postdoc	6	6	14	13	30	18	20	18	16	6	30
Ratio of overseas postdoc	40.0	40.0	53.3	62.9	50.0	57.1	58.3	55.0	54.3	76.9	40.0

World Premier International Research Center Initiative (WPI)

Appendix 4-4. Status of Postdoc Employment at Institutions of Postdoctoral Researchers

*List each researcher in 1 line. If the list exceeds this form, please add extra pages.

Japanese Postdocs

Period of project participation	Previous Affiliation Position title (Country)	Next Affiliation Position title (Country)
2008.4.1-2009.9.30	Graduate School of Medicine, Kyoto University, Postdoctoral Researcher, (Japan)	Institute for Frontier Medical Sciences, Kyoto University, JSPS Postdoctoral Fellowship, (Japan)
2008.10.16-2009.10.15	Graduate School of Frontier Biosciences, Osaka University Specially Appointed Researcher (Japan)	Graduate School of Medicine, Osaka University, Specially Appointed Researcher, (Japan)
2008.4.1-2011.3.31	The department of internal medicine, Kyoto Hospital Medical doctor, (Japan)	Graduate School of Medicine, Kyoto University, Assistant Professor, (Japan)
2009.10.16-2011.3.31	Graduate School of Medicine, Osaka University, Specially Appointed Researcher, (Japan)	KAN Research Institute Inc., Researcher, (Japan)
2008.4.1-2011.3.31	Institute for Frontier Medical Sciences, Kyoto University, Part-time Lecturer, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2010.4.1-2011.3.31	Graduate School of Engineering, Kyoto University, Graduate Student, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2010.6.1-2011.6.30	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Technical Staff, (Japan)
2010.9.1-2011.6.30	Osaka University Hospital, Medical doctor, (Japan)	Eli Lilly Japan K.K., Clinical Research Physician, (Japan)
2011.4.1-2011.9.30	Institute for Protein Research, Osaka University, JSPS Postdoctoral Fellowship, (Japan)	Department of Chemical & Biomolecular Engineering, Johns Hopkins University, Post-Doctoral Research Fellow,（U.S.A）

2009.4.1-2012.3.31	Graduate School of Medicine, Osaka University, JSPS Postdoctoral Research Fellow, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2010.4.1-2012.3.31	Graduate School of Medicine, Kyoto University, JSPS Postdoctoral Research Fellow, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2011.4.1-2012.3.31	Graduate School of Frontier Biosciences, Osaka University, Graduate Student, (Japan)	Graduate School of Medicine, Osaka University, Specially Appointed Researcher, (Japan)
2010.4.1-2012.6.15	School of Medicine, University of California San Diego, Postdoctoral researcher, （USA）	Institute for Virus Research, Kyoto University, Assistant Professor, (Japan)
2011.4.1-2012.7.31	Institute for Frontier Medical Science, Kyoto University, Postdoctoral researcher, (Japan)	National Hospital Organization Osaka Minami Medical, Medical Staff, (Japan)
2010.4.1-2012.10.15	Graduate School of Life Science, Hokkaido University, Graduate Student, (Japan)	The Institute of Medical Science, The University of Tokyo, Assistant Professor, (Japan)
2010.4.1-2012.12.31	Takeda Pharmaceutical Company Limited Medical writer, (Japan)	Astellas Pharma Inc., Researcher, (Japan)
2009.4.1-2013.3.31	Murakami Medical Hospital Asahi University, Internal medicine doctor, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2009.4.1-2013.3.31	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Technical Staff, (Japan)
2010.4.1-2013.3.31	Graduate School of Medicine, Osaka University, Graduate Student, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2010.4.1-2013.3.31	Graduate School of Science, Nagoya University, Assistant Professor, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor

		(Full-time), (Japan)
2011.4.1-2013.3.31	School of Medicine, Iwate Medical University, Postdoctoral researcher, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2012.4.1-2013.3.31	Graduate School of Frontier Biosciences, Osaka University Graduate student, (Japan)	Graduate School of Medicine, Osaka University, JSPS Postdoctoral Fellowship, (Japan)
2010.4.1-2013.3.31	Graduate School of Frontier Biosciences, Osaka University, Specially Appointed Researcher, (Japan)	Graduate School of Frontier Biosciences, Osaka University, Specially Appointed Researcher, (Japan)
2012.4.1-2013.3.31	L'Oreal Paris Japan Researcher, (Japan)	Institute for Academic Initiative, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)
2010.4.1-2013.4.15	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Technical Staff, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Technical Staff, (Japan)
2010.1.1-2013.4.30	Paul O' Gorman Leukaemia Research Centre, Division of Cancer Sciences and Molecular Pathology, Section of Enperimental Haematology, University of Glasgow, Gartnavel General Hospital（UK）	Babraham Institute, Researcher（UK）
2010.4.1-2013.5.15	Frontier Research Center for Applied Atomic Sciences, Ibaraki University Part-time researcher, (Japan)	NARA Institute of Science and Technology, Part-time researcher, (Japan)
2010.6.1-2013.6.30	Research Institute of Molecular Pathology, Postdoctoral researcher, (Austria)	National Institute for Basic Biology, Researcher, (Japan)
2011.4.1-2013.11.30	RIKEN Research Center for Allergy and Immunology, Junior Research Associate, (Japan)	Immunology Frontier Research Center, Osaka University, Endowed Chair Associate Professor, (Japan)
2013.4.1-2014.3.31	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	Graduate School of Medicine, Osaka University, Specially Appointed Researcher, (Japan)

2013.4.1-2014.6.30	Graduate School of Medicine, Kyoto University, Graduate Student, (Japan)	Institute for Frontier Medical Sciences, Kyoto University, Specially Appointed Researcher, (Japan)
2012.4.1-2014.8.31	Graduate School of Frontier Biosciences, Osaka University, Graduate Student, (Japan)	AbbVie GK,(Japan)
2013.4.1-2014.8.31	Graduate School of Medicine, Nagoya University, Graduate Student, (Japan)	Graduate School of Frontier Biosciences, Osaka University, Assistant Professor, (Japan)
2012.4.1-2015.5.31	Graduate School of Pharmaceutical Sciences, Osaka University, Graduate Student, (Japan)	Kanazawa University, Researcher,(Japan)
2011.8.1-2015.7.31	Research Associate, Department of Cell Biology, Johns Hopkins University, USA	RIKEN Center for Life Science Technologies, Engineer, (Japan)
2012.11.16-2015.11.30	Postdoctoral fellow, University of Pennsylvania school of medicine, Dept. of Cell & Developmental Biology, USA	Kanazawa University, Assistant Professor,(Japan)

Overseas Postdocs

Period of project participation	Previous Affiliation Position title (Country)	Next Affiliation Position title (Country)	Nationality
2008.3.1-2008.8.15	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	Department of Microbiology, Yogi vemana University, Associate Professor (India)	India
2008.1.1-2010.2.28	Graduate school of Medicine, Osaka University, Part-time Technical Staff, (Japan)	(Pohang University of Science and Technology: POSTECH), Research Assistant Professor （Korea）	Korea
2008.8.1-2010.7.15	Blood Research Institute, Blood Center of Wisconsin, Pre-doctoral Fellow, (U.S.A)	St Jude Children's Research Hospital, (USA) Postdoctoral Fellow (U.S.A)	China
2009.5.16-2010.7.19	Become Japan Corporation, Principal Software Engineer, (Japan)	DeNA Co. Ltd., Engineers, (Japan)	USA
2008.3.1-2010.8.30	Graduate School of Engineering, Osaka University, JSPS Postdoctoral Fellowship, (Japan)	Graduate School of Engineering, Osaka University, JSPS Postdoctoral Fellowship for Foreign Researcher, (Japan)	Korea

2008.4.1-2010.8.30	Graduate School of Medicine Osaka University, Part-time Technical Staff, (Japan)	RIKEN, Postdoctoral Researcher, (Japan)	Korea
2009.11.1-2010.9.30	Graduate School of Frontier Biosciences, Osaka University, JSPS Postdoctoral Fellowship for Foreign Researchers, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)	UK
2008.11.1-2011.3.31	National Institute of Public Health, Researcher, (Korea)	Childbirth	Korea
2008.4.1-2011.3.31	Graduate School of Medicine, Osaka University, Graduate Student, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)	China
2008.4.1-2011.3.31	Research Institute for Microbial Diseases, Osaka University, JST Researcher, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)	UK
2010.6.16-2011.3.31	University of Hyogo, JST researcher, (Japan)	Xiamen University, Research Fellow, (China)	China
2010.10.1-2011.8.8	Graduate School of Computer Science and Systems Engineering, Kyushu Institute of Technology, Graduate Student, (Japan)	Department of Chemistry, University of Ottawa, Postdoctoral Research Fellow, (USA)	Cuba
2010.8.16-2011.9.30	Graduate School of Natural Science and Technology, Okayama University, Teaching Assistant, (Japan)	n/a	Jordan
2009.4.1-2011.10.31	Laboratory of Allergy and clinical Immunology, Department of Life Science, (Pohang University of Science and Technology: POSTECH), Postdoctoral Fellow, (Korea)	(Pohang University of Science and Technology: POSTECH), Postdoctoral Research Fellow （Korea）	Korea
2010.12.1-2011.10.31	University of Ulsan, Postdoctoral Fellow, (Korea)	n/a	Korea
2009.5.16-2011.11.15	Center for High Performance Computing, University of Utah, Visiting Fellow, （USA）	National Institute of Biological Resources (NIBR), Researcher （Korea）	Korea
2008.10.1-2012.3.31	The Institute of Medical Science, the University of Tokyo, Postdoctoral Fellow,	Epidemiology and Public Health, Facultad de Medicina Veterinaria, Ibague Colombia, Universidad del	Columbia

