(Compile in English within 3 pages.)

Host institution	Osaka University	
Head of host institution	Toshio Hirano, Osaka University, President	
Research center	Osaka University Immunology Frontier Research Center	
Center director	Shizuo Akira, Osaka University, Professor (WPI IFReC)	
Chief center-project officer (in October 2007)	Shizuo Akira, Osaka University, Professor (WPI IFReC)	
Project summary	IFReC aims to advance imaging and bioinformatic technologies by integrating them into experimental immunology for spatio-temporal studies from the molecular to the whole body level. This approach will provide comprehensive understanding of the immune system. Such advancement of basic immunology will improve medical strategies for diagnosis and treatment of pathogens and immune-related diseases through translational research. We shall further improve the research administration system so that domestic and overseas researchers can devote themselves to their research.	
Mission statement and/or center's identity	IFReC aims to comprehensively understand immune dynamism. To this ultimate goal, we shall integrate imaging and bioinformatic technologies with experimental biology in order to study a wide range of spatio-temporal phenomena from the molecular to the whole body level. We believe this integrated approach will not only deepen our systematic understanding of the immune system but will also facilitate the basic research results to be targeted to medical applications through translational research. Thus, advancement in our understanding of basic immunology can improve medical strategies for the body's defense against infectious diseases, cancers, diagnosis and treatment of immune-related diseases. Through these endeavors, we shall establish a solid foundation for IFReC to be a truly internationally renowned research center.	
Research fields	Fields: Immunology, Bioengineering and Bioinformatics Importance: Research into the immunological response to pathogens is important in prevention, diagnosis and treatment of various immune-related disorders and diseases. Despite extensive as well as intensive studies, it still remains unclear how immune cells actually interact with each other <i>in vivo</i> . Thus, it is of great and immediate importance to develop new technologies that can track as well as artificially control immune responses. Toward this end, it is necessary to make a breakthrough in traditional immunology by integrating imaging and informatics methodologies into immunology. Immunology at Osaka University is internationally acclaimed in its highest quality in addition to being recognized globally as among the foremost institutions regarding imaging and bioinformatics. Therefore, it is most pertinent to create an immunology research center here where domestic and overseas researchers in those different disciplines can come together to earnestly work towards a "comprehensive understanding of immune mechanisms <i>in vivo</i> ". This challenge to establish not only a new field of basic science but also overcome various immune-related diseases is of upmost importance.	
Research objectives	Integrating imaging technology and bioinformatics into immunology for a comprehensive understanding of immune dynamism, which enables controlling immune system for the prevention, diagnosis and treatment of immune diseases.	
Outline of management	The Center Director makes major decisions, to which the Administrative Director gives full support by handling practical matters via the administrative office. Important matters such as the annual budget and the appointment of PIs are to be approved by the center management committee and the board of representatives. The administrative office consists of the accounting and general affairs sections, and the research planning and management (RPM) office. The former two are composed of senior staff with rich administrative experience in the	

	University and English-speaking personnel. The RPM office consists of several
	PhD holders and English-speaking personnel to cover publication, organization of seminars and symposia, outreach activities etc. The Liaison Office within the framework of RPM supports researchers from abroad in various aspects such as immigration matters, grant applications, etc.
Researchers and other center staffs, satellites, partner institutions	IFReC is now composed of 27 research groups (immunology, 17; imaging, 7; bioinformatics, 3), of which 15 are headed by full-time PIs and 12 by PIs who have concurrent positions at the graduate schools, the Research Institute for Microbial Diseases (RIMD), of Osaka University, etc. As cooperative institutions, IFReC has concluded academic cooperation agreements with the Research Center for Allergy and Immunology (RIKEN), the Institute for Frontier Medical Sciences (Kyoto University) and the National Institute of Biomedical Innovation (NIBIO). Overseas partner institutions include Institute for Systems Biology (USA), Pohang University of Science and Technology (Korea), Indian Institute of Science Education and Research (India), the University of Auckland (New Zealand) and the Catholic University of Korea Seoul St. Mary's Hospital.
Administrative director	Takao Kodama, Osaka University, Professor (WPI IFReC)
	1) The RPM office ("Outline of management") deals with planning and logistics of scientific meetings, outreach activities, etc.
	 About two thirds of IFReC laboratories are housed in the Integrated Life Science Bldg., constructed in 2009 and the neighboring IFReC Research Bldg., constructed in 2011.
	3) Animal resource centers, radio-isotope experimental station and the core instrumentation facility are jointly operated by IFReC and RIMD. A list of core equipment, facilities and operational manuals will be available online in both English and Japanese.
	4) The Center for Information and Neural Networks (CiNeT) of the National Institute of Information and Communications Technology and RIKEN Quantitative Biology Center (QBiC) are scheduled to open within walking distance from IFReC. Both centers are headed by Professor Yanagida, a Deputy Director of IFReC. Their methodologies and technologies are common to those of IFReC, collaborations with these centers will help IFReC to advance interdisciplinary researches.
Outline of research environment	5) Budget for equipment will be allocated to invite PIs from institutions outside Osaka University. Budgets for consumables and supplies will also be provided to new PIs to start research at maximum efficiency without losing time.
	6) Based on advice and/or suggestions by the working group of the WPI program committee and the International Advisory/Review Board, the center director will set up a research environment appropriate for a WPI center.
	 7) International research conferences will be organized at least once a year. 8) IFReC has introduced platforms for collaboration of immunologists with imaging and bioinformation researchers as follows:
	 imaging and bioinformatics researchers as follows: The "Research Support Program for Fusion of Different Fields" (2009) to provide IFReC's young researchers in different disciplines with the financial supports to start collaborative studies. They have been succeeded by the double mentor fellowship/scholarship program (2011) to support graduate students or young post-doctoral fellows engaged in interdisciplinary projects under supervision by two PIs in different disciplines.
	- The IFReC colloquia have been established to facilitate mutual interactions between IFReC researchers by giving opportunities to young researchers to present their innovative research topics.
	i) Criteria and methods to be used by IFReC for evaluating the center's global standing
Outline of indicators for evaluating a center's	a) <u>Major contributions to main research areas</u> - Are PIs leading and advancing main research areas and corresponding fields?
global standing	 b) <u>Creation of new research areas</u> - Are PIs opening or creating new research areas and corresponding fields? c) Contribution to human welfare - Are there any accomplishments from this
	c) <u>Contribution to human welfare</u> - Are there any accomplishments from this center which have made great contributions to increases of quality of

