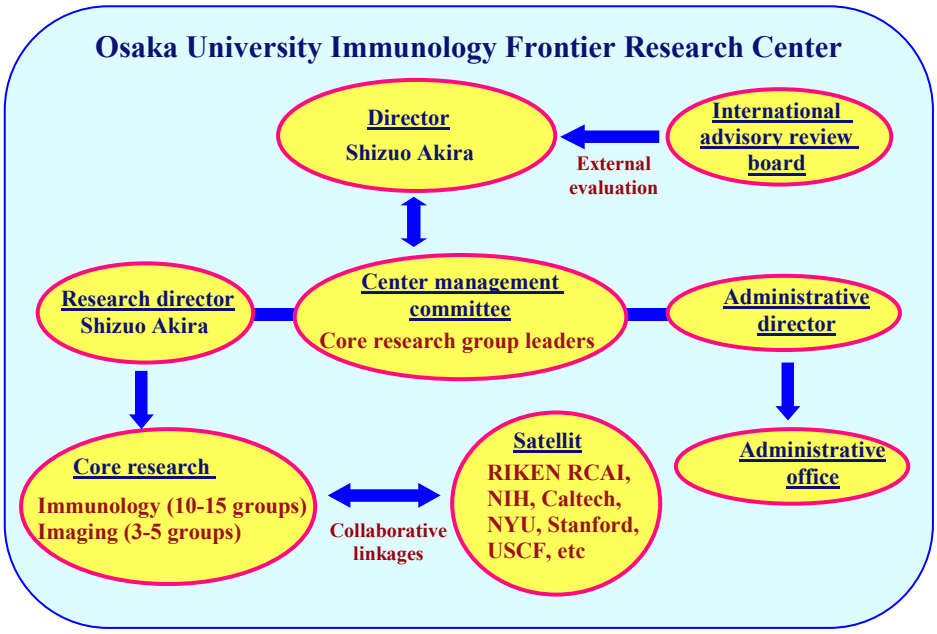
Summary of Proposal

Host institution name	Osaka University
Head of host institution	Kiyokazu Washida, Osaka University, President
Prospective center director	Shizuo Akira, Osaka University, Professor (WPI IFReC)
Prospective administrative director	Norio Furushiro, Osaka University, Professor (WPI IFReC)
Title of center project	Osaka University Immunology Frontier Research Center
Center name	Osaka University Immunology Frontier Research Center (IFReC)
Project Summary	The aim of this program is to unveil the whole picture of dynamic immune system by employing a variety of imaging techniques to visualize the immune cells within live animals. We will attempt to improve an imaging technology, which allows us to track the dynamic behavior of immune cells and their communications more directly and understand how immune cells respond to non-self such as pathogens and cancers in vivo. Based on these basic studies, we will seek to develop new strategies for diagnosis and treatment of various diseases including infectious diseases, autoimmune diseases, allergy and cancer.
Research fields	Fields: Immunology and Bioengineering Relevant fields: Biosciences, Precision and mechanical engineering Importance: Research on the immune system, which deals with the host defense mechanism against invading microbial pathogens, is important in treatment of various diseases including infectious disease, allergy, inflammation, autoimmune disease, and immunodeficiency, all of which are intimately associated with abnormality in the immune response. Although numerous studies have focused on identifications of cells and factors involved in the immune system, it still remains unclear how immune cells actually interact each other in the in vivo immune organs in response to infections or in pathological conditions. Thus, it will be necessary to develop a new imaging technology that tracks the immune response as well as a method to artificially control the immune response in the future. In foreign countries, the incorporation of the imaging technology into immunology research has already started. However, such movement is not seen in Japan, and both fields are still isolated. The immunology in Japan, especially Osaka University, is internationally acclaimed in its high quality of basic research. Therefore, creating a research center for immunology in Osaka University in which domestic and overseas researchers come together, and explore the in vivo imaging of the immune system is imperative to establish not only an new field of basic science but also overcome the above-mentioned diseases.
Research objectives	Development of an imaging technology for visualization of immune system in vivo and a new method based on the imaging technology that controls immune system for the treatment of immune diseases
Outline of management	Dr. Norio Furushiro, who is familiar with managements in English, will head the administration department. The administration department will have three sections: the research management section consisting of 2-3 members with PhD degree, and accounting section and general affairs section each consisting of a senior supervisor with rich administrative experiences in the University, and several bilingual or English-speaking full-time and part-time personnel. The research management section deals with planning and logistics of scientific meetings sponsored by the Research Center, public information and liaison, and issues relating to intellectual properties. Center management committee consisting of center director (Chairman), administrative director, Principal Investigators will make mid-to-long term plan of the Center based on advices by the International Advisory/Review Board. The center director, based on suggestions by the center management committee, will make decisions on major issues necessary for center's managements, such as researchers' salaries, appointment of new researchers and administrative director. The University president will approve the center director's decisions on major issues necessary for center's managements.
Researchers and other center staffs	Our center will have about 200 people, including investigators, reseachers and staffs by the year of 2010. The number of Principal Investigators will be about 20. List of the name of main PI: Shizuo Akira, Tadamitshu Kishimoto, Toshio Hirano, Masayuki Miyasaka, Hitoshi Kikutani, Taroh Kinoshita, Atsushi Kumanogoh, Kiyoshi Takeda, Hisashi Arase, Shimon Sakaguchi, Takashi Saito, Tomohiro Kurosaki, Fritz

	Melchers, Toshio Yanagida, Junji Seki, Yoshichika Yoshioka, Takashi Jin, Yutaka Hata List of the name of satellite organizations and other partner institutions: RIKEN Research Center for Allergy and Immunology, National Institutes of Health, Harvard University, New York University, Stanford University, California Institute of Technology, University of California San Francisco
Outline of research environment	○ Research management section consisting of people with PhD degree will be set up in the administration department. The research management section deals with planning and logistics of scientific meetings sponsored by the Research Center, public information and liaison, and issues relating to intellectual properties. The administration department also includes accounting section and general affairs section each consisting of a senior supervisor with rich administrative experiences in the University, and several bilingual or English-speaking full-time and part-time personnel. These administration staffs will fully support researchers so that researchers do not have to spend their time in paper work and other administrative functions. ○ Budget for equipments will be allocated to invite PIs from institutions outside Osaka University. Budget for consumables and supplies will also be provided to PIs so that those PIs are able to start research at maximum efficiency without losing time. To facilitate acquisition of competitive research grants from domestic funding sources, the research management section in the administration department will help PIs from abroad in application. ○ Postdocs will be hired through advertisement of positions on major journals, such as Nature and Immunity, and their home pages. ○ Dr. Norio Furushiro, who is familiar with managements in English, will head the administration department. The administration department will have three sections: the research management section, accounting section and general affairs section. ○ The center director will organize the International Advisory/Review Board consisting of ten-odd renowned immunologists. The International Advisory/Review Board will conduct evaluation of research groups' achievement every or every other year. The center director will determine principal investigators' salaries based on the evaluation by the International Advisory/Review Board. ○ The main research building (ten floors and 9,400 square m) will be constructed by March 2009 with University budget and external donation, and most of its space will be used for the Research Center. ○ The Research Center will organize international research conferences once a year. ○ Based on advices and/or suggestions by the International Advisory/Review Board, the center director will set up research environment suitable for international researchers.
Outline of indicators for evaluating a center's global standing	i) Criteria and methods to be used for evaluating the center's global standing in the subject field The following points will be evaluated not only quantitatively by numbers of publications, their citation and so on but also by external reviews of the reviewing committee that consists of internationally leading scientists in the corresponding fields. (a) Major contributions to main research areas: Are principal investigators of this center leading and advancing main research areas as major players in the corresponding fields? (b) Creation of new research areas: Are principal investigators of this center opening or creating new research areas in the corresponding fields? (c) Contribution to human life: 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 of diseases? ii) Results of current assessment made using said criteria and methods (a) Major contributions to main research areas: Principal investigators of this center have been leading main research areas of the immunology field (Shizuo Akira in research of innate immunity; Shimon Sakaguchi in research of regulatory T cells; Tadamitsu Kishimoto and Toshio Hirano in research of cytokines), which are obvious from an enormous number of citations of their papers. Toshio Yanagida is also a pioneer of the single molecule imaging. (b) Creation of new research areas: Principal investigators of this center are currently opening new research areas (Takashi Saito in the single molecule imaging analysis of immune responses; Hitoshi Kikutani and Atsushi Kumanogoh in immune regulation by semaphorins). (c) Contribution to human life: Tadamitsu Kishimoto and his colleagues developed anti-IL-6 receptor therapy for inflammatory diseases, which is highly expected for treatment of various immunological diseases such as rheumatoid arthritis. iii) Goals to be achieved through the project (at time of interim and final evaluations) Goals at time of interim - To keep current levels and global standing of immunological research of this center. - To further grow new research area that were opened by this center and make them major ones in the corresponding area. - To establish technical and theoretical basis of intravital and noninvasive single cell analysis of immune responses. Goals at final evaluation - To establish the methodology of intravital and noninvasive single cell analysis of immune responses. - To combine the above methodology with basic immunological knowledge obtained