	(Japan)	Tolima, Assistant Professor （Columbia）	
2010.1.1-2012.3.31	Department of Preventive Veterinary Medicine, Molecular Immunology and Pathogenic Microorganism, Jilin University, Graduate Student,（China）	Jilin University, Changchu, Associate Professor（China）	China
2010.4.1-2012.7.31	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	n/a	Sri Lanka
2009.10.1-2012.7.31	The Institute of Medical Science, the University of Tokyo, Visiting Researcher, (Japan)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)	Belgium
2011.9.1-2012.9.15	Miller School of Medicine, Diabetes Research Institute, Postdoctoral Fellow, (U.S.A)	Immunology Frontier Research Center, Osaka University, JSPS Postdoctoral Research Fellow for Foreign Researchers, (Japan)	Nigeria
2012.8.1-2013.3.31	Guangzhou Institute of Advanced Technology, Chinese Academy of Sciences (GIAT), Principal Investigator, (China)	n/a	China
2009.4.1-2013.3.31	Research Institute for Microbial Diseases, Osaka University, JST Postdoctoral Researcher, (Japan)	n/a	China
2009.4.1-2013.3.31	Hanoi University of Science, Lecturer, (Vietnam)	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)	Vietnam
2010.4.1-2013.3.31	Platform Computing Beijing Branch, Senior 2nd-line Technical Support Engineer and Team leader,（China）	IBM Investment Company Limited, Technical Support Professional, (China)	China
2009.4.1-2013.3.31	Department of Clinical Pharmacology, Niigata University of Pharmacy and Applied Life Sciences, Postdoctoral Fellow, (Japan)	Graduate School of Medicine, Osaka University, JSPS Postdoctoral Fellowship for Foreign Researchers, (Japan)	India
2010.9.1-2013.3.31	Max Planck Institute for Infection Biology, Department of Lymphocyte Development, Postdoctoral Fellow,	Immunology Frontier Research Center, Osaka University, Specially Appointed Assistant Professor (Full-time), (Japan)	Germany

	(Germany)		
2009.4.1-2013.3.31	Institute of Pharmacology, Center of Biomedical Medicine and Pharmacology, Medical University of Vienna, Graduate Student, (Austria)	n/a	Austria
2011.9.1-2013.6.30	College of Life Science, East China Normal University, Graduate Student, (China)	n/a	China
2010.8.16-2013.8.15	Immunology Division, Indian Institute of Toxicology Research, Scientist, (India)	n/a	India
2010.3.1-2013.8.15	Stem Cell and Development Biology, Genome Institute of Singapore, Pre-doctoral Fellow, (Singapore)	Guangzhou Institutes of Biomedicine and Health, Researcher, (China)	UK
2010.7.16-2013.9.30	Centre of Biological Resources, Teaching Hospital of Nancy/INSERM U724, Cellular and Molecular Pathologies of Nutrition, School of Medicine, University Henri Poincare, Nancy, Research Assistant, (France)	RIKEN Center for Life Science Technologies, Researcher, (Japan)	France
2012.7.1-2013.11.15	Department of Chemistry, University of California, Irvine, Postdoctoral Researcher, (U.S.A)	Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, JSPS Postdoctoral Fellowship for Foreign Researchers, (Japan)	China
2010.7.1-2013.12.31	Graduate School of Frontier Biosciences, Osaka University, Specially Appointed Researcher, (Japan)	n/a	China
2011.4.1-2014.3.31	Applied Molecular Biology Lab, School of Life Science, Jawaharlal Nehru University, Graduate Student, (India)	Hokkaido University, Researcher,(Japan)	India
2010.4.1-2014.3.31	Immunology Frontier Research Center, Osaka University, Temp staff (Technician), (Japan)	n/a	France
2011.4.1-2014.3.31	School of Life Sciences, Jawaharlal Nehru University, India	n/a	India

2010.4.1-2014.3.31	Immunology Frontier Research Center, Osaka University, Temp staff (Technician)(Japan)	n/a	France
2011.9.1-2014.4.30	Kyushu University, JSPS Postdoctoral Research Fellow for Foreign Researchers, (Japan)	n/a	Thailand
2008.2.1-2014.5.15	n/a	Institute for Genetic Medicine, Hokkaido University, Postdoctoral fellow,(Japan)	China
2013.4.1-2014.6.15	Graduate School of Medicine, Osaka University, Graduate Student, (Japan)	School of Medicine, University of Pennsylvania Postdoc researcher（USA）	Korea
2013.1.1-2014.9.30	Graduate School of Frontier Sciences, The University of Tokyo, Specially Appointed Researcher, (Japan)	Institute for Virus Research, Kyoto University, Specially Appointed Researcher, (Japan)	Indonesia
2014.4.1-2014.9.30	Graduate School of Medicine, Osaka University, Assistant Professor, (Japan)	Graduate School of Medicine, Division of Health Sciences, Osaka University, Assistant Professor, (Japan)	Taiwan
2014.10.1-2014.11.15	Immunology Frontier Research Center, Osaka University, JSPS Postdoctoral Research Fellow for Foreign Researchers, (Japan)	Dana Farber Cancer Institute, Harvard University Instructor/Research Fellow （USA）	Nigeria
2011.1.1-2014.12.31	Postdoctral fellow, Department of Dermatology, Seoul National University College of Medicine, Korea	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	Korea
2011.4.16-2015.1.15	Immunology Frontier Research Center, Osaka University, Research Fellow,(Japan)	Ewha Womans University Mokdong Hospital, Research Professor/Clinical Assistant Professor(Korea)	Korea
2011.4.1-2015.3.31	Postdoctoral Researcher, Department of Microbiology and Immunology National Cheng Kung University, Taiwan	Immunology Frontier Research Center, Osaka University, JSPS Postdoctoral Research Fellow for Foreign Researchers, (Japan)	Taiwan
2012.1.16-2015.3.31	Graduate School of Life and Environmental Sciences, University of Tsukuba, Graduate Student, (Japan)	n/a	Tunisia
2014.5.1-2015.4.30	Research Institute for Microbial Diseases, Osaka University, Specially Appointed Researcher, (Japan)	Research Institute for Microbial Diseases, Osaka University, JSPS Postdoctoral Research Fellow for Foreign Researchers, (Japan)	China

2014.12.16-2015.7.31	Graduate student, University of Texas Medical Branch, USA	n/a	Taiwan
2015.2.1-2015.7.31	Ph.D. Student, Middle East Technical University (METU),Turkey	n/a	Turkey
2015.4.1-2015.10.31	Institute for Virus Research, Kyoto University, Technical Staff, (Japan)	LINE Fukuoka Software, Engineer(Japan)	Swiss
2014.11.16- 2015.11.15	Immunology Frontier Research Center, Osaka University, JSPS Postdoctoral Research Fellow for Foreign Researchers, (Japan)	Novartis, Researcher(Slovenia)	Slovenia
2013.1.16-2015.12.31	n/a	Institute for Virus Research, Kyoto University, Specially Appointed Assistant Professor, (Japan)	China
2015.4.1-2015.12.31	Graduate School of Biomedical Science, Tokyo Medical and Dental University, Graduate Student, (Japan)	National Institutes of Health Postdoctoral, fellow（USA）	Egypt

World Premier International Research Center Initiative (WPI)

Appendix 4-5. 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.

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

World Premier International Research Center Initiative (WPI)

Appendix 4-6. 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- (Osaka International Convention Center)	600
Feb. 12-13, 2009	The 2nd International Symposium of IFReC -Dynamics of Immune Responses- (Osaka University)	400
May 11, 2009	International Symposium -Frontier Immuno-Imaging- (Osaka University)	60
May 25-27, 2009	The International Symposium -Immune Regulation: Present and Future- (Osaka International Convention Center)	900
June 18-19, 2009	Joint Symposium by SIgN & IFReC -Integrating Immune Networks with Immuno-Imaging- (Singapore)	300
Sep. 18-19, 2009	The International Symposium by IFReC & International Vaccine Institute -Regulation of Innate Immunity- (Seoul, Korea)	150
Nov. 6, 2009	International Workshop -Bioinformatics in Immunology- (Osaka University)	80
June 1-2, 2010	The 4th International Symposium of WPI IFReC -Immunology at the Forefront- (Osaka University)	450
June 17-18, 2010	Joint Workshop by IFReC & New Zealand immunologists (Osaka University)	70
Nov. 3-4, 2010	IFReC & Chinese Society of Immunology Joint Symposium (Hangzhou, China)	80
Mar. 1-2, 2011	The International Symposium "Towards Comprehensive Understanding of Immune Dynamism 2011" (Osaka University)	200
Nov. 16-17, 2011	IFReC & Institute for protein Research Joint Seminar-Multilevel Systems Biology: Genomes, Structures, and Networks- (Osaka University)	80
Dec. 18-20, 2011	IFReC & Convergent Research Consortium for Immunologic Disease Joint Symposium (Seoul, Korea)	300
Mar. 1-2, 2012	The Immunoparasitology Meeting (Osaka University)	120
May 22-23, 2012	International Symposium -Dynamism of Immune Reactions & Regulation- (Osaka International Convention Center)	600
Oct. 29-31, 2012	The International Symposium "Towards Comprehensive Understanding of Immune Dynamism 2012" (Osaka University)	200

Nov. 18-20, 2013	The International Symposium "Towards Comprehensive Understanding of Immune Dynamism 2013" (Osaka University)	200
Jan. 15, 2014	Malaria Immunopathology Symposium (Osaka University)	50
Feb. 22-23, 2015	The 6th International Symposium of WPI IFReC -Immunology at the Forefront- (Grand Front Osaka)	250
Jan. 21-22, 2016	The 7th International Symposium of WPI IFReC -Immunology at the Forefront- (Grand Front Osaka)	300

World Premier International Research Center Initiative (WPI)

Appendix 5-1. Host Institution's Commitment

1. Contributions from host institution

(1) Fund, Personnel

* Regarding "Fund" entry, describe with reference to the items in the Progress Report (Jisseki-hokoku-sho) based on Article 12 of the Grant Guidelines (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.