	human life in various ways, such as developing therapeutic or diagnostic means?				
	ii) Results of current assessment made using said criteria and methods				
	a) Major contributions to main research areas:				
	Immunology: Akira, innate immunity; Sakaguchi, regulatory T c Kurosaki, differentiation of lymphocytes; Kishimoto, cytoki Bio-imaging: Yanagida, single molecule imaging; Yoshioka, MRI imag Smith, Raman microscopy; Kikuchi, chemical imaging.				
	b) Creation of new research areas:				
	Saito, single molecule imaging analysis of immune responses; Kumanogoh, immune regulation by semaphorins; M. Ishii, two-photon imaging of bone tissues <i>in vivo</i> .				
	c) <u>Contribution to human welfare</u> :				
	Kishimoto, anti-IL-6 receptor therapy for inflammatory diseases; Hatazawa, integrated PET/MRI system as diagnostic means for various diseases; Coban, Malaria immunology; K. Ishii, vaccine science.				
	iii) Goals to be achieved through the project (at time of final evaluation)				
	 To establish methodologies of intravital and noninvasive imaging of immune cells and immune-related molecules and those of systems biology for understanding of the immune network. 				
	 To open a new vista for controlling immune system for the prevention, diagnosis and treatment of immune diseases 				
Securing research funding	Osaka University will provide support to meet the necessary expense, on of Grant-in-aid (about 13.5 hundred million yen/year) and Research Grants Principal Investigators.				
Appropriations plan	FY 2012 2013 2014 2015 2016 Total				
(Exchange Rate: JPY/USD=80)	Cost (\$ millions) 16.68 16.68 16.68 16.68 83.4				
	1) As stated in its mid-term strategic target and plan, Osaka University will provide every possible support for IFReC to become a true WPI center.				
	2) The University has entitled the IFReC Director to manage and operate the center and to make decisions regarding substantive personnel and budget allocation as are the Deans and Directors in other faculties in the University. Thus, the Director can make top-down decisions and reformation of project-oriented improvements of research environments.				
	3) Osaka University will make every effort to support IFReC so it can establish its foundation to become a WPI center by providing available resources that would be either greater or equal to the WPI project grant.				
	4) If researchers from other departments in the University are working concurrently at IFReC, the University will support resource sharing/exchange between the WPI and the other departments.				
Summary of host institution's commitment	5) The existing annual salary employment system of Osaka University is applied to IFReC employees. If, however, the system does not fit in well with the operation of IFReC as a WPI center, the university will consider revising its present internal system for IFReC's operation.				
	6) Concerning the planning and logistics of running large-scale research projects, research staff at the Support Office for Large-Scale Education and Research Projects will collaborate with IFReC staff. The Office for International Planning and Programs will support IFReC to promote research collaborations with scholars and institutions overseas.				
	7) To facilitate interdisciplinary researches at IFReC, the University will make necessary arrangements for IFReC researchers to collaborate with those of CiNeT and QBiC (See "Outline of research environment).				
	 8) Osaka University has established the Gender Equality Promotion Office to provide career support and encouragement for young scholars who will be next-generation researchers, which will be beneficial for IFReC to increase the number of female PIs and junior researchers. 				

3. Research Center Project (in English)

Host institution	Osaka University			
Head of host institution				
	Toshio Hirano, Osaka University, President			
Research center	Immunology Frontier Research Center			
Center director	Shizuo Akira, Osaka University, Professor (WPI IFReC)			
Chief center-project officer(in October 2007)	Shizuo Akira, Osaka University, Professor (WPI IFReC)			
Project summary	 Briefly describe the general plan of the project. We aim to unveil the whole picture of the dynamic immune system by integrating the methodologies of bio-imaging and bioinformatics into immunology. Thus, we shall make every effort to improve these methodologies to track more directly the behavior and communications of immune cells within live animals and to understand their collective or systematic behavior in response to non-self, such as pathogens and cancers. Based on these basic studies, we shall seek to develop new strategies for the prevention, diagnosis and treatment of various immune-related disorders and diseases. To this ultimate goal, we shall establish the Osaka University Immunology Frontier Research Center (IFReC) consisting of 25 - 30 world-class principal investigators together with domestic and overseas institutions that will function as satellites or partners. A research-supporting and administrative system will be established to provide a research environment of international standards where all of IFReC researchers can devote themselves to research. 			
	 In our initial plan, bioinformatics was not emphasized. Over the first years, a consensus has emerged within the organization that cutting computational methods are indispensable to advance immunology facilitate collaboration between immunology and imaging groups. T reflected as a change made in the plan. 			

	- The research planning and management office has been established within the administrative office to cover a wide range of research supporting logistics to build a superb environment where all of IFReC researchers can devote themselves to research.				
	\cdot Briefly and clearly describe the mission statement and/or the project's identity as WPI center.				
Mission statement and/or center's identity	IFReC aims to comprehensively understand immune dynamism. To this end, we shall integrate imaging and bioinformatics technologies with experimental biology in order to reveal spatio-temporal and/or the collective behavior of immune-related cells and molecules <i>in vivo</i> . This integrated approach will not only deepens our systematic understanding of the immune system but also facilitate basic research results to be targeted to medical applications through translational research. Thus, advancement in our understanding of basic immunology improves medical strategies for the body's defense against infectious diseases and cancers, and diagnosis and treatment of immune-related diseases.				
	Along with these research efforts, we shall further improve the research administration system, which provides a research environment of international standard, where both domestic and overseas researchers can devote themselves to research. Through these endeavors, we shall establish the solid foundation for IFReC to be a truly internationally renowned research center.				
 (1) Research fields Describe in simple words 	s and phrases within one line the research field of the project.				
Immunology and Bioer					
	from among $(1 - \overline{7})$ below, specifying the interdisciplinary field(s) that the project				
	stry, ③Material sciences, ④Electronics engineering and information sciences, ical engineering, ⑥Physics, ⑦Mathematics				
①Biosciences, ④Elec engineering	tronics engineering and information sciences, ⑤Precision and mechanical				
 Describe the importance Japan's advantages. 	of the proposed research, including domestic and international R&D trends in the field and				
Research on the immune system, which is composed of cells, tissues and organs to defend the body against invading microbial pathogens, is of fundamental importance in prevention, diagnosis and treatment of various immune-related disorders and diseases. Although numerous studies have focused on the identification of immune cells and their factors, it still remains unclear how they actually interact with each other <i>in vivo</i> in response to infections or in pathological conditions. Thus, it is of great and immediate importance to challenge such unsolved issues. Toward this end, it is necessary to develop new technologies that track immune responses, methods to artificially control immune responses by integrating imaging and informatics methodologies into immunology. This is nothing short of an attempt to make a breakthrough in traditional immunology. Immunology in Osaka University is internationally acclaimed in its highest quality. In addition, the University is also globally recognized as being among the foremost institutions regarding imaging and bioinformatics. Therefore, it is most pertinent to create a new research center for immunology in Osaka University where domestic and overseas researchers in those different disciplines come together to earnestly aim to achieve a "comprehensive understanding of immune mechanisms <i>in vivo</i> ".					
If centers in similar fields already exist in Japan or overseas, please list them.					
The National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA					
(2) Research objectives					
Describe in a clear and ea	asy-to-understand manner the research objectives that the project seeks to achieve by the				