	by conventional immunology research of this center and to present new paradigm for understanding the immune network.
Securing research funding	Osaka University will provide support to meet the necesally expence, on top of Grant-in-aid (about 15 -20 hundred million yen/year)and Reserch Grants for Principal Investigators. . Note: Past record of competitive research grants for Principal Investigators 2002: 6.76 million dollars or 811 million yen; 2003: 9.39 million dollars or 1.127 billion yen; 2004: 9.48 million dollars or 1.137 billion yen; 2005: 9.20 million dollars or 1.104 billion yen ; 2006: 9.60 million dollars or 1.152 billion yen; Average 8.88 million dollars or 1.066 billion yen.
Summary of host institution's commitment	WPI will be the top priority in the mid-term strategic target and plan, and Osaka University will give full support by implementing institutional reforms that are necessary for formation of the WPI and improving the research systems. (1) Osaka University will assist the WPI to perform every possible support for operation and research activities of WPI. Osaka University will provide supports to the WPI resources that would be either greater or equal to the WPI project grant. (2) The WPI will be recognized as a department within the university. Osaka University will provide the Center Director with the entitlement to manage and operate the WPI. The Center Director is entitled to make decisions regarding substantive personnel and budget allocation as are the Deans and Directors in other faculties in Osaka University. An Administrative Director will support the Center Director and he will be responsible for office management so that the Director's decisions are kept to the bare essentials. Osaka University will support the Center Director's research environment. (3) Osaka University will support resource sharing/exchange between the WPI and other departments. (4) To maintain the excellent research environment for the WPI, the center 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. (5) A new research building of ten floors with 9400m2 of space will be constructed by March 2009 for the Research Center. Osaka University will also provide laboratory space on the campus to accommodate research groups, which will join the Research Center before the new research building is completed. To meet the space requirements for an animal facility for newly coming research groups, Osaka University will construct a new block of animal facilities and provide it for the Research Center's use. (6) Osaka University will start a new "one stop service office" for international researchers and students in 2007. This all-in-one service aims to improve both the research and living conditions for visitors from abroad. Information including the research and daily life on campus and in the surrounding area has already been released on the web information service site "GCN-Osaka & Worldwide". Osaka University has established three Overseas liaison offices for Education and Research. Their central task is to collect and transmit information, and scout highly talented researchers. All the faculties and overseas offices of Osaka University will assist the WPI so as to become the "World Premier International Research Center".

Research Center Project

Host institution name	Osaka University
Head of host institution	Kiyokazu Washida, President
Title of center project	Osaka University Immunology Frontier Research Center
Center name	Osaka University Immunology Frontier Research Center (IFReC)
Project summary	・ Briefly describe the general plan of the project. The aim of this program is to unveil the whole picture of dynamic immune system by employing a variety of imaging techniques to visualize the immune cells within live animals. We will attempt to improve an imaging technology, which allows us to track the dynamic behavior of immune cells and their communications more directly and understand how immune cells respond to non-self such as pathogens and cancers in vivo. Based on these basic studies, we will seek to develop new strategies for diagnosis and treatment of various diseases including infectious diseases, autoimmune diseases, allergy and cancer. To this end, we will invite 10-20 world-class principal investigators to Osaka University Immunology Frontier Research Center as core scientists in the project and expand by forming a linkage with domestic and overseas institutions that will function as satellites. ・ Include a chart that illustrates the center's overall structure including its collaborative linkages with other domestic and foreign institutions, its system of external evaluation, and its management framework 

(1) Research fields

・ Fill in the name of the research field of the project.

Immunology and Bioengineering

・ Choose relevant fields from among ①－⑦ below, specifying the inter disciplinary field(s) that the project addresses.

Biosciences, Precision and mechanical engineering

①Biosciences, ②Chemistry, ③Material sciences, ④Electronics engineering and information sciences, ⑤Precision and mechanical engineering, ⑥Physics, ⑦Mathematics

・Describe the importance of the proposed research, including domestic and international R&D trends in the field and Japan's advantages.

The research on immune system, which is the host defense mechanism against invading microbial pathogens, is therapeutically important with regards to treat various diseases (infectious disease, allergy, inflammation, autoimmune disease, and immunodeficiency, etc.) in which the immune system takes part. Although numerous studies have focused on identifications of cells and factors involved in the immune system, it still remains unclear how immune cells are actually changed in response to infections or in pathological conditions in vivo. Thus, it will be necessary to develop a new imaging technology that tracks immune responses as well as a method to artificially control the immune response in the future. In foreign countries, the uniting type of research on immunology and the imaging technology has already started. However, both fields are still isolated and it has not become uniting in Japan. The basic research on immunology in Japan, especially Osaka University, is internationally in a very high level. Therefore, creating a research center for immunology in Osaka University in which domestic and overseas researchers gather that aims to image the immune system in vivo is important to establish not only an new field of basic science but also overcome the above-mentioned diseases.

・If centers in similar fields already exist in Japan or overseas, please list them.

Basel Institute for Immunology, Basel, Switzerland (1971-2001)

(2) Research objectives

・Describe in a clear and easy-to-understand manner the research objectives that the project seeks to achieve by the end of the grant period (in 10 years). 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.

○Explore the technology of in vivo imaging of immune system.
We aim to develop a new technology for visualization of immune cells in vivo through the merging of the two fields of immunology and bioengineering. This technology will provide us to understand the dynamics of immune system in normal and pathological conditions. New findings obtained through imaging of the immune reaction will lead to development of new strategies for diagnosis and treatment for various immune diseases including autoimmune diseases, immunodeficiency, allergy and inflammation as well as for development of vaccines for pathogens and tumors.

・Describe concretely the research plan to achieve the objectives, and any related past achievements by the host institution.

We will attempt to develop a new technology that can visualize the dynamics of immune system at the level of one living cell. To this end, we will extensively invite world-class researchers in the fields of immunology and imaging. Through mutual interactions of both fields of researchers, we will attempt to design new probes suitable for MRI and multi-photon microscopy that can track one immune cell in vivo. We will apply those probes to visualize how immune cells respond to antigens and how immune cells behave in the pathological conditions like autoimmune diseases, allergy and inflammation. Based on the knowledge which we will obtain with this system, we will establish a new paradigm of in vivo immune response and apply the new theory for treatments of immune-related diseases. Notably, Osaka University is famous for immunology, especially innate and adaptive immunity and cytokine network that have been originally discovered by and extensively studied in this university. Osaka University has also conducted a world-top class research in the field of engineering. This is a merit to perform a collaborative work between immunologists and engineers as well as to invite researchers domestic and from overseas. Moreover, Osaka University has an MRI/NMR system (11.7T) with a high resolution that is rarely housed in other laboratories of Japan, which is indispensable for achieving our project.

(3) Management

i) Prospective center director

・ Fill in the name of the prospective center director, his/her age (as of 1 October 2007), current affiliation and position title, and specialties. Describe his/her qualifications to be the center director.

Name; Shizuo Akira
Age; 54
Affiliation and title; Professor, Immunology Frontier Research Center, Osaka University
Specialties; Immunology
Qualifications; Professor Shizuo Akira has been obtaining several big grants in Japan, including CREST, ERATO and 21 century COE, and he, as a project leader of these grants, has successively published so many papers concerning innate immunity with high citation. These findings clearly demonstrate that he has an ability to manage and organize a big grant program. Moreover, the fact that he has obtained several international awards and topped a list of highly cited researchers in the field of Immunology is attractive to many domestic and foreign researchers involved in immunology research as well as in the imaging research, and will make them participate in the establishment of this world-premier immunology center as principal investigators and satellite researchers.

・ Attach a biographical sketch of the prospective center director using Appendix 2.

・ How does the prospective center director intend to construct the center and what is his/her vision of objectives to be achieved? Provide a synopsis written by the prospective center director (free format).