(2007-2012)

<Fund> **(million yen)**

Fiscal Year	2007	2008	2009	2010	2011	2012
Personnel	106.20	318.15	234.83	220.34	335.46	350.60
- Faculty members (including researchers)	96.73	283.49	203.22	171.46	217.88	216.02
Full-time	0	0	0	0	53.83	45.39
Concurrent	96.73	283.49	203.22	171.46	164.05	170.63
Postdocs	2.11	29.95	31.43	40.80	47.85	55.60
RA etc.	0.17	0	0	0	0	11.41
Research support staffs	0	0	0	0	10.64	10.45
Administrative staffs	7.19	4.71	0.18	8.08	59.09	57.12
Project activities	253.64	143.03	600.05	268.12	177.22	200.53
Travel	0.77	0.94	0.88	10.27	6.81	4.70
Equipment	987.63	691.90	2229.8	33.00	118.93	0.15
Research projects	23.24	28.42	27.43	73.12	49.20	44.30
Total	1371.48	1182.44	3092.99	604.85	687.62	600.28

<Personnel> **(person)**

Fiscal Year	2007	2008	2009	2010	2011	2012
Personnel	34	36	42	49	66	119
- Faculty members (including researchers)	22	29	33	36	38	37
Full-time	0	0	0	0	5	4
Concurrent	22	29	33	36	33	33
Postdocs	7	7	8	11	12	12
RA etc.	4	0	0	0	0	51
Research support staffs	0	0	0	0	5	8
Administrative staffs	(1) 1	0	1	(2) 2	(11)11	(11)11

(2013-2016)

<Fund> **(million yen)**

Fiscal Year	2013	2014	2015	2016	Total
Personnel	358.26	310.46	369.64	358.68	2962.62
- Faculty members (including researchers)	226.35	225.00	287.55	275.69	2203.39
Full-time	53.78	23.49	26.90	24.39	227.78
Concurrent	172.57	201.51	260.65	251.30	1975.61
Postdocs	32.91	26.58	27.88	26.06	321.17
RA ect.	21.86	0	0	0	33.44
Research support staffs	10.99	8.16	8.44	11.51	60.19
Administrative staffs	66.15	50.72	45.77	45.42	344.43
Project activities	312.56	235.62	224.18	224.18	2639.13
Travel	4.29	4.65	0.60	0.60	34.51
Equipment	0.31	262.41	190.83	205.41	4720.37
Research projects	36.61	34.77	63.26	57.37	437.72
Total	712.03	847.91	848.51	846.24	10794.35

<Personnel> **(person)**

Fiscal Year	2013	2014	2015	2016	Total
Personnel	131	78	81	75	711
- Faculty members (including researchers)	47	49	54	51	396
Full-time	5	7	7	7	35
Concurrent	42	42	47	44	361
Postdocs	12	12	13	9	103
RA etc.	51	0	0	0	106
Research support staffs	7	6	5	6	37
Administrative staffs	(12)14	(9) 11	(8) 9	(8) 9	(62)69

(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 (Bldg. C)	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	2014.3.31
Quantitative Biology Center (QBiC)	145	Laboratory, experimental room	2014.4.1	In operation
Center for Information and Neural Networks (CiNet)	410	MRI Room	2013.4.1	In operation
BioSystems Building	100	experimental room	2015.4.1	In operation

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.

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.

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

3) Osaka University Distinguished Professor System (April 1, 2013)
-Awards leading researchers with outstanding achievements a special title of "Osaka University Distinguished Professors" and an allowance of up to six million yen a year. Ten distinguished professors were selected; Akira and S. Sakaguchi being two.

4) Performance-related annual salary system (January 1, 2014)
-Pays 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 accept overseas researchers as a world premier research institution.

5. 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	54

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

Name	Total number of users
International House	56
International Student Dormitory	4
Guest House of the Research Center for Nuclear Physics	45
Kasugaoka House	11

③ Apartments for university employees (University apartments)

Name	Total number of users
Tsukumodai Apartment	24
Momoyamadai Apartment	1
Sakuranotyou Apartment	1

④ Nursery school in university campus (Takenoko and Machikane Child-care Centers)

Name	Total number of users
Takenoko Child-care Center	2
Machikane Child-care Center	1

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	3	Yanagida	Namba	Seymour	
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
Network Administration Office	20

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.

(Implementing datability)
In line with Osaka University's datacentric approach, the Institute for Datability Science was launched (April 2016) to become a leading player in big data society by gathering the intellectual, scientific and technological assets at the university under the concept of datability. The institute will pursue data science, new methods of science through datability or the responsible utilization of usable big data in a sustainable form for the future. In that process, we will make full use of high level communications technology, such as artificial intelligence to create a new horizon for technology and science in life sciences, medicine, dentistry, pharmacology, science and engineering and the humanities and implement interdisciplinary research in order to promote the creation of new societal, public, and economic value. This will accelerate interdisciplinary research at IFReC and offer new opportunities for interdisciplinary co-creation.

World Premier International Research Center Initiative (WPI)

Appendix 5-2. The Host Institution's Mid-term Plan

(1) Excerpts from the Osaka University Medium-Term Plan for the 2nd period (2010 - 2015) related to IFReC's position within the University

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添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.

Extract: The Medium-term goals of Osaka University

The Medium-term goals will be implemented for the six year period from April 1, 2010 until March 31, 2016.

(Promoting world top class research)

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.

Extract: The Medium-term plans of Osaka University

2. Measures to achieve research goals

(1) Measures to achieve the goals in terms of the standard of research and the results from the research

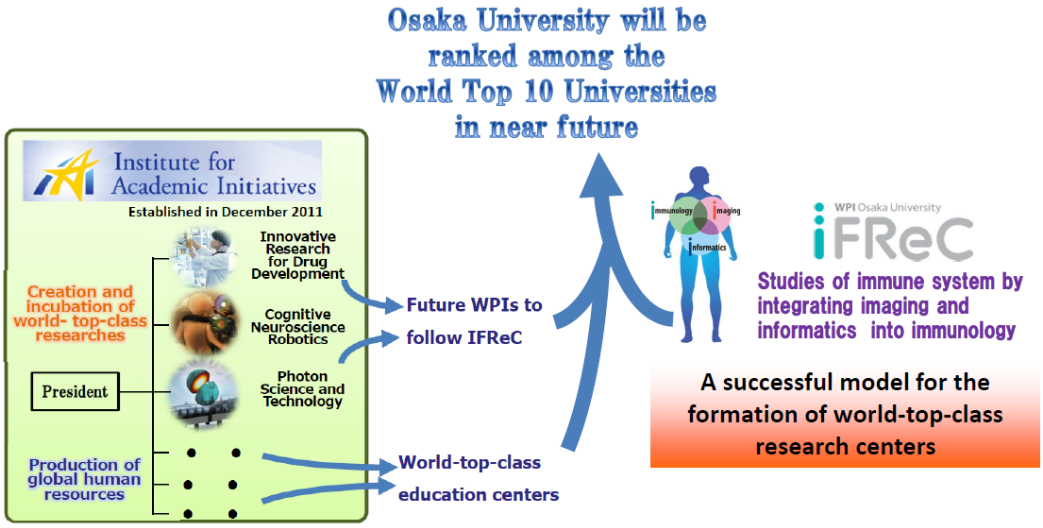
(Enhancement of the fundamental research)

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.

(Promoting priority research projects)

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.

(2) The IFReC's position within Osaka University, the Institute for Academic Initiatives (2012 - 2015)



IFReC's position within Osaka University Immunology is the research area with the longest tradition at Osaka University and leads the world in the field*. Thus, immunology is of great importance to Osaka University and IFReC is its symbol. In fact, IFReC is the highest level research center in the university and a successful model for the formation of a world-top-class research center, and as such, is positioned to lead the University its goal to be one of the top 10 universities in the world in future. (*"Essential Science Indicators" by Thomson Reuters)

Why Osaka University supports IFReC While IFReC is expected to further promote research in immunology with related interdisciplinary areas including clinical applications and drug development, the establishment of IFReC has created a number of ripple effects that are accelerating system reform in the university. For this reason, Osaka University will continuously provide financial and administrative support to IFReC.

The Institute for Academic Initiatives, Osaka University was established in 2011 to implement the principal strategy for future development of Osaka University, creating and nurturing new world-top-class research groups as candidates for future WPIs. The initiatives include financial reform and reallocation of academic positions, a vision of management. For the financial reform of the university, effective utilization of various financial resources have been reconsidered to promote fundamental research and human resource development and the redistribution of overhead charges for research projects from the government and industry, donations, and hospital gains. To advance education and research, reallocation of academic positions is underway to the most necessary divisions in the university, and to schools and institutes proposing superior future plans. The heads of such schools and institutes can use those extra positions at their discretion.

Osaka University's support to IFReC In this way, Osaka University will provide continuous financial support to IFReC with academic positions mainly for principal investigators. The total budget and the number of researchers will be the same as those of the present WPI-Program.

(3) 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～

World Premier International Research Center Initiative (WPI)

Appendix 5-3. Transition in the Number of Female Researchers

* Enter the number and percentage of female researchers in the top of each space from 2010 to 2015 and the total number of all the researchers in the bottom.

(person)

		FY2010	FY2011	FY2012	FY2013	FY2014	FY2015	Final goal
Researchers		35,20.2%	35,20.2%	39,21.3%	35,18.8%	35,19.5%	16,12.5%	38,21%
		173	173	183	186	179	127	180
	Principal investigators	1,3.7%	1,3.7%	1,3.8%	1,4.0%	1,3.7%	1,3.7%	3,10%
		27	27	26	25	27	27	30
	Other researchers	34,23.3%	34,23.3%	38,24.2%	34,21.1%	34,22.3%	15,15%	35,23%
		146	146	157	161	152	100	150

World Premier International Research Center Initiative (WPI)
Progress Plan (For Final Evaluation)

Host Institution	Osaka University	Host Institution Head	Shojiro Nishio
Research Center	Immunology Frontier Research Center	Center Director	Shizuo Akira

* Write your report **within 6 pages**.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

1. Mid- to Long-term Research Objectives and Strategies Based on the Center's Results during Funded Period

Describe new challenges in the Center's research objectives and plans after the funding period ends. If major adjustments will be made in the Center's operation, such as newly set research themes/objectives or a change in the director, describe the strategic background to the adjustments.