end of the grant period. In describing the objectives, the following should be articulated in an easily understandable manner: What new domains are expected to be pioneered by fusing the target fields. In the process, what world-level scientific issues are sought to be resolved. What is the expected impact of the scientific advances to be achieved on society in the future.

We aim to Integrate imaging technology and bioinformatics into immunology to study the properties and functions of immune-related cells and molecules for a comprehensive understanding of immune dynamism. To date, research in immunology has been carried out mostly using *in vitro* methods, wherein immune cells are isolated from animals such as mice and individually examined using various methods of cell biology; similarly, immune-related molecules have traditionally been examined in isolation by biochemical and/or biophysical methods to reveal structure-function relationships. As a result of such studies, a number of immune cells and cytokines have been discovered, and signaling pathways in various immune responses have been outlined.

However, the immune system of a mouse or human is one composed of a large number of multiple cell types forming a complex network. Many of these cell types interact directly or indirectly through intermediary molecules such as cytokines. In addition, immune cells are generally in constant motion throughout the entire body interacting with many types of tissue. We will reveal the dynamics of this cellular and molecular network through the integration of biological, biochemical, and imaging data using information technology and complex systems simulations. This challenging endeavor is of importance not only to establish a new field of basic science but also to overcome various immune-related diseases. Furthermore, such developments will establish a solid foundation of medical immunology.

Describe concretely the research plan to achieve these objectives.

<Research plan – General>

It is hardly possible to reach our ambitious goal of a "comprehensive understanding of immune dynamism" using an *in vitro* approach alone. Our alternative strategy is to examine and analyze immune cells and molecules *in vivo* as they naturally exist in a living organism. There already exist a number of *in vivo* methods; however, they are not yet as mature as the *in vitro*-based methods. Hence, one of our goals is to advance novel *in vivo* immunology methods. The first step in this process is to form fruitful collaborations between researchers with various theoretical and experimental backgrounds, and with proven experience in solving major problems in immunology. The collaborative spirit used to develop new *in vivo* methods is expected to generate not only breakthroughs in immunology, but also to strengthen more basic disciplines such as physics, chemistry, and information technology.

<Experimental and computational plans>

Well-armed with animal and instrumental facilities as described below (section 5), we will pursue:

- a) Selective visualization of multiple types of immune cells and molecules, hopefully simultaneous visualization and/or with good temporal resolution
- b) Non-invasive or at least side-effect free observation and measurements of cells and molecules
- c) Measurement of cellular activities and dynamics of immune-related substances in whole live animals
- d) Development of tools and expertise for processing, storing, and extracting useful information from large amounts of imaging and biological data
- e) Simulation and prediction of immune networks based on results obtained (as outlined above) both at the molecular and cellular levels

Three lines of innovation that are essential for experimental research to attain objectives a-c (above) are currently ongoing at IFReC:

- i) Improvement of techniques of optical microscopy: Attempts are being made to push the performance of instruments to their limits by modifying the hardware and to visualize the dynamics of cells in live animals and molecules in cells by using novel probes or reagents.
- Development of probes suitable for "selective visualization of specific cells or molecules and to discriminate them from an ensemble of similar targets" and "detection of structural changes of immune-related molecules and organelles".
- iii) Installment of cutting-edge instruments such as a Raman microscope and an advanced 11.7T MRI for minimally-invasive observations and measurements. These instruments will be customized in hardware and software for improvement of their performance by experienced researchers, so as to optimize the technologies for immunology-based research purposes

and/or experimental subjects.

In addition to on-going projects in bioinformatics groups (structure/function prediction of proteins involved in immune responses; simulation of signal transduction cascades and transcriptional regulatory network in immune cells; and advanced data processing for imaging), we have set two objectives for information processing and systems-oriented studies:

- i) Improvement of computational facilities for the flow and availability of data from the imaging, informatics and immunology groups;
- ii) Reinforcement of human resources of computational research both in qualitative and quantitative aspects.

<Plans for Medical Immunology through Translational research>

Since IFReC was launched in 2007, we have been well aware that the center is highly expected to contribute to improvements in society's health by clinical application of inventions/discoveries made through basic research. Hence, several IFReC PIs have been recruited from the medical school of the University, and two of them have concurrent appointments with the University Hospital. Furthermore, two new laboratories specialized in human immunology and immune diseases were set up in 2010 (Coban, malaria immunology; Ishii, K., vaccine science).