・ If possible, attach a letter (s) of recommendation for the prospective center director from researchers with world-standard achievements in the subject field.

ii) Prospective administrative director

・Fill in the name of the prospective administrative director, his/her age (as of 1 October 2007), current affiliation and position title. Describe his/her qualifications to be the administrative director.

Name: Norio Furushiro
Age: 63
Affiliation: International Student Center, Osaka University
Position title: Director and Professor
Qualifications: Dr. Norio Furushiro, the Director of the International Student Center and Professor of Osaka University, is familiar with managements in English, and organization and administration system of Osaka University.

・Attach a CV of the prospective administrative director (free format).

iii) Composition of administrative staff

・Concretely describe how the administrative staff is organized.

Dr. Norio Furushiro, who is familiar with managements in English, will head the administration department. The administration department will have three sections: the research management section consisting of 2-3 members with PhD degree, and accounting section and general affairs section each consisting of two senior supervisors with rich administrative experiences in the University, and several bilingual or English-speaking full-time and part-time personnel. The research management section deals with planning and logistics of scientific meetings sponsored by the Research Center, public information and liaison, and issues relating to intellectual properties.

iv) Decision-making system

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

Center management committee consisting of director (Chairman), administrative director and a few principal investigators will make mid-to-long term plan of the Center based on advices by the International Advisory/Review Board. The director, based on suggestions by the center management committee, will

make decisions on major issues necessary for center's managements, such as researchers' salaries, appointment of new researchers and administrative director.

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 center's managements, such as researchers' salaries, appointment of new researchers and administrative director. The University president will make appointment of director, determine the salary of director and make evaluation of the center's performance.

(4) Researchers and other center staffs

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 2007	Final goal (Date: April, 2010)
Researchers from within the host institution	10	10	10
Foreign researchers invited from abroad	1	2	5
Researchers invited from other Japanese institutions	6	6	7
Total principal investigators	17	18	22

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

(At the beginning)

Ten Professors from within Osaka University (Shizuo Akira, Tadamitsu Kishimoto, Toshio Hirano, Masayuki Miyasaka, Hitoshi Kikutani, Taroh Kinoshita, Atsushi Kumanogoh, Kiyoshi Takeda, Hisashi Arase and Toshio Yanagida) will set up and start the Research Center with Shizuo Akira as the director. Two immunologists from RIKEN (Takashi Saito and Tomohiro Kurosaki) will join the center as Professors. Prof. Melchers, as a part-time principal investigator, will start preparation to set up research group while he will advise the director about organization of an international research center in Immunology based on his enormous experiences in organizing Basel Institute for Immunology for twenty years. Two members in imaging science (Yoshichika Yoshioka and Takashi Jin) will come to Osaka University and set up labs in space provided by the University. Junji Seki and Yutaka Hata will also join as a part-time principal investigator. Their labs will be located in the same building as Yanagida's lab and they will all together form "Imaging group".

(At the beginning of FY 2009)

When the new main research building is completed, Prof. Shimon Sakaguchi will join.

(By the beginning of FY2010)

We will recruit two, preferably young, principal investigators from abroad through international solicitation.

・Attach a list of principal investigators who are expected to join the center at the time of the application using Appendix 1. 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 rest of PIs who are to be invited in the future.

We plan to invite two principal investigators from abroad by April 2010. We will invite highly active young investigators at Associate or Assistant Professor level. We will offer them full support including equipped research laboratory and office, 3-4 post-doc positions, 2-3 support staffs and 5-year research fund. Our strategy is to bring forth examples of foreign young principal investigators who are successful in research operation in Japan, in turn, to attract more foreign investigators of high potential. We also plan to actively recruit top-level researchers from abroad by providing higher salary and good research environment. While investigators who are considered as top-quality researchers will be strongly supported by the center,

investigators whose evaluation by the international advisory review board is low have to leave the center. This will increase the mobility of scientists as well as maintain and further upgrade scientific standards of the center.

・Attach a biographical sketch of each investigator using Appendix 2.

・As for the researchers invited from abroad or from other Japanese institutions, attach a letter of intent from each of them to join the center project (free format).

b) Total members

	Numbers		
	At beginning	At end of FY 2007	Final goal (Date: April, 2010)
Researchers (Number of foreign researchers among them and their percentage)	49 (12, 24%)	82 (25, 30%)	147 (47, 32%)
Principal investigators (Number of foreign researchers among them and their percentage)	17 (1, 6%)	18 (2, 11%)	22 (5, 23%)
Other researchers (Number of foreign researchers among them and their percentage)	32 (11, 34%)	64 (23, 36%)	125 (30, 34%)
Research support staffs	28	34	44
Administrative staffs	9	15	15
Total number of people who form the “core” of the research center	86	131	206

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

(At the beginning)

Thirty or more researchers at levels of Assistant Professors and post-doctoral fellows, at least eleven of them being foreign researchers, will be hired in seventeen research groups. About 30 technicians and secretaries will be hired and nine of 15 administrative staffs will be hired. In total, the Research Center will be consisted of 86 or so members at the beginning.

(At the end of FY2007 or the beginning of FY2008)

The number of researchers at levels of Assistant Professors and post-doctoral fellows will be increased to 50 or more. Among them 19 or more will be foreign researchers. We will also hire 10 graduate students as Research Assistants (Four of them will be foreign students). The total number of technicians and secretaries will be increased to 34. The administrative department will become fully staffed with 15 members. Total number of members in the Research Center will be 130 or so at the beginning of FY2008.

(By the beginning of FY2010)

Three more principal investigators (one from Kyoto and two from abroad) will join the center by this time. More researchers at levels of Assistant Professor and post-doctoral fellow will be hired for these new research groups and other groups, and the total number of researchers at these levels will be 90-100. We will hire 20 more Research Assistants. Total number of support staffs will be 44. In total, the center will have about 200 members. We will recruit highly capable non-Japanese scientists from Asian countries as well as Japanese female scientists with high priority throughout the program.

ii) Collaboration with other institutions

・ If the “core” forms linkages with other institutions, domestic and/or foreign, by establishing satellite functions, fill in 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

Overseas

NIH (Ronald Germain, Deputy Chief, Laboratory of Immunology and Chief, Lymphocyte Biology Section, NIAID)

New York Univ. (Michael Dustin, Professor, Skirball Institute of Biomolecular Medicine)

California Institute of Technology (Scott Fraser, Director, Biological Imaging Center, Beckman Institute)

Harvard Medical School (Ulrich H. von Andrian, Professor, Department of Pathology)

Stanford University School of Medicine (Mark Davis, Professor, Department of Microbiology and Immunology)

University of California San Francisco (Jason Cyster, Professor, Department of Microbiology and Immunology)

The center will provide each satellite lab costs to hire several postdoctoral fellows. Researchers in the center and satellites will regularly visit each other and exchange the information to upgrade the scientific standard in imaging. These interactions will provide an environment for the training of young immunologists. We will attempt to have strong connections with various molecular imaging programs in addition to these satellites, in which more innovative researches will be expected.

・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 Appendix 1, and provide a biographical sketch of each using Appendix 2.

Not applicable

・If the “core” forms organic linkages with other institutions, domestic and/or foreign, without establishing satellite functions, fill in the names of the partner institutions and describe their roles and linkages within the center project.

(５) Research Environment

・Concretely describe measures to be taken to satisfy each of the requirements outlined below, including steps and timetables.

□) 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.

Research management section consisting of 2-3 members with PhD degree will be set up in the administration department. The research management section deals with planning and logistics of scientific meetings sponsored by the Research Center, public information and liaison, and issues relating to intellectual properties. The administration department also includes accounting section and general affairs section each consisting of two senior supervisor with rich administrative experiences in the University, several bilingual or English-speaking full-time and part-time personnel. These administration staffs will fully support researchers so that researchers do not have to spend their time in paper work and other administrative functions.

ⅱ) 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.

Budget for equipments will be allocated to invite PIs from institutions outside Osaka University. Budget for consumables and supplies will also be provided to PIs from abroad so that those PIs are able to start research at maximum efficiency without losing time. To facilitate acquisition of competitive research grants from domestic funding sources, the research management section in the administration department will help PIs from abroad in application.

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

Postdocs will be hired through advertisement of positions on major journals, such as Nature and Immunity, and their home pages.

ⅳ) 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.