IFReC was established as a WPI center in recognition of the advanced research achievements produced in immunology. IFReC's mission is to combine the fields of immunology, imaging and informatics to comprehensively understand the dynamics of the immune systems. At the time, the fusion of different fields for advanced interdisciplinary research was both revolutionary and futuristic. Ten years on and the importance of interdisciplinary research is extremely high. A high percentage of the papers in international journals are the outcomes of this research. During this time, IFReC has published more than 1000 papers with the average number of citations at 38.4 and an h-index of 84. In addition, IFReC researchers have had several new discoveries of elements in the immune system and cell signaling pathways. When IFReC was launched, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) established interdisciplinary research as a major mission of the WPI program and the results are highly acclaimed internationally. IFReC has produced research outcomes in medicine and basic immunology that are recognized by the Program Committee to be of a world-top-class standard and worthy of the World Premier Status.

To date, immunology research at Osaka University has created many novel research outcomes, technological innovation and intellectual property. Of particular note is the research by IFReC PI, Kishimoto which produced the immunosuppressive drug Tocilizumab (trade name Actemra), effective for the treatment of rheumatoid arthritis and now holding a significant position in the market, is the first bioactive drug developed from research in Japan. Due to achievements such as this, IFReC is attracting significant attention from overseas for its immunology and life science research from both researchers and many large international pharmaceutical companies.

As we begin the 21st century, the advancement of cutting edge research is a critical policy for not only advanced but also developing countries. The Max Planck Institute in Germany is an example of the formation of a structure to sustainably advance cutting edge research into the future. IFReC is acclaimed as one of the top research centers for immunology in the world, however, our role as a WPI center in Japan is not yet complete. The development of IFReC should be seen as three phases over the long term. The first 10 years are the major first step, next is maintaining that momentum. In the next 10 year phase, emphasis is on the support of world-leading researchers and the precise setting of new goals to encourage proactive investment into new horizons.

IFReC was not awarded continued support at the WPI assessment for extension and from 2017 will become a permanent research institution of Osaka University.

1-1 "IFReC, a cradle for innovative immunologists"

At IFReC, senior and young researchers, whose fields are very different, have gathered to promote "fusion" studies, each contributing their own specialties. A unique and vibrant research environment has been formed with a collection of top-class researchers, excellent facilities and an effective research support system. The researchers fostered here will grow through friendly rivalry and attempts to challenge new interdisciplinary research projects in an ever-improving environment. Here, researchers to develop IFReC and immunology in the future, especially those who promote fusion studies and those who are expected to succeed internationally will be fostered and utilized through the strengthening technology of bioinformatics and imaging during

the period of preparation for the next stage after the WPI grant. IFReC will serve as a hub for international brain circulation based on active recruiting and mobility of young researchers. Also, the internationalization system nurtured in the WPI program will be dispersed in the university to encourage the globalization of Osaka University. International visibility as a WPI in Japan will be further increased and the ability to trust in Japanese science will be encouraged.

(1) Collaboration with QBiC: Researchers at IFReC and QBiC, located in the same campus, are working together to solve important issues in immunology. Spatio-temporal and collective behavior of immune molecules and cells are observed using cutting-edge imaging methods and the big data obtained are analyzed with computer-aided theories of systems biology to model the immune system as a whole. In this way, we can understand how the immune system and its dynamics are generated by interaction of its various elements such as molecules and cells under variable conditions. IFReC will provide an excellent research environment for young researchers to find a way to control the system behavior, ultimately leading to development of new immunotherapy and to promote study of different fields.

(2) IFReC serving as a hub for international brain circulation: For young researchers to become veteran researchers in the international circulation of brain talent, appropriate mentorship by a principle investigator at a research institute and an appropriate research environment are indispensable. At the same time, it is desirable to expand the network of individual researchers and advertise research achievements in the field. It is necessary for IFReC to set up a research collaboration hub and to support young researchers more through outreach and public relations activities. With these measures, IFReC researchers will be able to obtain higher positions at other institutions, thereby attracting more external researchers.

1-2. Generation of innovative immunotherapeutics

At IFReC, the application of research outcomes to medical/clinical immunology has been accelerated through cooperation with the University Hospital. We recognize that development, deployment and transfer of new insights into immune-regulating mechanisms attained at IFReC, are crucial to address intractable diseases, which will be a major step toward contributing to human welfare by preventing and/or curing various diseases that have a major impact on the quality of life. This contribution, through application to medical/clinical immunology, will also provide a practical platform to nurture young researchers to become capable in both basic and translational immunology. Listed below are major projects for such challenges.

(1) Development of innovative immune-regulating techniques: The innate immune system takes part in a wide range of diseases and/or their symptoms such as cancer metastasis and infiltration, allergies, metabolic syndromes, heart diseases, autoimmune diseases, even psychiatric disorders and so on. IFReC has elucidated the affect and influence on diseases by post-transcriptional regulation of cytokine mRNA. This achievement has developed into research on key players in innate immune responses—the roles of monocyte/macrophage subsets. These studies will open up a new path and contribute to IFReC's international superiority. Based on the achievements obtained from such studies, IFReC will develop novel techniques regulating innate immune responses, leading to prevention and/or cure of the diseases described above.

(2) Development of innovative cancer immunotherapy: The aim of cancer immunotherapy is to evoke and enhance effective anti-tumor immune responses by targeting various immune responses. Recent clinical studies have shown that several immunotherapeutic agents are of significant help in treatment of advanced cancers via control of regulatory T (Treg) cells and resulting activation of effector T cells. Small molecules that selectively target Treg cells and stimulate innate immunity have been discovered. Application of these small molecules for therapy is planned.

(3) Development of novel diagnostic and therapeutic strategies for autoimmune diseases: Approximately one third of the diseases designated as of concern by the Ministry of Health, Labor and Welfare are immune-related diseases. Although symptoms of rheumatoid arthritis can be dramatically improved owing to the development of antibody-based medicine such as anti-IL-6 antibody, success via conventional treatment continues to be poor in other autoimmune diseases including systemic lupus erythematosus and autoinflammatory diseases such as Crohn's disease. Information on these pathological conditions collected by medical scientists in the clinic will be analyzed based on bioinformatics methodology, and a framework to develop novel antibody-based medicine will be established through diagnosis of symptoms of autoimmune diseases and evaluation of therapy effects via collaboration between basic immunologists and researchers developing medicines.

(4) Promotion of new drug development with innovative PET/MR and PET/CT imaging A number of candidate compounds for new drugs which affect immune phenomena

have been synthesized based on basic immunology research at IFReC. PET/MR facility for small animals is established based on the Good Laboratory Practice in Osaka University to enable selection of the most suitable compound as a new drug at the preclinical stage. Once selected, a first-in-human microdosing PET study can be conducted by the Good Manufacturing Practice-based PET facilities in Osaka University Hospital (only one in Asia). Whole-body pharmacokinetics/dynamics in humans can be analyzed during very early stages of new drug development. These combined preclinical and clinical PET imaging studies will facilitate drug development for immunotherapy and improve safety.

(5) Forefront vaccine development: Outcomes from studies at IFReC are expected to make considerable contributions to development of next-generation vaccines based on molecular designing. These include searching methods for protective antigens on the basis of molecular immunology and structural biology, novel adjuvants on the basis of research outcomes in innate immunity and techniques to regulate mucosal immunity on the basis of research outcomes in mucosal immunity, etc. Vaccine target diseases now include a broad range of diseases from infectious diseases and cancer to many other lifestyle-related diseases. IFReC will promote research and development studies of vaccines against these diseases through implementation of industry-academia-government joint cooperation through active exchanges of researchers at the Research Institute for Microbial Diseases, Osaka University, the National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN), and the Research Foundation for Microbial Diseases of Osaka University (a vaccine manufacturer).

2. Management System of the Research Organization

2-1. Describe the Center's Research Organizational Management System that will Execute the Research Strategy and Plan Described above.

- In Appendix 1, list the PIs who will ensure that the Center's project is sustained and advanced after the funding period ends.
- In Appendix 2, diagram the Center's organizational management system.

IFReC management has produced outstanding achievements as a WPI. The current research organization and operation structure will be maintained to the extent possible to fully utilize the advantages. Namely, 1. top-down decision making by the Director, 2. use of generous discretionary expenses, 3. Research Planning and Management Office (RPMO) in administration staffed with personnel familiar with the needs of researchers, and 4. staff in the general affairs and accounting sections who are capable in English. Only through the evolution of these systems can a truly high quality international environment be achieved. The internationally acclaimed Winter School, the international symposium, participation in international exchange by Osaka University and the attention of international media all contribute significantly to the elevation of Osaka University's international university ranking.

To systematically conduct research in the mid- to long-term, IFReC will encourage further participation of PIs and form a system for seamless progress from basic research to medical/ clinical immunology. In addition, researcher involvement in drug and diagnostic development will ensure researchers have a greater awareness of and commitment to social contribution. The center will also form its own system to acquire the funding to achieve these goals.

(1) PI organization with strong potential New PIs will encourage the seamless development of basic research toward application to medical and clinical immunology and will further promote interdisciplinary research. In particular, three new concurrently appointed PIs will be added in FY2017. (1) Yukinori Okada is a specialist in bioinformatics, his focus is on genomic drug discovery. He became a professor in the Osaka University Graduate School of Medicine at the age of 35. He was also awarded second prize for the Baelz Prize in 2012. (2) Toshihide Yamashita has succeeded in publishing several papers in top journals such as Nat Med over the past few years in neuroimmunology elucidating the molecular mechanisms of regeneration of damaged neural connections. He was awarded the Osaka Science Prize in 2011. (3) Takashi Nagasawa, leader in research on hemopoietic stem cells. He was awarded the Takeda Prize for Medical Science in 2014. In addition, young PIs will be placed on the newly established tenure track to be discussed later.

(2) Use of outstanding researchers In IFReC's 10 year history many young researchers have left to find positions at universities, research organizations, and companies in Japan and overseas promoting the flow of personnel. On the other hand, the average age of PIs is rising. IFReC will not simply cease research when a researcher reaches a certain age. In the US in particular, researchers with the potential and energy to continue producing outstanding outcomes are offered the opportunity to continue after retirement. It can be said that

scientific standards in the US lead the world due to the continuity of and the ability to hand down research heritage. At IFReC, if researchers are able to continue to achieve outstanding research outcomes and publish papers in top international journals as well as acquiring external funding of 100 million yen per year, they will be provided with a research environment. Young researchers will have opportunities as PIs. It is vital to maintain a high research standard across generations.