In order to more aggressively accelerate clinically oriented research, IFReC will make several practical steps:

- Support to on-going collaborative projects of IFReC researchers with clinical researchers at the medical school of the University
 - Multimodal (CT/PET/MRI) morphological and functional imaging for diagnosis of various diseases
 - Clinical application of a cancer vaccine and development of new biologics to treat autoimmune diseases such as rheumatoid arthritis in collaboration with pharmaceutical companies.
- b) Support collaborations with other institutions
 - Development of strategies to control chronic inflammatory diseases through revealing how dendritic cell subsets exert their immunostimulatory functions (RIKEN RCAI)
 - Development of stem cell-based immunotherapy including mesenchymal stem cells and intestinal stem-like cells that could ameliorate inflammatory bowel diseases by preferentially inhibiting the production of inflammatory cytokines. (Seoul St. Mary's Hospital and POSTECH)

In addition to supporting these on-going or scheduled projects, IFReC encourages their researchers to set up new projects with clear prospects for medical immunology. To construct a better platform for this, IFReC is now preparing to:

- c) Establish a consortium for clinical medicine-oriented immunology composed of PIs belonging to the medical school of the University as its core members. This is to invite clinicians who are interested in deeper investigation of clinical samples which are routinely collected during the treatment of patients suffering from immune-related diseases. Plans include:
 - Opening a clinical sample collection center in the IFReC research building for researchers to use the collected samples. Using the samples, research projects will be scheduled to search for bio-markers of immunological disorders such as systemic lupus erythematosus, juvenile idiopathic arthritis, and polymyositis/Dermatomyositis and to analyze the proteins or gene expression of immune-regulatory molecules of peripheral blood mononuclear cells of such patients to find therapeutic targets.
 - Discussion forums for clinical immunology research; participants include clinicians from local hospitals as well as IFReC researchers.
- Propose a joint project search for therapeutic molecular targets for immunological disorders and cancers for the Health Labour Sciences Research Grants in collaboration with NIBIO.

(3) Management

i) Center director

• Provide the name of the center director, his/her age (as of 1 April 2012), , specialties, and brief career profile(within 5 lines).

Name; Shizuo Akira Age; 59

Specialties; Immunology

Profile; Ph. D., Osaka University, Graduate School of Medicine (1984) Associate Professor, Institute for Molecular and Cellular Biology, Osaka University (1995) Professor, Hyogo College of Medicine (1996-1999) Professor, Research Institute for Microbial Diseases, Osaka University (1999-present) Center director, Immunology Frontier Research Center, Osaka University (2007-present)

ii) Administrative director

• Provide the name of the administrative director, his/her age (as of 1 April 2012), and his/her brief career profile(within 5 lines).

Name; Takao Kodama

Age; 70

- Profile; Ph.D., Nagoya University, Graduate School of Science (1970) Associate Professor, Okayama University School of Dentistry (1981-1992) Professor, Kyushu Institute of Technology (1992-2005) Research Manager, Japan Science and Technology Agency (2005-2008) Administrative director, Immunology Frontier Research Center, Osaka University (2009-present)
- iii) Composition of administrative staff

· Concretely describe how the administrative staff is organized.

Dr Takao Kodama, who has a long career of scientific research as well as experience in research management and coordination, is in charge of the overall administration system of IFReC. The system is composed of three sections: the accounting section, the general affairs section and the research planning and management (RPM) office. Each of the former two sections is staffed with English-speaking personnel supervised by two senior staff with rich administrative experience in the University. The RPM office is headed by Dr Kodama, consisting of six PhD holders and several English-speaking personnel. The office is to make a research environment with smooth communication among researchers and support staff and close contact with the Administration Bureau of Osaka University by covering:

- (a) Organization of seminars and symposia
- (b) Outreach activities
- (c) Management of matters related to intellectual properties such as material transfer actions and management of matters relating to the health and safety at IFReC
- (d) Preparation of a database of information on external competitive research funds in English for overseas researchers' convenience. For each of these tasks, a person with a PhD has been assigned
- (e) Purchase procedures for instrumentation

iv) Decision-making system

· Concretely describe the center's decision-making system.

The center Director makes major decisions, to which the Administrative Director gives full support by acting as a coordinator among the deputy directors and by executing management actions through the reformed administrative office. The Administrative Director also acts as liaison between the director and trustees of the host institute and between IFReC and the MEXT/JSPS WPI office. Important matters such as annual budget and the appointment of PIs, or equivalent, are to be approved by the center management committee and the board of representatives.

v) Allocation of authority between the center director and the host institution's side

· Concretely describe how authority is allocated between the center director and the host institution's side.

The University president will approve the mid-to-long term plan of the center and the center director's decisions on major issues necessary for the center's management, such as researchers' salaries, appointment of new researchers and administrative director. The University president will appoint a director, determine the director's salary and evaluate the center's performance. In addition, the Center's Director, Deputy Directors, Administrative Director and Trustees and Vice Presidents of the University hold briefings as needed.

(4) Researchers and other center staffs, satellites, partner institutions

i) The "core" to be established within the host institution

a) Principal Investigators (full professors, associate professors or other researchers of comparable standing)

~	Numbers		
	At beginning	At end of FY 2011	Final goal (Date: March, 2017)
Researchers from within the host institution	10	14	15
Foreign researchers invited from abroad	1	2	3
Researchers invited from other Japanese institutions	6	11	12
Total principal investigators	17	27	30

· Describe the concrete plan to achieve final staffing goal, including steps and timetables.

 Attach a list of principal investigators using the Appendix. Place an asterisk (*) by names of the investigators considered to be ranked among the world's top researchers. Describe the policy and strategy for inviting the Pls who are to be included after 1 April 2012.

b) Total members

	Numbers		
	At beginning	At end of FY 2011	Final goal (Date: March, 2017)
Researchers	49 < 12, 24%>	173 < 53, 31%> [35, 20%]	180 < 61, 34%> [38, 21%]
Principal investigators	17 < 1, 6%>	27 < 6, 22%> [1, 4%]	30 < 8, 27%> [3, 10%]
Other researchers	32 < 11, 34%>	146 < 47, 32%> [34, 23%]	150 < 53, 35%> [35, 23%]
Research support staffs	28	61	50
Administrative staffs	9	29	30
tal number of people who form e "core" of the research center	86	263	260

• Enter the total number of people in the columns above. In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [] brackets.

• Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing the main researchers, particularly principal investigators.

To increase the number of female principal investigators, IFReC is to:

- Invite more female speakers to IFReC-organized scientific meetings.
- Make and use a reservoir of female talented young researchers of international level, exploiting the fact that a number of young female students and post-doctoral fellows participated in the Winter School held in January, 2012, who had been selected among many contesting applicants (see page 9, Hold international research conferences).
- More aggressively publicize the University's support systems for gender equality in planning and promotion ((5). Research environment
 Other measures to ensure that top-caliber researchers from around), which would be effective to terms of recruitment.
- ii) Collaboration with other institutions
- If the "core" forms linkages with other institutions, domestic and/or foreign, by establishing satellite functions, Provide the name of the partner institution(s), and describe the role of the satellite functions, personnel composition and structure, and collaborative framework between the host institution and the said partner institutions (e.g., contracts to be concluded, scheme for resource transfer).