Dr. Norio Furushiro, the Director of the International Student Center and Professor of Osaka University

who is familiar with managements in English, will head the administration department. The administration department will have three sections: the research management section consisting of 2-3 members with PhD degree, and accounting section and general affairs section each consisting of two senior supervisor with rich administrative experiences in the University, several bilingual or English-speaking full-time and part-time personnel.

v) 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 Advisory Board consisting of ten-odd renowned immunologists. The International Advisory Board will conduct evaluation of research groups' performance every or every other year. The director will determine principal investigators' salaries based on the evaluation by the International Advisory Board.

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

The main research building (ten floors and 9,600 square m) will be constructed by March 2009 with University budget and external donation, and 80% of its space will be used for the Research Center. After many of core research groups move into the new building, Osaka University will seek budget to renovate the old building these research groups are currently using.

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

The Research Center will organize international research conferences independently or in connection with the annual Awaji International Forum on Infection and Immunity, which is organized since 2001 by the Research Institute for Microbial Diseases, Osaka University. In this forum, we will often include a brainstorming session by inviting top scientists in other research areas, including genomics, physics and mathematics, which may provide unexpected new frontiers in immunology research. Especially, genomics is an important component since genome-environment interaction appears to be linked to immunological disorders.

viii) 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.

Based on advices and/or suggestions by the International Advisory Board, the director will set up research environment suitable for international 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

The following points will be evaluated not only quantitatively by numbers of publications, their citation and so on but also by external reviews of the reviewing committee that consists of internationally leading scientists in the corresponding fields.

(a) Major contributions to main research areas: Are principal investigators of this center leading and advancing main research areas as major players in the corresponding fields?

(b) Creation of new research areas: Are principal investigators of this center opening or creating new research areas in the corresponding fields?

(c) Contribution to human life: 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 of diseases?

ii) Results of current assessment made using said criteria and methods

(a) Major contributions to main research areas:

Principal investigators of this center have been leading main research areas of the immunology field (Shizuo Akira in research of innate immunity; Shimon Sakaguchi in research of regulatory T cells; Tadamitsu Kishimoto and Toshio Hirano in research of cytokines), which are obvious from an enormous

number of citations of their papers. Toshio Yanagida is also a pioneer of the single molecule imaging.

(b) Creation of new research areas:

Principal investigators of this center are currently opening new research areas (Takashi Saito in the single molecule imaging analysis of immune responses; Hitoshi Kikutani and Atsushi Kumanogoh in immune regulation by semaphorins).

(c) Contribution to human life:

Tadamitsu Kishimoto and his colleagues developed anti-IL-6 receptor therapy for inflammatory diseases, which is highly expected for treatment of various immunological diseases such as rheumatoid arthritis.

iii) Goals to be achieved through the project (at time of interim and final evaluations)

Goals at time of interim

- To keep current levels and global standing of immunological research of this center.
- To further grow new research area that were opened by this center and make them major ones in the corresponding area.
- To establish technical and theoretical basis of intravital and noninvasive single cell analysis of immune responses.

Goals at final evaluation

- To establish the methodology of intravital and noninvasive single cell analysis of immune responses.
- To combine the above methodology with basic immunological knowledge obtained by conventional immunology research of this center and to present new paradigm for understanding the immune network.

(7) Securing research funding

i) Past record

・Indicate the total amount of research funding (e.g., competitive funding) secured by principal investigators who will join the center project. Itemize by fiscal year (FY2002-2006) taking into account the percentage of time each will devote to research activities at the center vis-à-vis the total time they spend conducting research activities（"Effort ②" in Appendix 2）. For example, if this percentage is 70%, then 70% of his/her research funds can be counted in calculating the total amount of research funds.

Past record of competitive research grants for Principal Investigators

2002: 6.76 million dollars or 811 million yen; 2003: 9.39 million dollars or 1.127 billion yen; 2004: 9.48 million dollars or 1.137 billion yen; 2005: 9.20 million dollars or 1.104 billion yen ; 2006: 9.60 million dollars or 1.152 billion yen; Average 8.88 million dollars or 1.066 billion yen.

ii) Prospects after establishment of the center

・ Based on the past record, 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（"Effort ②" in Appendix 2）. Be sure the prospects are realistically based on the past record.

The specific measurements are as follows:

1) Indirect cost: 3.7 million dollars or 450 million yen.
2) Construction of main research building: 1.8 million dollars or 210 million yen.
3) Provision of other research space: 0.1 million dollars or 10 million yen.
4) Partial payment of Principal Investigators' salaries: 1.3 million dollars or 150 million yen.
5) University budget for Principal Investigators: 0.3 million dollars or 40 million yen.
6) Competitive Research Grants for Principal Investigators: 8.7 million dollars or 1.05 billion yen.
7) Facilitation of external donations: 0.8 million dollars or 100 million yen.

Total: 16.7 million dollars or 2.01 billion yen.

Others

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

After project funding ends and the project turns out to be successful, one possible initiative will be integration of the Immunology Frontier Research Center and Osaka University International Research Center for Infectious Diseases: the latter is a currently operating research center focusing on infectious diseases and will function complementally with the proposed Immunology Frontier Research Center. Such integration will include reorganization of related departments in Osaka University and will lead to the next

generation world premier international research center.

- Describe expected ripple effects（e.g., how the proposed 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）.

The Osaka University International Research Center for Infectious Diseases described above will be eventually reformed following the Immunology Frontier Research Center as a model of world-level research centers.

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

- If one or more of the projects applying for Global COE program have some connections with this research center project, list the project title(s) , outline(s), group leader(s) and the relationship(s) with this project.

Project title: System Dynamics of Biological Function
Outline: this project is planned to develop imaging technology, to analyze dynamics of various biological networks, and to perform modeling and simulation of such networks.
Group leader: Toshio Yanagida
Relationship: Toshio Yanagida, a group leader, is also a principal member of this center project. Both projects focus on imaging technology and mutually interact each other.

Center Director's Vision

Osaka University Immunology Frontier Research Center

Shizuo Akira, M.D., Ph.D

Director

1. Objectives to be achieved

The aim of this program is to unveil the whole picture of the dynamic immune system by employing a variety of imaging techniques to visualize the immune cells within live animals. We will attempt to improve the imaging technologies, which will allow us to track the dynamic behavior of immune cells and their communications more directly and to understand how immune cells respond to non-self components, such as pathogens and cancers, in vivo. Based on these basic studies, we will seek to develop new strategies for the diagnosis and treatment of various diseases, including infectious diseases, autoimmune diseases, allergies and cancers. To this end, we will invite 10-20 world-class principal investigators to the Osaka University Immunology Frontier Research Center as core scientists in the project and expand the program by forming links with domestic and overseas institutions that will function as satellites.

2. Background

Immunology is a medical science that investigates the mechanisms of the host defenses that protect the body against microbial infection (1). Although the immune system is essential for eliminating infectious pathogens from the host, malfunction of this system gives rise to various immunological disorders, such as autoimmune diseases, allograft rejection and allergic responses. Effective immune responses to pathogens and protective immunity against reinfection with the same pathogen are generated through a complex immune network exerted by various types of immune cells, including T lymphocytes, B lymphocytes, dendritic cells, macrophages and natural killer (NK) cells. These immune cells distinguish between self and non-self, and elicit integrated host defense responses as a system to efficiently eliminate invading pathogens. The fundamental characteristics of the mammalian immune system are the motility and migratory behavior of immune cells, which are originally derived from bone marrow cells. Immune cells leave the bone marrow and circulate in the blood. Subsequently, some of these cells enter lymphoid organs, such as the thymus and lymph nodes, and some re-enter the blood and move to tissues or organs throughout the body. The cell-cell interactions among different immune cells are also important for immune responses. In particular, cells of the innate and adaptive immune systems communicate extensively in the lymphoid organs, and the communication between the cells determines the overall immune responses in the body. The activities of these immune cells are also influenced by non-immune cells, including fibroblasts, epithelial cells and endothelial cells.