(3) Introduction of a tenure track to train young PIs A tenure track system will be introduced to enable the employment of young PIs, including women and foreigners, using the network created by the Winter School. New PIs will be provided start up and financial support using existing programs such as the Research Support Program for Combined Research and the Travel Expense Support Program for Young Researchers with the aim of training the next generation of IFReC core researchers.

(4) Use of corporate vitality toward medical and clinical immunology development The level of basic immunology, medicine and clinical medicine at IFReC is evaluated extremely highly. To expedite the translation of these outcomes to applied research, early investigation of intellectual property feasibility at an early stage is vital. One strategy is to consult with experts such as pharmaceutical companies. The comprehensive agreement with a pharmaceutical company detailed in 2-2 is an attempt to expedite applied research. An Open Research Laboratory will be opened on campus including a joint research department and collaborative laboratories with industry researchers and intellectual property specialists on permanent staff to enable prompt discussions (see 2-2). Research laboratories and research institutes at leading universities overseas have already accepted personnel from a broad industry spectrum and are improving their ability to compete on a global stage. One of IFReC's overseas partner institutions— Singapore Immunology Network (SIgN, Singapore)—has not only international pharmaceutical companies but the food industry, such as Nestle, involved in research. This example demonstrates that greater diversity in access to industry may be sought with plans to become the largest center for industry, government and academic cooperation.

(5) Enhanced function as a hub for international brain circulation To maintain a research level that is world top level, it is vital to ensure a diversity of ideas by proactively employing researchers from overseas or having researchers in Japan gain overseas experience. To function as an international brain circulation hub, IFReC is investigating the potential for cooperative research centers with overseas institutions to encourage IFReC researchers through mutual training via exchange of young researchers. Potential partners include the Max Planck Institute (Germany), La Jolla Institute (USA), SIgN, and Melbourne University (Australia) (possible new partnership agreement). In addition, further reinforcement of the international symposium, the Winter School and outreach activities for researchers will develop and enhance IFReC's research activities and the visibility of researchers.

(6) Preservation of the research support system Currently, staff, including PhD holders in the RPMO provide a variety of support to researchers. From FY2017, as detailed later, IFReC will be strengthening collaboration with industry. It is necessary to consider cooperation with industry particularly for use of intellectual property. In addition, greater cooperation with a wider range of researchers both overseas and in Japan will increase competitiveness and support the formation of a dynamic hub for brain circulation. To achieve these measures, it is important to train staff who support research within the organization such as administration and technical staff, and promote their activities. Those staff members who have extensive experience in the environment of international competitiveness at IFReC are highly skilled and have been hired as planners for entrepreneurial think tanks or hired as regular staff by Osaka University. These moves by staff are highly motivating for younger staff and further contribution is made to human resources in Japan.

2-2. Initiatives and Plans that will Impel System Reforms

Describe the Center's action plan that embodies the basic policies of the National University Reform Plan or Independent Administrative Agency Reform Plan, and the Center's plan and strategies that lead to host institution reforms either directly or via ripple effects (also to other institutions, if applicable). Describe also the Center's strategies for fostering and securing the next generation of researchers (e.g., introduction of tenure tracks), and the system for enhancing the Center's organizational management, such as the implementation/verification PDCA system.

The activities originating from IFReC reflected in the system reform being implemented by Osaka University in its OU Vision 2021 (see 3-1) are too numerous to mention. Globalization of education, refined learning environment and campus life, promotion of international joint research through cross–appointments, a research administrator (URA), commercialization of

translational research through a medical-dental-pharmaceutical network, outreach activities, a one stop acceptance-dispatch-exchange support system, a multicultural and multilingual campus environment etc. Our mission is to continue to influence system reform at the university. In particular, for the promotion of Osaka University-style comprehensive university-industry cooperation, the following leading examples demonstrate the importance to Osaka University of an "International Advanced Research Organization" (provisional name) for the acquisition of new competitive research funding.

A new framework to take advantage of corporate vitality To ensure the independence of IFReC management and research beyond the end of the WPI grant in 2017, a new contract for "University-Industry Co-Creation" in the form of a comprehensive collaboration contract was concluded with Chugai Pharmaceutical Co., Ltd. for one billion yen a year for 10 years (2017-2026). This contract solidifies the foundation for IFReC's continued development after the WPI grant. The benefits gained by the company via this contract are preferential disclosure of research outcomes and first right of refusal to apply for joint research, intellectual property or licensing. These rights are restricted to the comparative percentage of IFReC's total expenses supplied by the company thereby guaranteeing the independence of researchers. In addition, other companies are free to apply for joint research on topics other than those selected by the pharmaceutical company. IFReC's policy is to proactively seek collaboration and joint research with other industry entities.

Plans for an open innovation laboratory to utilize corporate vitality The Open Innovation Laboratory will promote the establishment of a joint research department or cooperative laboratory based on joint research between IFReC researchers and industry in IFReC or within Osaka University. This measure will stabilize IFReC's operations, encourage collaboration with various companies, and achieve the university's mission as a national university of Japan.

3. Center's Position within Host Institution and Measures to Provide It Resources

Describe the Center's future plans with regard to the following points after the funding period ends.

3-1. From a Mid- to Long-term Perspective, the Position of the Center within the Organization of the Host Institution

Describe where the Center will be placed within the host institution's overall organizational strategy under the leadership of the institution's president.

- In Appendix 3, diagram the Center's position within the organization of the host institution, and describe that positioning using excerpts from the institution's mid- to long-term plan. If the plan has not been established yet, describe the consideration being given to the Center's positioning.

Looking toward its 90th anniversary, Osaka University has created the "OU Vision 2021" for the third six-year mid-term goal period—considered the "period of evolution"—to guide continuous efforts for self-reform. OU Vision 2021 removes the barrier between university and non-university as well as the barrier between departments at the university to build five pillars that open up knowledge at the university to the world and for the benefit of human society. These pillars are; Open Education, Open Research, Open Innovation, Open Community and Open Governance.

Based on these pillars, the university aims to evolve into a place for orchestration and co-creation of knowledge through the outstanding pursuit of scholarship and actively seeking integrated study of knowledge that crosses academic disciplines, as well as cooperation with diverse members of society.

Open Research Osaka University aims to create and deepen diverse knowledge from world-top-level basic research and interdisciplinary research. Due to a new strategy of establishing an International Advanced Research Institute (provisional name) to act as an incubator for the creation of new world-leading academic domains including composite domains of different fields; Osaka University intends to sustain IFReC, which is recognized as an institute with outstanding research capability and sophisticated research facilities, and to create world top-level research centers that emulate IFReC. Osaka University is expected to approve the transition of IFReC as a 10 year provisional position in the university (by the end of WPI support; March 2017) to a permanent research organization based on a comprehensive agreement with a private company. The host institute will support IFReC with its exceptional research capability, as well as its global visibility, as a leading research center of Osaka University.

Open Innovation Osaka University was ranked first in Japan (18th in the world) in

Thomson Reuter's "the World's Most Innovative Universities 2015," which is measured based on universities' contribution to industry. This acknowledges the pioneering measures Osaka University has taken for university-industry cooperation. In its Open Innovation strategy, the university promotes the OU style of "University-Industry Co-Creation" to discover questions for new basic research on the basis of social needs and achieve an open, reciprocal flow of knowledge. IFReC's active involvement in Open Innovation is expected by utilizing its outstanding research capability and pioneering role for cooperation with the industry, Osaka University will continue to provide IFReC with financial and technical support for development from basic to medical and clinical immunology. The collaboration with a private company described in 2-2 is one measure for the university to advance beyond the framework of the Management Expenses Grant by introducing corporate vitality into the university, a government strategy stipulated in the 5th Science and Technology Basic Plan, and the university expects IFReC to be a forerunner of these measures.

Open Community Osaka University aims to build an Open Community, which will realize a campus of diversity encompassing culture, language and gender. For this aim, the university continues to establish infrastructure that supports globalization on campus. IFReC is expected to contribute to globalization of the university by contributing to international brain circulation.

3-2. Host Institution's Action Plan for Sustaining and Advancing the Center as a World Premier International Research Center (e.g., positioning, financial resources)

IFReC, as a core member of the "International Advanced Research Organization" (provisional name) at Osaka University will focus its future activity on becoming an open innovation hub for brain circulation open not only to researchers of Osaka University but also to industry. The expected external funds from industry will make it possible to create a foundation for IFReC's research activities. Osaka University will implement the following plan.

Assignment of permanent positions (researchers and staff): Osaka University has provided IFReC with seven research support administrative staff, enabled researchers to join on cross-appointments for diversity, and in FY2015, provided tenure positions for overseas researchers (one professor and two associate professors). Further, the university plans to offer five further tenure positions (including two professors) for three laboratories.

Maintenance and management of common facilities: Osaka University plans to support IFReC by incurring costs related to the maintenance of core and common facilities and the animal facility for infectious diseases.

Ensuring IFReC operating costs through collaboration with industry: The president of Osaka University and the chairman of Chugai Pharmaceutical, Co., Ltd. concluded the comprehensive agreement described in 2-2 on 19th May, 2016. For IFReC, this ensures a large part of the budget required for its operation. However, it is insufficient to fully carry out the missions of a WPI because, for accounting reasons, there are conditions that must be fulfilled for fundamental research, educational activities of the university, social contribution, globalization of University, etc. In order that IFReC functions as an international hub of brain circulation, research activities at IFReC should directly contribute to the career of researchers. Researchers must be able to start immediately after their arrival at IFReC, be provided necessary support for legal compliance to conduct research, and be able to gain experience to obtain grants and to manage their own research projects and achieve satisfactory results. In addition, outreach activities for recruiting capable young researchers and international symposia and Winter Schools, which are effective for young researchers to forge personal networks with peers, are important for IFReC. Securing and developing human resources such as URAs are key to continuously providing the above support for researchers. Therefore, financial support from Osaka University and MEXT is vital for IFReC to carry out the WPI missions and contribute to develop medical/clinical immunology as a world leading WPI institute beyond the first 10 years.