Domestic

- RIKEN Research Center for Allergy and Immunology
- Kyoto University, Institute for Frontier Medical Sciences
- The National Institute of Biomedical Innovation
- If some of the principal investigators will be stationed at satellites, attach a list of these principal investigators and the name of their satellite organizations using the Appendix.

Not applicable

• If the "core" forms organic linkages with other institutions, domestic and/or foreign, without establishing satellite functions, provide the names of the partner institutions and describe their roles and linkages within the center project.

Domestic None

Overseas

- Institute for Systems Biology (Alan Aderem, Director) Seattle, USA
- Pohang University of Science and Technology (Inhwan Hwang, Chairman, Division of Life Science & Division of Integrative Bioscience and Biotechnology), Pohang, Korea
- Indian Institute of Science Education and Research (Vinod K Singh, Director), Bhopal, India
 The University of Auckland (P. Rod Dunbar, Director, Maurice Wilkins Center), Auckland, New Zealand
- The Catholic University of Korea Seoul St. Mary's Hospital (Tae-Kon Hwang. President). Seoul, Korea

Researchers in the center and these satellite/partner institutions will visit each other and exchange the information to upgrade the scientific standard of both sides. These interactions will provide an environment for the training of young immunologists and facilitate integration of different scientific disciplines.

(5) Research Environment

- Concretely describe measures to be taken to satisfy each of the requirements outlined below, including steps and timetables.
 - O Provide an environment in which researchers can devote themselves exclusively to their research, by exempting them from other duties and providing them with adequate staff support to handle paperwork and other administrative functions.

As described above (3), the Research Planning and Management office headed by the Administrative Director deals with planning and logistics of scientific meetings, public information and liaison, and issues relating to intellectual properties, etc. Several PhD holders with research experience and bilingual staff have been posted. Together with general affairs and accounting sections, this office fully supports researchers so that they do not have to spend their time on paper work and other administrative functions.

O Provide startup research funding as necessary to ensure that top-caliber researchers invited to the center do not upon arrival lose momentum in vigorously pursuing their work out of concern over the need to apply immediately for competitive grants.

Each PI from abroad is allocated a start-up research fund for the first three years from the WPI's direct budget. To newly recruited PIs from domestic institutions, some amount of the fund is also given as a "set-up research fund". In order to facilitate a new era of immunology as well as making breakthroughs in related scientific disciplines, "The Research Support Program for Fusion of Different Fields" is available to young researchers. The program is to encourage them to challenge new but difficult project tasks, for which it would be otherwise hard to obtain financial support from outside sources. Start-up budgets (3 million yen per year for 3 years) are provided for each project. The projects are annually reviewed by IFReC PIs in a hearing open to all IFReC researchers.

O As a rule, fill postdoctoral positions through open international solicitations.

In principle, postdocs will be hired through advertisement of positions in major journals, such as Nature and Immunity, and the IFReC web-page.

O Establish English as the primary language for work-related communication, and appoint administrative personnel who can facilitate the use of English in the work process.

It is one of the IFReC's administration policies that at least two thirds of the total staff be bilingual, using English as the primary working language. In addition, there exists the Liaison Office as a virtual organization within the framework of the RPM office to support researchers from abroad in various aspects such as immigration matters, providing a living support service as well as bilingual notices, announcements and helping with grant applications.

O Adopt a rigorous system for evaluating research and a system of merit-based compensation. (For example, institute a merit-based annual salary system primarily for researchers from outside the host institution. As a basic rule, the salaries of researchers who were already employed at the host institution prior to the centers' establishment are to be paid by the host institution.)

The director will organize the International Scientific Advisory Board (ISAB) consisting of internationally renowned scientists in the fields of immunology, bio-imaging and bioinformatics. The Board will conduct an evaluation of the research groups' performance every other year. The center's Director will use the ISAB evaluation as reference material to determine PIs' salaries and their contract renewal.

Concerning the procedure for evaluation of other staff, standardized forms have been created specific to the position of the staff. Three forms have been generated to evaluate 1) the Specially Appointed Associate Professor/Assistant Professor/Lecturer; 2) Specially Appointed Researcher; and 3) the Technician/Administrative staff. Points of evaluation range from the work performance and other areas such as: the involvement in the laboratory; research management; achievements; application/acquisition of external funds; progress in combined research projects; and contribution to the WPI program. Points are relative to the staff's position. The evaluation data will be used as reference material to determine staff salaries and their contract renewal.

O Provide equipment and facilities, including laboratory space, appropriate to a top world-level research center.

About 50% of the space of the Integrated Life Science Building (ten-storey, 9,258 m²) constructed in 2009 are allocated for the use of IFReC. Located next to this building is the IFReC animal resource center (four-storey, 2482 m²; 5000 cages for 25,000 SPF mice, constructed in 2009) and the IFReC research building (nine-storey, 6,592 m², constructed in 2011). The close proximity of these buildings will facilitate the interactions of IFReC researchers of various fields with each other, and further promote their collaborative research.

The facilities including the radio-isotope experimental station, core instrument facility and three animal resource centers that are distributed between both IFReC and the Research Institute of Microbial Diseases and made available to all members of both institutes. In order to better organize and manage these facilities, an associate professor and a few technicians are posted.

In addition, cutting-edge instruments such as a Raman microscope and an advanced 11.7T MRI for minimally-invasive observations and measurements have been installed at the expense of the

AKIRA project from the Funding Program for World-Leading Innovative R&D of Science and Technology budget. These instrument's hardware and software have been customized by experienced researchers to improve their performance so as to optimize the technologies for immunology-based research purposes and/or experimental subjects. Although use of appropriate probes would be sometimes required, we can expect to be able to track certain immune cells at the whole animal level (it is already possible at the tissue level) or molecules in a cell, and/or to directly measure cellular composition in immune cells.

A full list of all core equipment and facilities will be made available online to all members of staff in English and Japanese. All operational manuals will also be available in both Japanese and English.