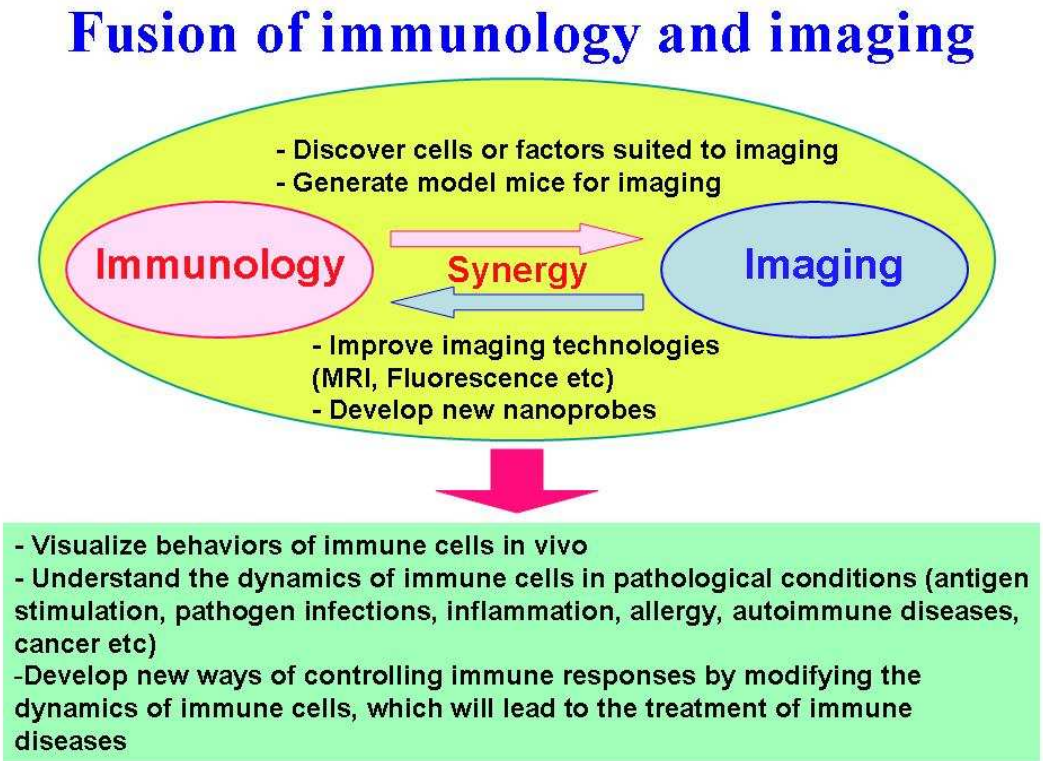
To date, research in the immunology field has either been carried out by isolating immune cells from the body and examining the cells in vitro or by using in

vitro cultured cell lines. Although such studies have provided many new insights into different immunology fields, we are still unable to draw the whole picture of immunological responses or predict the outcome of immune responses when a certain pathogen invades the body. Recently, in order to circumvent such drawbacks, we became aware of the necessity to study such immune responses in a spatiotemporal manner. Given the importance of the spatiotemporal organization of lymphoid organs in the establishment of immune reactions, as well as the importance of analyzing immune cell activation at the single cell level, immune cell and molecular imaging techniques are vital for future developments in immunology research.

The imaging techniques for visualizing the immune system are still in the early stages of development. To extend our understanding of the functions of the immune system in vivo, new technologies are needed to examine cells and molecules that are more deeply located in tissues, fainter and smaller, as well as to clarify the biochemical events that occur on a very rapid timescale. The ability to simultaneously monitor an increasing number of cell types and tissue structures is the key to developing a robust understanding of how tissue organization, extracellular factors and cell movements combine to support the development of useful immune responses. In order to overcome such imaging challenges, interdisciplinary efforts in physics, computer science and immunology are required. Despite such hurdles, the imaging techniques have rapidly been applied to the immunology field worldwide, particularly in the United States. In fact, a conference named “Imaging Immune Responses” was held during this year’s Keystone Symposia. Currently, immunology research in Japan is very strong. We have made great contributions to the progression of immunology research, which are highly appreciated worldwide. However, we have to admit that our imaging of the immune system is behind that of the United States. The next 10 years of development in the immunology field definitely relies on whether or not we can gain priority in imaging of the immune system in vivo. To sustain the international domination of immunology in Japan, I propose to establish a new Immunology Research Center in which immunologists can study the immune system by utilizing in vivo imaging techniques, and produce further innovations in bio-imaging for immunology research through interactions with researchers who are engaged in the development of imaging systems. By integrating the immunology and imaging fields, we will be able to understand the dynamic interactions of immune cells and their activation. This will allow us to manipulate the immune system, leading to the development of vaccines for infectious diseases based on novel strategies, concepts for immune therapies for various infectious diseases and cancers, and methods for treating autoimmune diseases.

3. Members and groups participating in the research center

Japanese immunologists have accomplished tremendous contributions to the development of modern immunology. In particular, Osaka University has won worldwide acclaim for its outstanding achievements. The late Yuichi Yamamura, the former President of Osaka University, initiated cancer immunotherapy using bacterial extracts in Japan, and became a founder of the Japanese Society for Immunology. Among the outstanding immunologists who have studied under Dr. Yamamura, Tadamitsu Kishimoto has become an internationally acclaimed specialist in cytokine research through his discovery of interleukin (IL)-6. Researchers disciplined under the supervision of Dr. Kishimoto have also made fine contributions to the field of immunology. For example, Toshio Hirano studied IL-6 biology and its signaling, Shizuo Akira revealed the mechanism of pathogen recognition by innate immunity (2) and Hitoshi Kikutani clarified the role of the semaphorin family in immune responses. Eminent immunologists of Osaka University will participate in the new center. The researchers will include Shizuo Akira (as Director), Tadamitsu Kishimoto, Toshio Hirano, Masayuki Miyasaka, Hitoshi Kikutani, Taroh Kinoshita, Atsushi Kumanogoh, Kiyoshi Takeda and Hisashi Arase. In addition, Shimon Sakaguchi (Kyoto University), Takashi Saito (RCAI) and Tomohiro Kurosaki (RCAI) will be invited to join the center.



All of these researchers have made great contributions to a variety of fields in immunology. In particular, Shimon Sakaguchi discovered regulatory T cells, which are now a hot topic in immunology, and his joining will enhance our status as a world-premier immunology center. Furthermore, Fritz Melchers will join the center as a principal investigator. He was a director of the Basel Institute for Immunology from 1980-2001, and President of the International Union of Immunological Societies from 1998-2001. He is now a senior research group leader at the Max Plank-Institute for Infection Biology (Berlin, Germany). I believe his joining will definitely strengthen the international prestige of the center.

Toshio Yanagida is renowned for single-molecule imaging in individual cells. Furthermore, he recently set up the High Performance Bioimaging Research Facility in Osaka University, which houses an 11.7 Tesla magnet Magnetic Resonance Imaging (MRI) system. Junji Seki and Yoshichika Yoshioka are specialists in imaging techniques, while Takeshi Jin and Yutaka Hata (University of Hyogo) are experts in developing molecular probes for imaging and computational image processing, respectively.

In an attempt to promote bioimaging techniques in our center, we plan to set up six satellites in foreign laboratories (all in the United States), which have made great advances in bioimaging. These researchers will include: Mark Davis (Stanford University), a specialist in single-cell imaging; Ronald Germain (NIH), Michael Dustin (New York University), Jason Cyster (UCSF) and Ulrich H. von Andrian (Harvard University), experts in intravital two-photon imaging; and Scott Fraser (California Institute of Technology), a specialist in MRI.

4. Planned activities of the center

4.1. Generation of immuno-imaging core facilities

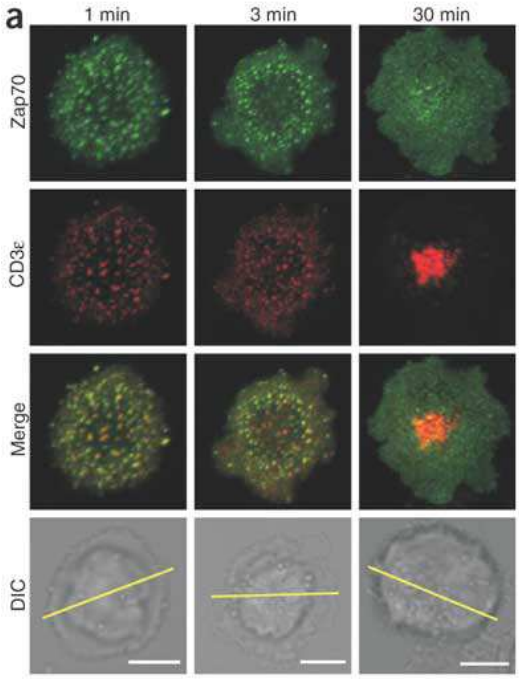
Immune responses against pathogens within the body proceed as follows: 1) pathogen recognition by innate and adaptive immune cells, and subsequent activation of these cells; 2) communication between immune cells and their maturation in lymphoid organs, such as the lymph nodes and spleen; and 3) systemic and local immune responses. For imaging of the immune reactions in each step, it is necessary to apply appropriate and different techniques. The imaging techniques now being utilized in the immunology field is composed of three parts.