World Premier International Research Center Initiative (WPI)

Appendix 1. List of Principal Investigators for Progress Plan

- If the number of principal investigators exceeds 10, add columns as appropriate.
- Place an asterisk (*) by the name of the investigators who are considered to be ranked among the world's top researchers.
- Give age as of 1 April 2017
- For investigators who cannot participate in the center project from its beginning, indicate the time that their participation will start in the "Notes" column.

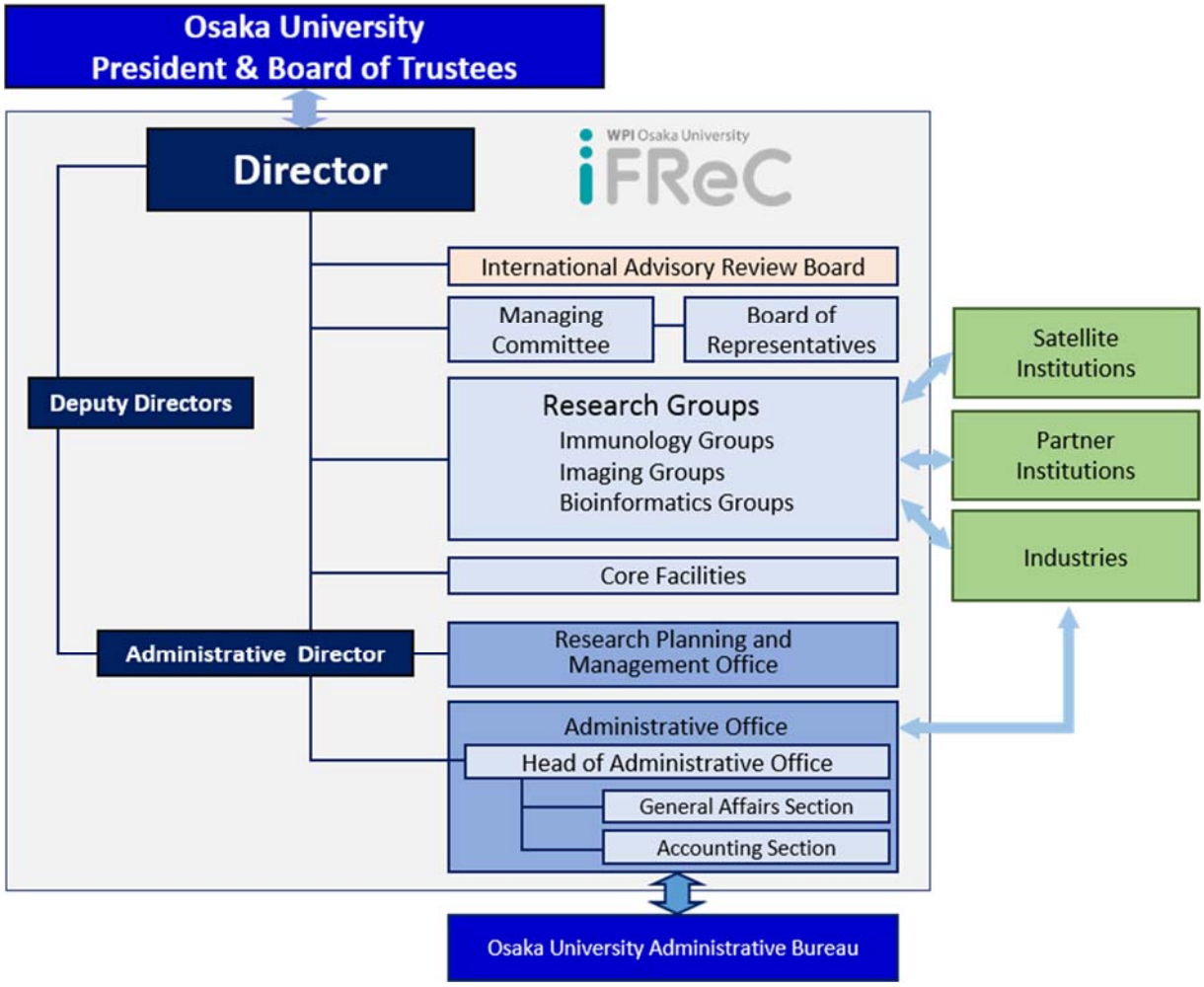
Name	Age	Current affiliation (organization, department)	Academic degree and current specialties	Notes (Enter "new" or "ongoing")
1. Shizuo Akira*	64	Director and Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	Ongoing
2. Tomohiro Kurosaki*	61	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology and molecular biology)	Ongoing
3. Hisashi Arase*	51	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	Ongoing
4. Atsushi Kumanogoh*	50	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	Ongoing
5. Kiyoshi Takeda*	50	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Immunology)	Ongoing
6. Ken Ishii*	48	Project Leader, National Institute of Biomedical Innovation (NIBIO)	MD, PhD (Immunology, Vaccine Science)	Ongoing
7. Cevayir Coban	44	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Clinical Microbiiology)	Ongoing
8. Kazuhiro Suzuki	41	Associate Professor, WPI Immunology Frontier Research Center	MD, PhD (Immune cell dynamics	Ongoing
9. Masahiro Yamamoto	38	Professor, Research Institute for Microbial Diseases, Osaka University	PhD (Immunology)	Ongoing
10. Seymour Benjamin John	44	NICT Invited Executive Researcher and Wellcome Trust Intermediate Clinical Fellow (Cambridge University)	PhD (Neurological Science)	Ongoing

11. Yoshichika Yoshioka*	63	Professor, WPI Immunology Frontier Research Center, Osaka University	DSc (Biophysics)	Ongoing
12. Jun Hatazawa*	63	Professor, Graduate School of Medicine, Osaka University	MD, PhD (Nuclear Medicine)	Ongoing
13. Kazuya Kikuchi	51	Professor, Graduate School of Engineering, Osaka University	PhD (Chemical Biology)	Ongoing
14. Masaru Ishii	43	Professor, Graduate School of Frontier Biosciences, Osaka University	MD, PhD (Bioimaging)	Ongoing
15. Nicholas Isaac Smith	42	Associate Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Engineering / Applied Physics)	Ongoing
16. Yutaka Hata*	55	Professor, Graduate School of Engineering, University of Hyogo	PhD (Computer Engineering)	Ongoing
17. Daron M. Standley	49	Professor, WPI Immunology Frontier Research Center, Osaka University	PhD (Chemistry)	Ongoing
18. Nagata Shigekazu*	67	Professor, WPI Immunology Frontier Research Center	PhD (Molecular/Cell Biology)	Ongoing
19. Taroh Kinoshita*	65	Professor and Deputy Director, WPI Immunology Frontier Research Center, Osaka University	PhD (Immunology, Biochemistry)	Ongoing
20. Shimon Sakaguchi*	66	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	Ongoing
21. Takashi Saito*	66	Group Director, RIKEN, Research Center for Integrative Medical Sciences	PhD (Immunology)	Ongoing
22. Hitoshi Kikutani*	66	Professor, Research Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	Ongoing
23. Tadamitsu Kishimoto*	77	Professor, WPI Immunology Frontier Research Center, Osaka University	MD, PhD (Immunology)	Ongoing

24. Fritz Melchers*	80	Max Planck Fellow	PhD (Immunology)	Ongoing
25. Toshio Yanagida*	70	Professor, Graduate School of Frontier Biosciences, Osaka University	PhD (Molecular imaging)	Ongoing
26. Tsuneyasu Kaisho*	57	Professor, Department of Immunology Institute of Advanced Medicine Wakayama Medical University	MD, PhD (Immunology)	Ongoing
27. Rikinari Hanayama	42	Professor, Department of Immunology Kanazawa University Graduate School of Medicine	MD, PhD (Cell Biology)	Ongoing
28. Yukinori Okada	36	Professor, Graduate School of Medicine, Osaka University	PhD (Bioinformatics)	New
29. Toshihide Yamashita	52	Professor, Graduate School of Medicine, Osaka University	PhD (Neurological Science)	New
30. Takashi Nagasawa	56	Professor, Graduate School of Medicine, Osaka University	PhD (Immunology)	New
31. Sho Yamasakai	48	Professor, Medical Institute of Bioregukation, Kyusyu University	PhD (Immunology)	New

World Premier International Research Center Initiative (WPI)