O Hold international research conferences or symposiums regularly (at least once a year) to bring the world's leading researchers together at the center.

IFReC will organize international research conferences, workshops or symposia at least once a year. In addition, to provide a new educational and networking venue for young researchers all over the world, IFReC and SIgN have reached an agreement to jointly organize a Winter School on Advanced Immunology every year. The school will be held annually, with the location alternating between Japan and Singapore.

O Other measures to ensure that top-caliber researchers from around the world can comfortably devote themselves to their research in a competitive international environment, if any.

Osaka University has established the Gender Equality Promotion Office to provide career support and encouragement for young scholars who will be next-generation researchers through the following:

- Implementation of a Research Supporter System to support female researchers who are having difficulty in securing time for research due to child birth, child-rearing, or nursing-care. This support is practiced by the University's Human Resource Bank that employs individuals who are studying at or have graduated from a graduate school in the same field and deploys these individuals as research assistants to researchers.
- Sharing information about research on gender equality through setting up a research network connecting in-campus faculty, staff at gender equality program divisions in local communities, gender equality promotion offices in companies and gender equality promotion offices at research institutions and universities throughout Japan.

The activities of this office will be expected to be beneficial for IFReC to increase the number of female PIs and junior researchers.

Referring to advice and suggestions given every year by the WPI working group and the program committee, the executive board of IFReC consisting of the center Director, Deputy Directors and Administrative Director make plans to improve the research environment for both domestic and overseas researchers.

(6) Indicators for evaluating a center's global standing

- · Describe concretely the following points.
- i) Criteria and methods to be used for evaluating the center's global standing in the subject field
- (a) Major contributions to main research areas: Are principal investigators of IFReC leading and advancing main research areas as major players in their respective fields?
- (b) Creation of new research areas: Are principal investigators of IFReC opening or creating new research areas in the corresponding fields?
- (c) Contribution to human welfare: Are there any accomplishments from this center, which have made great contributions to increase the quality of human life in various ways such as developing therapeutic or diagnostic means of diseases?
- ii) Results of current assessment made using said criteria and methods

(a) Major contributions to main research areas:

Principal investigators of IFReC have been leading main research areas of the immunology field (Akira in research of innate immunity; Sakaguchi in research of regulatory T cells; Kishimoto in research of cytokines), which is obvious from the enormous number of citations of their papers. Yanagida is also a pioneer of the single molecule imaging. In addition to these original PIs, most of the PIs appointed from April 2008 onward can be regarded as leading researchers in their respective fields.

(b) Creation of new research areas:

The collaboration of immunology groups with imaging and bioinformatics groups has gradually started to visualize the movement of molecules or cells they are dealing with, and to analyze the vast data obtained from microarray experiments and whole genome sequencing since IFReC was launched four years ago. To systematically enhance such collaborations, as a WPI center we introduced the "Research Support Program for Fusion of Different Fields" (2009). A total of 15 projects have been supported, a few of which have already been jointly published by different research groups and some others have reached the stage ready for publication. The program will be succeeded by the "Double Mentor Program" which is to encourage PhD students and young post-docs to engage in research projects jointly planned by senior researchers in different disciplines.

(c) Contribution to human welfare:

The development of an Anti-IL-6 receptor therapy for inflammatory diseases based on basic research by Kishimoto has been used in clinical practice and proved very effective. Hatazawa is a specialist of nuclear medicine and responsible for diagnostic imaging at the University Hospital. He has been developing an integrated PET/MRI system, which is to create a new fusion of morphological and functional imaging. This technology is expected to become a powerful diagnostic means for various diseases. We understand the importance of reinforcing the lines that allow for basic research to be translated in to that which may be of benefit to human welfare. In view of this, we recruited C. Coban (2010) and K. Ishii (2010) as PIs, who are specialists of Malaria immunology and vaccine science, respectively. We believe that their creative interaction with other IFReC members will make a great step forward and contribution to human welfare.

iii) Goals to be achieved through the project (at time of final evaluation)

- (a) To establish methodologies to quantitatively examine structural, spatial and temporal properties of immune cells and molecules in vivo.
- (b) To simulate the dynamics of immune network systems, both at the cellular and whole body level, by combining the data thus obtained in order to present new paradigms for understanding the immune network.
- (c) To open a new vista for clinical immunology through translational development of the basic research results.

(7) Securing research funding

Future prospects

- Describe the concrete prospects for securing resources that match or exceed the project grant.
- Calculate the total amount of research funding (e.g., competitive funding) based on the percentage of time the researchers devote to research activities at the center vis-à-vis the total time they spend conducting research activities. Be sure the prospects are realistically based on the past record.

We have mainly obtained the following budgets other than WPI budgets in FY2011 and expect nearly the same amount will also be ensured after FY2012 onwards.

- 1) Competitive Research Grants obtained by researchers: 1.82 billion yen
- 2) Personnel expenses provided by management expenses grant of Osaka University to employ researchers who have concurrent positions at IFReC and other department in the university: 217 million yen
- 3) Personnel expenses financed by Kishimoto Foundation Fellowships/Scholarships: 50 million yen

• Describe activities and initiatives to be taken after project funding ends.

One possible initiative will be the integration of IFReC and Osaka University International Research Center for Infectious Diseases (IRCID). Since IRCID is currently operating as a research center focusing on infectious diseases, it will functionally complement IFReC. Meanwhile IFReC has established good partnership with the Research Institute of Microbial Diseases (RIMD), the parent body of both centers, through the sharing of research facilities such as animal resource centers, the radio-isotope experimental station and the core instrumentation facility. Thus the new organization is expected to be capable of systematically conducting a wide range of research from basic to applied, such as molecular details in immune responses to vaccine development.

As described in **"5. Host Institution's Commitment"**, Osaka university has concluded collaborative agreements with the National Institute of Information and Communications Technology(NICT) and

Others

with Riken. Based on these agreements, two research centers, the Center for Information and Neural Networks (CiNeT) of NICT and the Quantitative Biology Center (QBiC) of RIKEN have been opened near IFReC. Professor Yanagida, an IFRec Deputy Director, has been appointed as the director of both centers. Technologies and methodologies of both centers are rather similar to those of IFReC, so collaborations with these centers will be made in due course and helping IFReC to advance interdisciplinary research necessary for initiating a new era of immunology. If both institutions function together closely and systematically with the IFReC/RIMD complex, an integrated life science center of global significance and presence could be established at Osaka University.