First, single-molecule imaging is used for visualizing the activation of intracellular signaling cascades in a single cell. Second, confocal and multiphoton microscopy techniques combined with surgical methods have recently enabled dynamic imaging of immune cells in situ. Third, various techniques, including positron emission

tomography (PET), MRI, computer tomography (CT) and luminescence imaging, can possibly be applied to the visualization of immune reactions in vivo in a non-invasive manner, although these technologies still require improvement in terms of their spatial and temporal resolutions. I will establish immuno-imaging core facilities in the new research building and utilize the High Performance Bioimaging Research Facility in Osaka University housing the 11.7 Tesla magnet MRI system. In the immuno-imaging core facilities, we will attempt to develop novel techniques for the imaging of immune responses in a single cell, in situ intravitally and in vivo in a non-invasive manner. Furthermore, these techniques will be applied to research in the immunology field by tight collaboration between the imaging groups and immunology groups.

4.1.1. Single-molecule imaging

Single-molecule imaging is a technique for visualizing fluorescently-labeled single molecules by fluorescence microscopy, mostly in living cells. High-sensitivity video microscopy has allowed us to monitor the behavior of multiple fluorescent molecules in individual cells. Furthermore, this technique provides information about the structures of the molecules themselves, as well as the microstructures surrounding the molecules. Intra- and inter-molecular fluorescent resonance energy transfer (FRET) between single fluorescent molecules provides information on the molecular structure. Thus, this technique is useful for visualizing signal transduction in immune cells by monitoring the behavior of signal transduction molecules. Considering the importance of signaling cascade activation in the responses to microbial infection and cytokines, broad application of this technology is vital for the future development of immunology research.



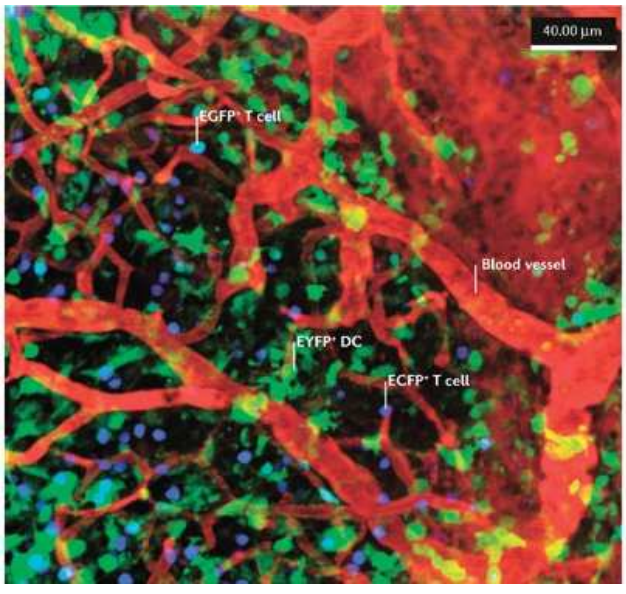
Visualization of microclusters formed by TCR complexes in T cells.
Yokosuka et al. Nat. Immunol. 6: 1253-1262, 2006

Dr. Yanagida is a pioneer in the development of single-molecule imaging, and has established various techniques. His group has succeeded in the direct detection of kinesin molecular motion, and also visualized epidermal growth factor (EGF)-EGF receptor complexes in living cells (3).

Dr. Saito has succeeded in the imaging of T cell receptor (TCR) microclusters and their behavior (4). In the proposed center, we will attempt to introduce these techniques in the immunology field. Dr. Saito will continue his research in the imaging of TCR signaling at RCAI, and maintain close contact with Dr. Yanagida's group in order to further improve the single-molecule imaging technology. For this purpose, we will have a satellite in the group of Mark Davis, an expert in this field, to introduce state-of-the art technology from his laboratory and exchange information regarding single-molecule imaging.

4.1.2 Imaging of cellular behavior and interactions in situ

Immune cells, including lymphocytes and dendritic cells, communicate with each other in response to infection with pathogens, and proper interactions of immune cells are critical for the establishment of immune responses against pathogens. Immune cells show a specific migratory behavior. After they leave the bone marrow, some cells enter secondary lymphoid tissues, such as the spleen and lymph nodes, or the thymus. The migration and trafficking of these cells are dynamically regulated. Furthermore, communication with T lymphocytes and stromal cells is critical for the proper differentiation and maturation of T cells in the thymus. Although previous studies have been performed using static methods, the importance of dynamic analyses of the immune system has been recognized.



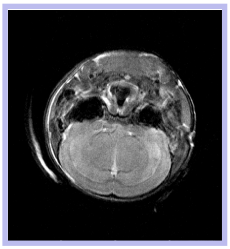
An example of two-photon microscopy imaging.
Germain et al. Nat. Rev. Immunol. 6: 497-507, 2006

Recent advances in the imaging of organs in situ, especially implemented in the United States, have enabled us to visualize cellular behavior and cell-cell interactions (5). The application of confocal and multiphoton fluorescence microscopy instruments has been combined with new surgical methods and techniques for fluorescent labeling of cells. In these imaging techniques, a cell type of interest is labeled using appropriate dyes or by expression of fluorescent proteins and then visualized using confocal and two-photon or multiphoton

microscopy. In small animals like mice, explant or intravital imaging is now possible in several immune organs, such as the lymph nodes, bone marrow and spleen.

However, these techniques have not been extensively applied in Japan, particularly in the field of immunology. We believe that this is due to the lack of opportunities to fuse the immunology and imaging fields in Japan. Therefore, in our center, I will create a research group that focuses on the imaging of immune cell dynamics. The group will consist of a group leader and two postdoctoral fellows. This group will work under the supervision of Dr. Saito, and intimately collaborate with the principal immunologists at the center. The group will be technically supported by Dr. Yanagida as well as the overseas satellites, including the groups of Ronald N. Germain, Michael Dustin, Jason Cyster and Ulrich von Andrian. A new facility equipped with multiphoton fluorescence microscopes and related apparatus for imaging will be established in the new research building. In this facility, several trained technicians will be hired to help with the imaging experiments carried out by immunologists.

4.1.3. Non-invasive monitoring of immune responses in vivo



The 11.7T MRI system at the High Performance Bioimaging Research Facility, Osaka University (left). Sample imaging of a mouse head using the 11.7T MRI (Brucker) (right).

Our ultimate goal is to develop techniques for non-invasive monitoring of the immune reactions to various stimuli in vivo. In order to understand dynamic immune responses, it is necessary to develop systems that effectively monitor how pathogens invade and spread in the body and how immune cells migrate and interact with each other in response to invading pathogens. To these ends, we need to improve the imaging techniques involving luciferase imaging, CT and MRI. Luciferase imaging is currently the best system for tracking the movement of cells in the body, although the image resolution needs to be increased. The new center will apply a luciferase real-time in vivo imaging system to monitoring the immune responses after pathogen infections in living mice. We will also use CT to monitor the inflammatory responses in mice. MRI is the most attractive technique for imaging of the immune system in the

whole body, although the spatiotemporal resolution needs to be greatly improved. This imaging technique is currently in its early stages, and is expected to make progress in the near future through the development of new nanoprobes that can detect immune cells and the generation of mice expressing a target protein for imaging (6). It is likely that MRI technology will become an indispensable tool for basic research as well as diagnosis. Dr. Yanagida will organize the imaging groups to make efforts toward improving the MRI techniques to allow monitoring of the dynamics of individual immune cells in live animals without invasion, through the use of the 11.7 T MRI available in Osaka University and collaboration with Scott Fraser, one of the world's leading experts in MRI.

4.1.4. Development of novel bioprobes

For successful immune cell imaging in vivo, excellent bioprobes need to be newly developed. Commonly used fluorescent dyes have limitations regarding their brightness and stability. Quantum dots are one of the recently developed fluorospheres that can potentially overcome these problems. Dr. Jin is an expert on quantum dots and will work on the development of new bioprobes for fluorescence. Furthermore, novel bioprobes for MRI detection urgently need to be developed.