Appendix 2. Diagram of Center Management System



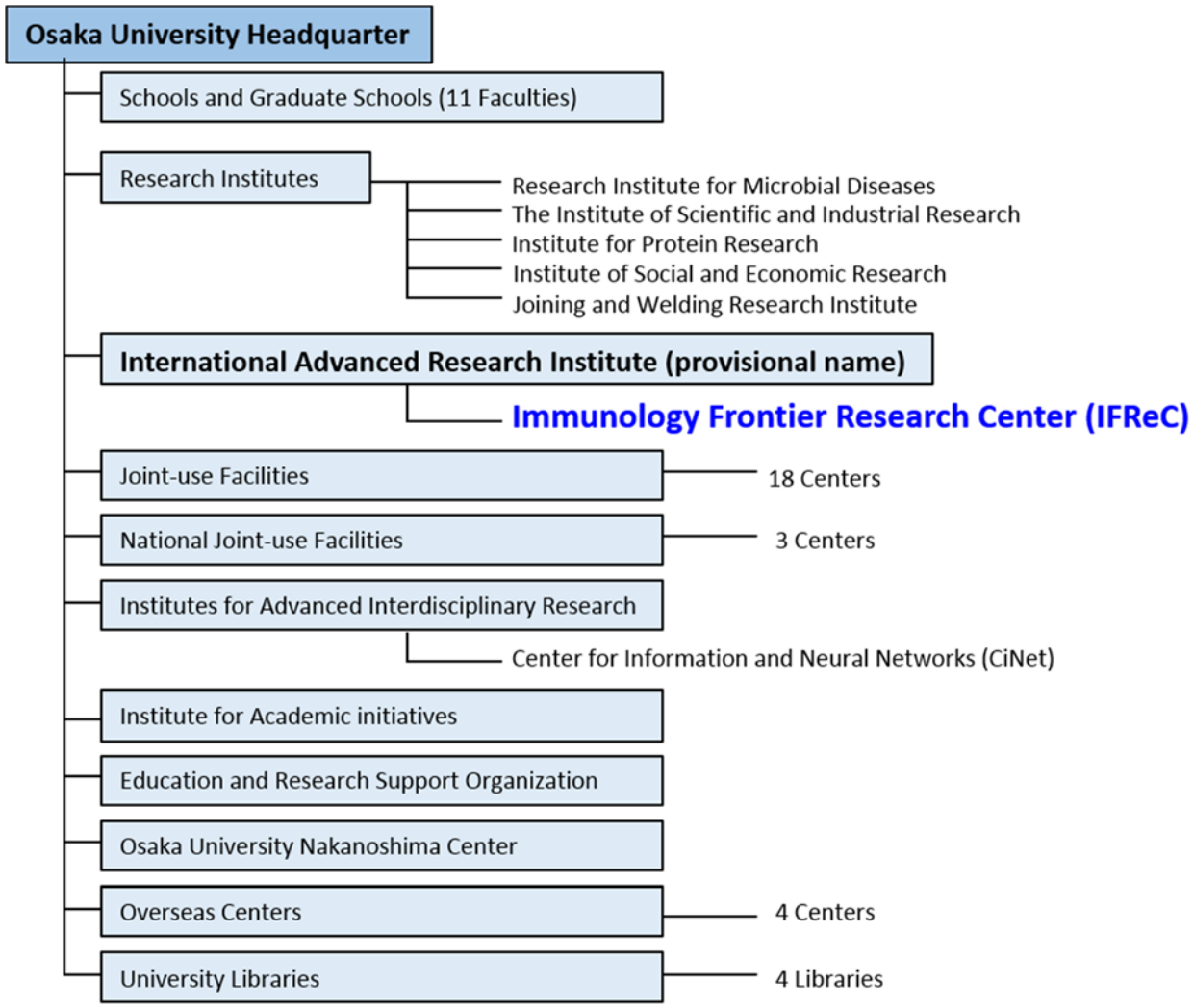
Osaka University authorizes the center director to make top-down decisions to establish a research environment for researchers to concentrate on their research, to simplify administrative procedures, and to streamline office work. Thus, the director makes major decisions, to which the administrative director gives full support by acting as a coordinator along with the deputy directors and by executing management actions through the administrative office. Important matters such as annual budget and the appointment of PIs, or equivalent, are approved by the center management committee and the board of representatives. The research planning and management office, consisting of several personnel with research experience and bilingual staff, handles various matters related to research. These include organizing symposia, seminars, outreach activities, management of matters related to intellectual property, matters relating to the safety and hygiene of the organization, purchase procedures for instrumentation, and management of collaborations with industry, etc.

World Premier International Research Center Initiative (WPI)

Appendix 3. Position of the Center within Host Institution

* Diagram the Center's position within the organization of the host institution, and describe that positioning using excerpts from the institution's mid- to long-term plan. If the plan has not been established yet, describe the consideration being given to the Center's positioning.

1. Diagram of the IFReC's Position within the Organization of Osaka University



IFReC's position within Osaka University

Immunology is the research area with the longest tradition at Osaka University and IFReC leads the world in the field. Thus, immunology is of great importance to Osaka University and IFReC, which was established as a WPI institution in 2007, is its symbol as the highest level research center in the world. It is a successful model for the formation of a world-top-class research center, because IFReC has developed research in immunology with related interdisciplinary areas including clinical applications and drug development, and has accelerated system reform in the university.

Osaka University intends to transition the 10 year limited position of IFReC by the end of WPI support (March 2017) and to sustain it as a permanent research center in a newly established organization "International Advanced Research Institute (provisional name)". In the organization, Osaka University anticipates the creation of other world top-level research centers that emulate IFReC. IFReC is thus positioned to lead the University toward the goals set in Osaka University (OU) Vision 2021.

2-1. Excerpts from the Osaka University Mid-term plan for the 3rd period (2016-2021) related to IFReC's position within the University

(Preface) Fundamental Goals of Osaka University

The world has a diversity of races, religions, languages, systems, and customs, etc. Although this diversity is indispensable for innovation and for human activities in a refined society, it may sometimes become an obstacle for sound development of global society. Human beings in the 21st century must establish a humane society through benefits brought from leading-edge science and technological development while solving social issues that arise from various social factors intertwined with each other. In order to address this social challenge, a university, as a seat of learning, must serve as a place for "orchestration and co-creation of diverse knowledge" by means of its academic discipline. This is the force to open up the future.

Osaka University (hereinafter the "University") will contribute to global society as a university established in Osaka, Kansai and inherits the spirit of its origins in Kaitokudo and Tekijuku. Toward this aim, the University provides an effective education and research environment in which excellent brains and talents gather from all over the world to compete with each other and develop their potential to the maximum. In our new platform for education and research, through creation of new academic disciplines by combining different fields as well as studies for acquisition of integrated knowledge beyond each field, the University aims to develop human resources who can; address, with unique approaches, social issues on a global scale that are caused by various factors intertwined with each other; who can promote cutting-edge science and technological development; and who can make a great contribution to the creation of an altruistic society. Through this process, the University aims to evolve into a world-leading research-oriented university that can meet expectations from global society.

The University also promotes collaborative innovation through mutual understanding and collaboration among people with diverse range of knowledge, skill, experience, position, etc., while seeking for advanced level of education and research that pursue the essence of academic disciplines. With the motto "Live Locally, Grow Globally," the University wishes to be a university that grows with society, hand in hand with wide range of partners such as local residents in and outside surrounding municipalities, and political, economic and industrial spheres, while fulfilling social responsibility as a national university corporation and bearing in mind its history of establishment with the support of general public in Osaka. Furthermore, the university is determined to undertake the responsibility and expectations given by global society; developing human resources who can take on revolutionary tasks to develop a vigorous society that grows sustainably, and creating new values.

(Period)

The Medium-term goals will be implemented for the six year period from April 1, 2016 until March 31, 2022.

(Goals for research)

(1) Goals for research level and results

・In order to accelerate innovation that will lead to change in society and to realize an enriched and peaceful society, the University promotes the basic and fundamental researches that pursue the essence of academic disciplines. For this purpose, the University creates new academic disciplines through fusion of different fields by making full use of our advantages in diversity on campus, and advances academic research.

(2) Goals for research implementation system, etc.

・With the aim of realizing "the orchestration and co-creation of diverse knowledge", the University will establish invigorating research environment of a global standard, which enables us to evolve into a world-leading research-oriented university

・The University advances research capability by promoting joint use of facilities and collaborative researches at Research Institutes and Research Centers and other institutes on campus, and strengthen their function.

(Other goals)

(1)Goals for cooperation with and contribution to the society

・In order to create open innovation that anticipates social needs, the University will fulfill its responsibilities expected from global society by strengthening and promoting strategic and comprehensive cooperation among industry, government and academia, as well as returning research results generated in the University back to the society in and outside Japan.
・In order to activate circulation of academic intelligence, the University will disseminate intellectual assets the University possesses, and engage in social contribution activities through coordination and collaboration with the society.
(2)Goals for globalization
・The University will reinforce its global expansion to exemplify its philosophy of orchestration and co-creation of diverse knowledge by raising its international profile and standing while implementing globalization throughout the university.
(3)Goals for funding, etc. based on stipulations in the Industrial Technology Enhancement Act
・For international standardization of innovation activities by the University, the University will facilitate the provision of funding and human/ technical support to designated business operators which are authorized to utilize research results based on Industrial Technology Enhancement Act, and thus accelerate commercialization of research results generated from technologies of the University while furthering educational and research activities.

2-2. Excerpts from the OU Vision 2021

~Omitted~

Looking toward the 90th anniversary of its founding in 1931, Osaka University has created the “OU Vision 2021” for the six-year third mid-term goal period—considered the “period of evolution”—to guide continuous efforts for self-reform. The OU Vision 2021 aims to implement the philosophy of the Osaka University Charter proclaimed as the university set forth in its new guise as National University Corporation Osaka University.

The main causes of lagging innovation in Japan include the wide barriers between the inside and outside of organizations and community that forms on the narrow inside of those barriers. OU Vision 2021 removes the barrier between university and non-university as well as the barrier between departments at the university to build five pillars that open up knowledge at the university to the world and for the benefit of human society. These pillars are; Open Education, Open Research, Open Innovation, Open Community and Open Governance. Osaka University will achieve the transversing of any potential, be it an interest or status. In other words, through the outstanding pursuit of scholarship and mastering of one’s own field and actively seeking integrated study of knowledge that crosses fields of knowledge, as well as cooperation with diverse members of society, the university will evolve into a place for orchestration and co-creation of knowledge.

~Omitted~

Open Research

【Vision】

For Open Research, Osaka University aims to become a world-leading comprehensive research university that contributes to the development of an enriched society and to the resolution of global issues by creating and deepening diverse knowledge from world-top-level basic research and cross-disciplinary research. In particular, Osaka University’s World Premier Research Institute (WPI), which is equipped with superior research capability and state-of-the-art facilities, and the joint-use / joint research centers, will lead the way.

In our current times of super big data there is a pressing need to realize a safe and secure society by creation of new intellectual value and advanced integrated utilization of big data. Leveraging Osaka University’s advanced information-related technologies; the university is exploring new scientific methods of “datability” or the responsible and sustainable use of the ultra-high volume of available data. Datability will expand into new areas of science and technology researches. These research foundations will produce researchers with high competence in research management and high ethical

standards and become a force to attract diverse personnel to Osaka University to contribute to academics in Japan.

【Goals】

Solidification and globalization

Promotion of basic research across all academic domains at Osaka University to cement a social base cultivated with diverse knowledge.

＜Action＞

1. Promote international joint research inviting excellent foreign researchers using the cross-appointment system and international joint laboratories.
2. Promote cooperation between Osaka University and the Center for Information and Neural Networks (CiNet) of the National Institute of Information and Communications Technology (NICT), and stronger collaboration with Quantitative Biology Center (QBiC) of the Institute of Physical and Chemical Research (RIKEN).
3. Implement the Co-creation of Knowledge Program to promote the collaboration between researchers from different disciplines across humanities and social science to the natural sciences.
4. Support for the acquisition of competitive research funding through coordination with office management and the research administrator (URA).