 Describe expected ripple effects (e.g., how the research center project will have trailblazing components that can be referred to by other departments in the host institution and/or other research institutions when attempting to build their own top world-level research centers).

If the collaboration of IFReC with CiNeT and QBiC is successful in integration of immunology with cutting edge-technologies of bio-imaging and bioinformatics, momentum would rise in researchers of other bioscience-related departments of Osaka University, as the University is among the foremost institutions regarding cutting-edge technologies including Raman spectroscopy, electron microscopy, atomic force microscopy, etc.

• Describe other important measures to be taken in creating a world premier international research center, if any.

As it is obvious that the whole environment should be favorable for IFReC to become a WPI center, in particular, for integration of different research fields, we are expecting the University to make the effort to:

(a) Support world class research development at CiNeT and QBiC

(b) Facilitate industry-academia collaboration by research teams at the Techno Alliance center to produce outcomes that meet social expectations

5. Host Institution's Commitment (in English)

To MEXT

Date January 30, 2012

Name of host institution: Osaka University Name and title of head of host institution: Toshio Hirano, President

Signature

I confirm that the measures listed below will be taken faithfully regarding "Osaka University Immunology Frontier Research Center" adopted under the World Premier International Research Center Initiative.

<Provision in host institution's mid-to-long-term plan>

• Describe clearly the host institution's mid-to-long-term strategy plan and how the center is positioned within that strategy.

In the Osaka University Medium-Term Plan for the 1st period (1st MTP, FY2004 - FY2009), it was stated that the research objective of the University is "to support development in science and industrial technology and flexibly handle research subjects of great urgency, such as applied and advanced research for human society and culture of the 21st century", which was in line with what the host institution of a WPI center should commit.

During the latter half of the 1st MTP, IFReC was actually selected as one of five WPI research centers and started its operation. In the Medium-Term Plan for the 2nd period (FY2010 - FY2015), the research objective has been further developed "to promote the world's top class research, advance knowledge in various research fields by fully utilizing the capacities of different research organizations of the university, and promote interdisciplinary research by establishing an innovation hub that supports both basic and applied research". This statement is a clear indication of the University's strong awareness of the reasons under which IFReC was selected, and its objective as a WPI center.

<Concrete Measures>

· Describe the concrete measures that the host institution will take to satisfy the following requirements.

(1) How it will support the center's need to secure resources that match or exceed the project grant through such means as competitive grants obtained by researchers participating in the project, in-kind contributions and other forms of assistance by the host institution (including partial payment of salaries, provision of research space), and/or external donations.

During the initial period between FY2007 and FY2010, Osaka University supported IFReC in establishing its foundation to become a WPI center by providing available resources that would be either greater or equal to the WPI project grant including:

- Allocation of all indirect costs of the WPI budget to be at the disposal of IFReC for the initial setting-up
- Construction of the Integrated Life Science (ILS) building (10-sroried, 9,258 m² of space) to provide laboratory space of real international standard for the core PIs of IFREC (2009)
- Finance support of construction of the IFReC Animal Resource Center for SPF animals (4-storied, 2,482 m² of space with 5,000cages for 25,000 mice)
- Provision of a tenured position to invite professor Sakaguchi from Kyoto University, who is an indispensable PI for IFReC to become a world-leading institution of immunology
- 5) Eligibility of IFReC researchers to apply intra-university competitive research funds
- 6) Assignment of two administrative staff employed by the university budget

Along with these existing measures, Osaka University will continue to make every effort to support IFReC securing resources that match or exceed the WPI budget.

(2) How it will institute a system under which the center's director is able to make substantive personnel and budget allocation decisions necessary to implementing the center project—a system, which in practice, allows the center director autonomy in making decisions regarding the center's operation. The University has entitled the Center Director to manage and operate the center by making decisions regarding substantive personnel and budget allocation. However, important matters such as annual budget and appointment of PIs are to be approved at the Center Management Committee and the Board of Representatives. The Administrative Director is authorized to give full support to the Director by acting as a coordinator among the Center Director and Deputy Directors and executing management actions through the reformed administrative office. Thus, the director can literally make top-down decisions and reformation of research environments so that IFReC PIs can devote themselves to research.

(3) The support it will provide to the center director in coordinating with other departments within the host institution when recruiting researchers for the center, while giving reasonable regard to the educational and research activities of those departments.

When a researcher from a different department in Osaka University joins the WPI as a full time researcher, Osaka University will support the replacement by indirect research expenses and/or other expenses. If a researcher at other departments in Osaka University is working concurrently at the center, he or she will be exempted from educational work. Osaka University will support resource sharing/exchange between the WPI and other departments.

(4) Its flexibility in applying, revising, or supplementing the host institution's internal systems as needed for the center to effectively implement new management methods (e.g., English-language environment, merit-based pay, top-down decision making) unfettered by conventional modes of operation.

To maintain the excellent research environment as a WPI center, IFReC will apply the existing employment system of Osaka University, including the annual salary system. If the present employee system of Osaka University does not fit in with the operation of the Center, then Osaka University will consider revising and supplementing the present internal system of Osaka University. The new system should be flexibly operated. Osaka University will support the WPI's enforcement to endorse the system and its operation as follows:

- 1) IFReC will ensure that the retirement allowance to be paid to the hired researcher is based on the total years of service to the Center and other institutions.
- The housing of international visiting professors will be arranged by IFReC so there is no need to pay neither the security deposit nor key money.
- To hire exceptional researchers, salaries can be changed from the existing system depending on their ability.
- Linguistically able English speaking administrative staff will be hired from both inside and outside the University, with on-the-job training after employment.

The aforementioned items will undergo examination as necessary by related departments of Osaka University.

As for housing of international visiting professors and researchers, accommodation of international standards (Kasugaoka House) was constructed in 2010. Here, several IFReC researchers and their families currently reside (part of the rent is subsidized from the WPI budget).

In addition, Osaka University established the Support Office for Large-Scale Education and Research Projects (LSERP) and the Office for International Planning and Programs (IPP) in 2009 and 2010, respectively. LSERP is to improve support systems for obtaining large-scale education and research projects for Osaka University, in order to fortify the planning and strategic functions for such projects. Several personnel with research experience together with PhD and bilingual staff have been recruited to the administrative office of LSERP.