4.1.5. Simulation and modeling

Data obtained by single-molecule imaging, multiphoton microscopy and MRI analysis should be integrated to generate a model based on the characteristic behavior of immune cells. However, given that dynamic 3D imaging data are so large, it is necessary to develop bioinformatic approaches for integrating such data. Dr. Hata is an expert in computing medical imaging data, such as MRI and CT. He will work with immunology groups to develop novel systems for modeling immune responses. This group will be technically supported by the group of Ronald N. Germain, an expert in the generation of models by applying systems biology approaches to the interpretation of imaging data. Once a dynamic model has been generated, it will be verified by the immunology groups with experimental approaches. Appropriate modeling will enable us to simulate the immune responses to specific pathogens in silico.

4.2. Application of imaging techniques to studies of immunology

The new techniques developed in the imaging core laboratory and new equipment introduced in the core facility will be applied by groups of immunology researchers. Details of the projects to be worked on by these immunology research

groups are described below.

4.2.1. Imaging of innate immune responses

The innate immune system directly recognizes infected pathogens, and plays an important role in the activation of adaptive immunity mediated by lymphocytes (2). Toll-like receptors (TLRs) and cytoplasmic receptors, such as NOD-like receptors and RIG-I-like receptors, are critical for the direct recognition of microbial components. These receptors trigger specific signal transduction cascades in response to their ligands (microbial components), leading to the production of proinflammatory cytokines and type I interferons. Dr. Akira's group will utilize single-molecule imaging techniques to visualize the behavior of the TLR molecules themselves, as well as TLR signaling molecules. This project will allow us to understand the dynamic molecular interactions of TLR signaling molecules. In addition, Dr. Akira will analyze the behavior of cytokine- and interferon-producing cells in response to pathogen infections in lymphoid organs and local infectious tissues using multiphoton microscopy. In addition, his group will maintain close contact with Dr. Yanagida's group to establish an MRI technique for imaging the time course of innate immune responses in vivo.

Dr. Takeda is a specialist in mucosal immunology, which maintains tolerance to nonpathogenic antigens. His group will pursue the imaging of immune cells at mucosal surfaces by generating reporter mice in order to monitor the regulatory functions of mucosal immune cells and analyze them intravitally using multiphoton microscopy.

Dr. Arase is an expert in the biology of NK cells and their specific receptors. His group will try to image the behavior of NK cells in response to viral infection using multiphoton microscopy.

Dr. Kinoshita clarified an essential role of GPI-anchor in host cell protection from autologous complement. To understand why GPI-anchored form of complement regulatory proteins is important for the self-protection, his group will investigate dynamic behaviors of complement proteins and GPI-anchored complement regulatory proteins on the cell surface using imaging approach.

Dr. Hirano has identified that zinc functions as a second messenger in the signaling pathway in dendritic cells. His group will attempt to visualize zinc behavior in response to immune activation using MRI techniques.

4.2.2. Imaging of acquired immune responses

The cells involved in acquired immunity, namely T and B lymphocytes, possess rearranged antigen receptors for recognizing invading pathogens. T and B cells with

proper antigen receptors are activated and undergo maturation for rapid responses that eliminate reinfection with the same pathogen.

Dr. Saito has been working on the imaging of T cell receptor (TCR) and its signaling molecules, and has revealed that the formation of TCR microclusters is a critical step for T cell activation. His group will further pursue the imaging of TCR signaling molecules using mouse genetics, and monitor T cell activation in situ by multiphoton microscopy. He will also attempt to generate MRI techniques for in T cell science.

Dr. Kurosaki is an expert in B cell signaling and immunology. His group will work on imaging of B cell receptor (BCR) signaling by single-molecule imaging. In addition, his group will analyze the B cell maturation process, known as the germinal center reaction, by multiphoton microscopy.

Appropriate activation of lymphocytes is mediated not only by antigen receptors, but also by signaling of co-stimulatory molecules. Drs. Kikutani and Kumanogoh have worked on CD40 and semaphorin family members in the activation of immune responses. Dr. Kumanogoh will investigate the roles of semaphorin family members in immune cell interactions using multiphoton microscopy, while Dr. Kikutani will analyze the effects of costimulatory molecules on lymphocyte trafficking in response to viral infection.

Dr. Sakaguchi is renowned for the discovery of regulatory T cells and the mechanism of immune suppression. Regulatory T cells play important roles in preventing aberrant activation of immune responses. His group will work on imaging the behavior of regulatory T cells as well as their interactions with other immune cells using multiphoton microscopy and MRI techniques.

4.2.3. Imaging of immune cell trafficking

Multiphoton microscopy techniques have traditionally been used to monitor the migration and trafficking of immune cells. However, the current techniques are not sufficient to clarify the reason why specific cell populations enter the secondary lymphoid organs through the endothelium. Dr. Miyasaka will develop a technique for monitoring the endothelial changes that occur in specific venules or lymphatics during leukocyte trafficking in real time. He will generate reporter mice to monitor the high endothelial venules and use these mice to visualize the endothelial transmigration of immune cells.

4.2.4. Development of new technologies for the assessment of autoimmune diseases

by imaging

Dr. Kishimoto discovered IL-6, an essential cytokine for inflammation, and has clarified its importance in immune responses against infection and the development of autoimmune diseases. He previously generated a monoclonal antibody that blocks the IL-6 receptor, and this is now used to treat human autoimmune diseases, such as rheumatoid arthritis and Newcastle disease. However, the molecular mechanism of the action of this antibody is still under investigation. Dr. Kishimoto will apply luciferase imaging and MRI techniques to elucidate the severity of experimental autoimmune diseases, and will also establish new methods for evaluating such diseases.

4.3. Establishment of domestic and overseas satellites

In an attempt to promote bioimaging techniques in our new center, we will have one domestic satellite and five satellites in foreign laboratories (all in the United States) that have made great advances in bioimaging.

First, we will have a satellite in RIKEN, RCAI (Yokohama). From this satellite, Takashi Saito and Tomohiro Kurosaki will participate in the establishment of the center as principal investigators. Dr. Kurosaki will move to Osaka University, while Dr. Saito will maintain groups in both the RCAI and Osaka University. I believe that this satellite is the key to the success of our research center, since many excellent researchers in the imaging field belong to RIKEN. For instance, Makio Tokunaga and Yasushi Seko are experts in single-molecule imaging, and Atsushi Miyawaki is famous for developing fluorescence molecules. Given that Dr. Saito is a core member for our research center for developing novel imaging techniques for immunology, I believe that he can collaborate with these researchers in RIKEN toward fusing these two fields.

The overseas satellite members will include Mark Davis (Stanford University), Ronald Germain (NIH), Michael Dustin (New York University), Jason Cyster (UCSF), Ulrich H. von Andrian (Harvard University) and Scott Fraser (California Institute of Technology). The researchers allotted to these satellites will work under the supervision of a chief investigator in each individual laboratory, and also exchange information on in vivo imaging with the members of our imaging groups to help improve our bioimaging techniques. The chief investigators and satellite researchers will regularly visit our center for discussions and seminars.

I will organize an international symposium on bioimaging of the immune system every year, at which the satellite leaders will present their updated findings. This international symposium will enhance the mutual interactions among our center, RCAI and foreign satellites, and definitely make our center’s mission visible worldwide.

5. Recruitment of foreign researchers and organization of the international symposium

I will organize an international symposium on bioimaging of the immune system every year, which will definitely make our center's mission visible worldwide.

I will set up two groups consisting of a foreign professor or associate professor and several researchers working under their direction. These two principal researchers will be selected by international public advertisements, and their research expenses will be provided for 5 years from this grant.

In the new building, I will secure space for visiting scholars who will perform short-term collaborative studies.

6. Summary

Finally, the main aims in this center are to promote the participation of principal immunologists in imaging research, and encourage them to regularly utilize such techniques in their own immunology research. I hope that new in vivo imaging techniques developed in the center will be utilized worldwide, and that our center will be recognized as one of the world-renowned immunology centers, particularly in bio-imaging. Studies performed in this center will lead to the generation of novel concepts for understanding the dynamics of immunology.

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Host Institution's Commitment

Date September 25, 2007

To MEXT

Name of host institution: Osaka University
Name and title of head of host institution: Kiyokazu Washida, President
Signature

I confirm that the measures listed below will be taken faithfully if "(project title)" is adopted under the World Premier International Research Center (WPI) 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.

Osaka University has from the start been committed to its mid-term strategic target as a university emphasizing research, aiming to produce unique and high quality results at the forefront of research. Notably, Osaka University is strongly focusing on "accomplishing high-level research results and playing a crucial role in the establishment of the World Premier International Research Center (WPI)". Osaka University will further encourage the study of Advanced Science and Technology fields to maintain its system of research practice.