~Omitted~

Center for world- leading research

Toward becoming one of the world's leading comprehensive research universities, Osaka University plans to establish multiple research centers at the top international level that maximize the strengths and individuality of the university in order to develop versatile and diversified research activities.

＜Action＞

1. Investigate the potential to establish an International Advanced Research Institute (provisional name) to act as an incubator for the creation of new domains for research based on world-leading academic domains including composite domains of different fields.
2. Continuation of the World Premier International Research Center (WPI) Immunology Frontier Research Center (IFReC) and the formation of a second and third world top-level research centers.
3. Promote the orchestration and co-creation of different fields through diverse methods such as humanities and social science approaches, brain and cognitive science, and photonics.

~Omitted~

Training promising young researchers

Provide young researchers, who hold the future of not only Osaka University but also the world, with a place where exciting and imaginative ideas are valued and where they can freely devote themselves to research activities.

＜Action＞

1. Implement the Co-creation of Knowledge Program to nurture diverse, original research, to enhance research capability that pioneers new horizons, and to train outstanding young researchers.
2. Train young researchers to proactively pursue their research through application of the Leading Initiative for Excellent Young Researchers and the Human Resources Discovery Support Project to produce global human resources with excellent leadership skills.
3. Train human resources who can advance science based on datability through on-the-job training at the Institute for Datability Science.

~Omitted~

Open Innovation

【Vision】

The key to solving the complex problems facing people globally and to building a better future is the advance of open innovation. As a world top-class innovative university, Osaka University will engage in further advanced university-industry collaboration.

Osaka University is causing a paradigm shift in the traditional style of university-industry cooperation. The goal of university-industry co-creation is to create new social values including technology and

services but also is expanded to cooperation both in and outside of Japan between different industries and in different areas taking into account the needs of users. Where diverse ideas and desires cross, new social problems arise. Osaka University is boldly facing the challenge on the new stage of open innovation to build a new system that shows society solutions to those problems.

University-industry co-creation as promoted by Osaka University offers the potential for mutual enlightenment of rich talent, ideas and sensitivities for all those involved. This is sure to develop human resources able to focus on the task at hand and create a cycle of value and people between society and the university.

【Goals】

Osaka University style of comprehensive university-industry cooperation

Promote the Osaka University style of open innovation university-industry cooperation under the catchphrase “University-Industry Co-Creation” to discover questions for new basic research on the basis of social needs and achieve an open, reciprocal flow of knowledge.

＜Action＞

1. Further advancement of the Joint Research Course and Collaborative Research Center unique to Osaka University.
2. Promote the discovery of creative research and technology seeds original to Osaka University and comprehensive university-industry co-creation from the basic research stage.
3. Develop new open innovation through the participation of researchers in the humanities and social science fields and female researchers etc.
4. Invigorate the formation of a Center of Innovation under the Radical Innovation and Entrepreneurship Program (COI STREAM).

Commercialization of translational research

Collaborate with manufacturers of pharmaceuticals and medical devices based in Osaka and the National Institute of Biomedical Innovation to conduct from basic research to translational research to create commercial products. Also, aim for the commercialization of medical, dental and pharmacological research outcomes through early approval of drugs.

＜Action＞

1. Conduct comprehensive joint research from the basic research stage with pharmaceutical manufacturers and medical device makers based in Doshomachi and other locations in Osaka.
2. Commercialize medical, dental and pharmacological research outcomes through early drug approval with the cooperation of core research hospitals and the Kansai-National Strategic Special Zone.
3. Enhance university-industry co-creation with affiliated businesses based in the Medical Center for Translational Research (Osaka University Hospital) and the Center for Dental Treatment (Osaka University Dental Hospital) to develop advancement of medical therapies.

~Omitted~

Open Community

【Vision】

Universities, as temples of learning are open to local and global society for the free exchange of knowledge. To put into practice its motto of “Live locally, Grow Globally”, Osaka University will work toward a flexible, open community that creates new value and in which everyone can exchange a wide variety of knowledge.

Following its roots in the civil spirit of Kaitokudo and Tekijuku, the university will contribute to local society as a center for academia, culture, the arts and medicine.

Close connections with various local leaders will enrich education and research through diligent exchange with people from diverse cultural backgrounds. To tackle the complex issues facing humanity and open up a future of hope, the university will refine structures within the institution for academic exchange using our global network, international cooperation, and international university-industry co-creation as well as activity at overseas centers.

An open community will be built, supported by a network covering several generations formed by graduates and former staff to realize a campus that gives birth to diversity encompassing culture, language and gender. Graduates and staff will always look back with pride and satisfaction on their

time at the university.
~Omitted~

Orchestration and co-creation of knowledge through expanded global network

Construct a dynamic network encompassing the president at the top to international joint research at the faculty level and overseas study by students with partner institutions around the world, to create an environment that optimizes the maximum true value of students and staff.
＜Action＞
1. Stronger collaboration with international organizations such as the United Nations and the World Health Organization and the Japan International Cooperation Agency and the Japan Agency for Medical Research and Development.
2. Enhance the functions of overseas centers and satellite offices in North America, Europe, East Asia and South East Asia and cooperation with partner institutions around the world to train global human resources through expansion of opportunities to study abroad.
3. Establish a one-stop system for exchange and a global campus environment that is multicultural and multilingual.
~Omitted~

Open Governance

【Vision】
Osaka University inherits a tradition of continuous self-reinvention, under its spirit of independent management and as a seat of learning the university has always aimed for greater heights of education, research and contribution to society in all fields. As universities have arrived at a crossroad in their existence, demands of Osaka University include emphasis on diversity and maximization of the potential of each and every student and member of staff. To focus the potential of each individual, achieve creation through self-reform in every department and make rapid progress to become a world-leading comprehensive research university; university operations will be balanced between leadership by the president and consensus of members to achieve highly-transparent open governance. Management in the mid to long term will be strategic and robust cultivating the superior skills of staff in specialist fields relating to university management such as internationalization, finance, administration and public relations. The construction of study, work, and research environments that are attractive to people will make Osaka University a force that will lead Japan into a glorious future.
~Omitted~

Efforts to secure, develop and utilize excellent staff

The university aims to be a workplace that, in severe fiscal conditions, optimizes the efficiency of the organization, personnel, and administration and rewards those who make significant contributions to the university. The university will offer opportunities for growth and a rewarding work environment where a diverse workforce produces quality results regardless of job category.
＜Action＞
1. Secure outstanding personnel with systems such as performance-linked salary and cross-appointments as well as cultivation and application of research administrators (URA) to assume responsibility for top class, international research strategies.
2. A training system to respond to globalization, and cultivation of experts with qualifications for profitable accounting, legal administration, intellectual property and IT.
3. Creation of an active and attractive workplace environment that emphasizes a work-life balance through flexible working hours.
4. Introduction of a reward system with new incentives based on impartial evaluations.
~Omitted~

World Premier International Research Center Initiative (WPI)

Appendix 4. Resource Allocation Plan for Sustaining and Advancing the WPI Center

Annual Plans (FY 2017 – FY 2021)					
<Fund >					(million Yen)
Fiscal Year	**2017**	**2018**	**2019**	**2020**	**2021**
- WPI grant	- (※)	- (※)	- (※)	- (※)	- (※)
- Funding from host institution	796.5	796.5	796.5	796.5	796.5
(details)					
Personnel	309.0	309.0	309.0	309.0	309.0
Project activities	224.1	224.1	224.1	224.1	224.1
Travel	0.6	0.6	0.6	0.6	0.6
Equipment	205.4	205.4	205.4	205.4	205.4
Other research projects	57.4	57.4	57.4	57.4	57.4
Costs of Satellites	0	0	0	0	0
- Funding from external sources	2,839.6	2,839.6	2,839.6	2,839.6	2,839.6
Total	3,636.1	3,636.1	3,636.1	3,636.1	3,636.1
<Personnel>					(person)
Fiscal Year	**2017**	**2018**	**2019**	**2020**	**2021**
- Personnel resources from host institution	268	268	268	268	268
- Faculty members (including researchers)	97	97	97	97	97
Full-time	51	51	51	51	51
Concurrent	46	46	46	46	46
- Postdocs	27	27	27	27	27
- RA etc.	56	56	56	56	56
- Research support staffs	71	71	71	71	71
- Administrative staffs	17	17	17	17	17

(*) Do not include expected grant.
- When entering amounts, round down numbers to the first decimal.
- When funding is stated in a range between two amounts, explain the reason for the lower and upper amounts and fluctuations between them.

< Measures to be implemented from FY 2017>

– Strategy and action plan for allocating personnel (posts) , space, and others measures required for the Centers' Progress.

1. Measures to ensure the appropriate number of members

IFReC will maintain the number of IFReC members and effectively use the grant obtained through the comprehensive collaboration agreement with a company. Osaka University has already provided three tenure positions and is considering providing five further positions. IFReC will set up a tenure track system to recruit new young PIs to be the next generation of core researchers in IFReC. In order to recruit overseas researchers, IFReC will continue international open recruitment, more actively conduct outreach activities, and collaborate more closely with international research institutions. IFReC will also maintain the number of research support staff to improve support for overseas researchers.

2. Measures to ensure appropriate space

The host institution preferentially provides IFReC with the use of three buildings (two research buildings and one animal facility). IFReC will lend space in the research building for the company with which Osaka University has concluded a comprehensive collaborative agreement (see Progress Plan 2-2), to conduct collaborative research smoothly. IFReC expects to promote collaborative research with other

companies using available space in buildings of IFReC or Osaka University.

3. Strategy and action plan to carry out other necessary measures

(1) IFReC has succeeded in reinforcing a financial foundation for its management. IFReC will promote collaborative research with the company based on the outcomes created from research of IFReC, and also proactively with other companies on the outcomes which the company does not select for collaboration. IFReC also expects to forge close relationships with other companies by setting up collaborative laboratories in Osaka University or IFReC to develop medical immunology and to further strengthen the financial foundation.

(2) IFReC will establish partnerships with international research institutions. IFReC will develop young researchers through interactions between IFReC and the institution, and promote research activities of the young researchers. It will strengthen functions of IFReC as a hub of brain-circulation.