One of the goals of IPP is to promote research collaborations with scholars and institutions overseas and to share the research results for the benefit of the global society, which is almost exactly what is mentioned in the WPI program, and hence beneficial to IFReC.

(5) Its accommodation of the center's infrastructural requirements (for facilities, e.g., laboratory space; equipment; land, etc.).

As described above (1), the University constructed the ILS building in 2009 to provide 11 IFReC PIs sufficient spaces to set up their laboratories. Next to this building, construction of a new IFReC research building (nine-storey, 6592m²) was completed in March 2011, where 9 IFReC laboratories moved into. This makes it possible for all of the full-time researchers of IFReC to assemble together.

The University-supported the construction of the IFReC animal resource center (1), which together with two animal resource centers of the Research Institute for Microbial Diseases, has made it possible for IFReC to use these centers for different experimental purposes.

The University has also made necessary arrangements for IFReC researchers to use equipment in other faculties.

(6) Other types of assistance it will provide to give maximum support to the center in achieving its concepts and objectives and becoming a world premier international research center in both name and deed.

The Support Office for International Students and Scholars, Osaka University (the Support Office), which was first established in 2007 within the International Student Affair Division, at Department of International Affairs, and then reformed as the present office in 2009, offers various types of assistance for international students and scholars and their families before and after their arrival in Japan. The primary goal of the Support Office is to help make the life of international students and scholars easier and more comfortable in Japan, the very existence and activity of the Support Office are quite beneficial to IFReC, since overseas researchers, now exceeding 30% of the total researchers, can concentrate fully on their academic activities throughout the duration of their stay in Japan.

The University also established the Gender Equality Promotion Office in 2010 to provide career support and encouragement for young scholars who will be next-generation researchers. This office will support IFReC to increase the number of female researchers, female PIs in particular.

Furthermore, the University concluded research collaboration agreements with NICT, (2009) and RIKEN (2010). Based on these agreements, QBiC of RIKEN started its operation in the University campus in 2011 and the research building of CiNeT is under construction in walking distance from IFReC. Both centers are headed by Yanagida, a Deputy Director of IFReC. The main focus at CiNeT is technological innovation for direct imaging of cellular activities, metabolism and systems analysis of cellular networks in the brain, while quantitative and comprehensive studies are performed to accurately predict and control complex biological phenomena at QBiC. Collaborations with these centers will be made in due course, helping IFReC to advance interdisciplinary researches necessary for open a new era of immunology.

List of Principal Investigators

· 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 2012.

• For investigators who cannot participate in the center project from 1 April 2012, indicate the time that their participation will start in the "Notes" column.

	Name	Age	Current affiliation (organization, department) and specialties	Academic degree	Notes
1	Shizuo Akira*	59	WPI Immunology Frontier Research Center, Osaka University (Immunology)	MD, PhD	
2	Tadamitsu Kishimoto*	72	WPI Immunology Frontier Research Center, Osaka University (Immunology)	MD, PhD	
3	Masayuki Miyasaka∗	64	Graduate School of Medicine, Osaka University (Immunology)	MD, PhD	
4	Hitoshi Kikutani*	61	Research Institute for Microbial Diseases, Osaka University (Immunology)	MD, PhD	
5	Taroh Kinoshita*	60	WPI Immunology Frontier Research Center, Osaka University (Immunology, Biochemistry)	PhD	
6	Atsushi Kumanogoh∗	45	Graduate School of Medicine, Osaka University (Immunology)	MD, PhD	
7	Kiyoshi Takeda*	45	Graduate School of Medicine, Osaka University (Immunology)	MD, PhD	
8	Hisashi Arase*		WPI Immunology Frontier Research Center, Osaka University (Immunology)	MD, PhD	
9	Shimon Sakaguchi∗	61	WPI Immunology Frontier Research Center, Osaka University (Immunology)	MD, PhD	

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10	Takashi Saito∗	61	RIKEN Research Center for Allergy and Immunology (Immunology)	PhD	
11	Tomohiro Kurosaki*	56	WPI Immunology Frontier Research Center, Osaka University (Immunology and Molecular Biology)	MD, PhD	
12	Fritz Melchers*	75	Max Planck Fellow (Immunology)	PhD	
13	Toshio Yanagida*	65	Graduate School of Frontier Biosciences, Osaka University (Molecular Imaging)	PhD	
14	Yoshichika Yoshioka*	58	WPI Immunology Frontier Research Center, Osaka University (Biophysics)	DSc	
15	Yutaka Hata*	50	Graudate School of Engineering, University of Hyogo (Computer Engineering)	PhD	
16	Daron M. Standley	44	WPI Immunology Frontier Research Center, Osaka University (Chemistry)	PhD	
17	Jun Hatazawa*	58	Graduate School of Medicine, Osaka University (Nuclear Medicine)	MD, PhD	
18	Jang Myoung Ho	43	WPI Immunology Frontier Research Center, Osaka University (Mucosal Immunology)	PhD	
19	Masaru Ishii	38	WPI Immunology Frontier Research Center, Osaka University (Bioimaging)	MD, PhD	
20	Kazuya Kikuchi	46	Graduate School of Engineering, Osaka University (Chemical Biology)	PhD	
21	Diego Miranda− Saavedra	36	WPI Immunology Frontier Research Center, Osaka University (Molecular and Cellular Biology)	PhD	
22	Cevayir Coban	39	WPI Immunology Frontier Research Center, Osaka University (Clinical Microbiology)	MD, PhD	

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23	Nicholas Isaac Smith	37	WPI Immunology Frontier Research Center, Osaka University (Applied Physics)	PhD	
24	Ken Ishii*	43	National Institute of Biomedical Innovation (Immunology, Vaccine Science)	MD, PhD	
25	Tsuneyasu Kaisho*	52	WPI Immunology Frontier Research Center, Osaka University (Immunology)	MD, PhD	
26	Kazuhiro Suzuki	36	WPI Immunology Frontier Research Center, Osaka University (Immune Cell Dynamics)	MD, PhD	
27	Rikinari Hanayama	37	WPI Immunology Frontier Research Center, Osaka University (Cell Biology)	MD, PhD	