The provisions of the mid-term strategic plan were set to accomplish the goals of the plan under the existing implemented systems. If the proposal with Osaka University is selected as one of the "WPI" projects, the University will give the top priority to develop "Osaka University Immunology Frontier Research Center" and subjoin in the mid-term strategic plan as effective measures to fulfill the research quality and research results. In addition, Osaka University will support the WPI for maintaining the research enforcement system. The WPI will be supplemented in the mid-term strategic plan.

Osaka University in its mid-term organization planning (2004-2009) described and published that one of the University's specific targets is the establishment of the Research/Education Center of Excellence in Microbiology and Immunology. The educational aspects of this planning is taking place through the 21st Century COE program entitled, "Combined program on Microbiology and Immunology" (2003-2007). This 21st Century COE program will be followed by a new proposal to the Global COE program. The research aspect of the planning consists of two parts. One focuses on infectious diseases. Osaka University established the "Osaka University International Research Center for Infectious Diseases" in 2005 including setting up the Research Collaboration Center on Emerging and Reemerging Infections in Thailand as a branch. The other part of the research aspects is to propose the "Osaka University Immunology Frontier Research Center" with its focus being Immunology as the "World Premier International WPI (WPI) Initiative". The two Centers will be functionally complimentary. If the proposal with Osaka University is selected as one of the WPI Initiative projects, formation of the WPI will be the top priority in the mid-term strategic target and plan, and Osaka University will give full support by implementing institutional reforms that are necessary for formation of the WPI and improving the research systems.

＜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.

Osaka University will assist the WPI to perform every possible support for operation and research activities of WPI. Osaka University will provide support to the WPI resources that would be either greater or equal to the WPI project grant.

The specific measures are as follows:

1) Indirect research expenses: 3.7 million dollars or 450 million yen.
2) Construction of main research building: 1.8 million dollars or 210 million yen.
3) Provision of other research space: 0.1 million dollars or 10 million yen.
4) Partial payment of principal investigators' salaries: 1.3 million dollars or 150 million yen.
5) University budget for principal investigators: 0.3 million dollars or 40 million yen.
6) Competitive research grants for principal investigators: 8.7 million dollars or 1.05 billion yen.
7) Facilitation of external donations: 0.8 million dollars or 100 million yen.
Total: 16.7 million dollars or 2.01 billion yen for each year.

(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 WPI will be recognized as a department within the university. Osaka University will provide the Center Director with the entitlement to manage and operate the WPI. The Center Director is entitled to make decisions regarding substantive personnel and budget allocation as are the Deans and Directors in other faculties in Osaka University.
An Administrative Director will support the Center Director and he will be responsible for office management so that the Director's decisions are kept to the bare essentials. Osaka University will support the Center Director's research environment.

(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 for the WPI, the Center 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:

- The WPI 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 WPI and there is no need to pay neither the security deposit nor key money.
- To hire exceptional researchers, their salaries can be changed from the existing system depending on his or her ability.
- High English ability administrative staff will be hired from both inside and outside the University. There will be on-the-job training after their employment.

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

University.

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

A new research building of ten floors with 9,600m² of space will be constructed by March 2009 for the Research Center. Osaka University will also provide laboratory space on the campus to accommodate research groups, which will join the Research Center before the new research building is completed. After many of the core research groups move into the new building, Osaka University will seek funds to renovate the old building these research groups are currently using.

To meet the space requirements for an animal facility for newly coming research groups, Osaka University will construct a new block of animal facilities and provide it for the Research Center's use.

(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.

In addition to the above, Osaka University will start a new "one stop service office" for international researchers and students in 2007. This all-in-one service aims to improve both the research and living conditions for visitors from abroad. Information including the research and daily life on campus and in the surrounding area has already been released on the web information service site "GCN-Osaka & Worldwide". This "one stop service office" does not only function as an information center, but also aims to reduce the burdens placed on international researchers and students related to immigration, by offering substantial support services such as visa application on their behalf. Osaka University has established three Overseas liaison offices for Education and Research in San Francisco (U.S.A), Groningen (The Netherlands) and Bangkok (Thailand). Their central task is to collect and transmit information, and scout highly talented researchers. All the faculties and overseas offices of Osaka University will assist the WPI so as to become the "World Premier International Research Center".

List of Principal Investigators

	Name	Current affiliation (organization, department) and specialties	Academic degree
①	Shizuo Akira*	Osaka University, Immunology Frontier Research Center, Laboratory o Host Defence, Research Institute for Microbial Diseases, Department of Host Defense (Immunology)	MD, PhD
②	Tadamitsu Kishimoto*	Osaka University, Graduate School of Frontier Biosciences, Laboratory of Immune Regulation, Immunology Frontier Research Center, Laboratory of Immune Regulation (Immunology	MD, PhD
③	Toshio Hirano*	Osaka University, Graduate School of Frontier Biosciences, Graduate Scho of Medicine, Laboratory of Developmental Immunology, RIKEN Research Center for Allergy and Immunology, Laboratory for Cytokine Signaling, Immunology Frontier Research Center, Laboratory of Developmen	MD, PhD
④	Masayuki Miyasaka*	Osaka University, Graduate School of Medicine, Laboratory o Immunodynamics, Immunology Frontier Research Center, Laboratory of Immunodynamics (Immunology)	MD, PhD
⑤	Hitoshi Kikutani*	Osaka University, Research Institute for Microbial Diseases Department of Molecular Immunology, Immunology Frontier Research Center, Laboratory of Molecular Immunology (Immunology	MD, PhD
⑥	Taroh Kinoshita*	Osaka University, Immunology Frontier Research Center, Laboratory o Immunoglycobiology, Research Institute for Microbial Diseases, Department of Immunoregulation (Immunology, Biochemistry	PhD
⑦	Atsushi Kumanogoh	Osaka University, Immunology Frontier Research Center, Laboratory o Immunopathology, Research Institute for Microbial Diseases, Department of Infectious Disease Pathology (Immunology	MD, PhD
⑧	Kiyoshi Takeda	Osaka University, Graduate School of Medicine, Laboratory of Immune Regulation, Immunology Frontier Research Center, Laboratory of Mucosal Immunology (Immunology	MD, PhD
⑨	Hisashi Arase	Osaka University, Immunology Frontier Research Center, Laboratory o Immunochemistry, Research Institute for Microbial Diseases, Department of Immunochemistry (Immunology)	MD, PhD
⑩	Shimon Sakaguchi*	Kyoto University, Institute for Frontier Medical Sciences, Department c Experimental Pathology, Immunology Frontier Research Center, Laboratory of Experimental Immunology (Immunology	MD, PhD
⑪	Takashi Saito*	RIKEN Research Center for Allergy and Immunology, Laboratory fo Cell Signaling, Immunology Frontier Research Center, Laboratory of Cell Signaling (Immunology	PhD
⑫	Tomohiro Kurosaki*	RIKEN Research Center for Allergy and Immunology,Laboratory fo Lymphocyte Differentiation, Immunology Frontier Research Center, Laboratory of Lymphocyte Diffentiation (Immunology and molecula	MD, PhD
⑬	Fritz Melchers*	Max Planck Institute for Infection Biology, Germany & University of Basel, Biozentrum, Dept. of Cell Biology, Switzerland (Immunology)	PhD
⑭	Toshio Yanagida*	Osaka University, Graduate School of Frontier Biosciences Laboratories for Nanobiology (Soft Biosystem Group), Immunology Frontier Research Center, Laboratory of Single Molecule Imaging	PhD
⑮	Junji Seki	National Cardiovascular Center Research Institute, Department o Biomedical Engineering (Biomechanics, Biorheology, Microcirculation), Immunology Frontier Research Center, Laboratory of Biomedica	DSc
⑯	Yoshichika Yoshioka	Advanced Medical Science Center of Iwate Medical University, Hig Field Magnetic Resonance Imaging Research Institute (Biophysics), Immunology Frontier Research Center, Laboratory of Biofunctiona	DSc
⑰	Takashi Jin	Hokkaido University, Research Institute for Electronic Science, Sectio of Intelligent Materials (Molecular Recognition Chemistry), Immunology Frontier Research Center, Laboratory of Nano-bio Materials (Imaging	DSc
⑱	Yutaka Hata*	Division of Computer Engineering, Department of Electrical Engineerin and Computer Sciences, Graduate School of Engineering, University of Hyogo (Computer Engineering), Immunology Frontier Research Center, Laboratory of Information System (Imaging)	PhD