FY 2008 WPI Project Progress Report
World Premier International Research Center (WPI) Initiative

Host Institution	Osaka University	Host Institution Head	Kiyokazu Washida
Research Center	Osaka University Immunology Frontier Research Center	Center Director	Shizuo Akira

Summary of center project progress

The scientific aim of this project is to create new concepts and strategies that will result in revolutionary methods for various immunology disciplines, with the ultimate goal of developing effective vaccines and advanced immune therapies for various infectious diseases and novel treatment for cancers and autoimmune diseases. To achieve this, we seek to combine immunology with imaging techniques in order to reveal the dynamic interactions of immune cells and their activation *in vivo*. For and through these activities, IFReC, with generous support from the host institution Osaka University, aspires to become an internationally visible and influential research center that attracts the best researchers from all over the world.

What follows is a summary of our progress for the fiscal year 2008.

1. Establishment of a new research group and invitation of Principal investigators:

We invited a new PI, Dr. Daron M. Standley, last October. He is an expert in bioinformatics by using the information from gene and chemistry studies and will be responsible for simulating protein structures, to clarify the body's immune response when viewed as a complex bio-system that will lead to establish a new bioinformatics group. Further recruitment of other foreign PIs by both the immunology and imaging groups is ongoing and is expected to intensify upon completion of the new research building.

2. Promotion of public recruitment and foreign Postdocs' employment:

Through public advertisements like those posted on Nature and our center's website, etc, we have employed 4 Postdocs from nearly 40 applicants. In order to employ excellent young researchers, we will continue to aggressively publicize our research positions.

3. Improving the research support system

We recruited a staff member holding a PhD in Research Management Section to manage symposia, seminars and PR and to coordinate meetings between research groups and have outsourced our PR to a designer with experience publishing science journals in English.
We also recruited a new professor (to be the administrative director from April 2009) with a long career in scientific research to be responsible for management and coordination. He is expected to facilitate the fusion between the immunology and imaging groups and act as a liaison with university authorities.

4. Partnerships with overseas institutions:

We have completed cooperative contracts with 6 oversea institutions where IFReC employed a Postdoc at each for the purpose of establishing and maintaining strong international scientific collaborations and extend IFReC's visibility. We also recently concluded an Academic Cooperation Agreement with the Institute for Systems Biology, Seattle, USA.

5. Encouragement of collaboration between immunology and imaging groups:

Joint seminars were held every 2-3 months for the purpose of deepening mutual understanding between the immunology and imaging groups. In addition, individual laboratories arranged meetings with other member laboratories to facilitate collaborations. A number of these collaborations have already resulted in paper submissions to peer-reviewed scientific journals.

6. Acceleration of research exchanges in international symposia:

The Second International Symposium of IFReC was held 12-13 February, 2009 at Icho-Kaikan, Osaka University. In this symposium, foreign and Japanese young researchers working actively on the forefront of immunology were invited to give talks about their most recent results.
Moreover, we will host a symposium in May of this year, inviting world-famous scientists in immunology including PIs from our cooperative oversea institutions which is followed by co-hosting symposium with the Singapore Immunology Network in June in Singapore. These symposia will promote further research exchanges with domestic and international institutions.

7. Arrangement of research space:

Due to unexpected obstacles at the construction site, the anticipated completion of the Integrated Life Science Building in March of 2009 has been delayed to the end of June this year. Meanwhile, construction of the new animal experimentation facility (Animal Resource Center for Infectious Diseases C) will be completed by the end of July 2009.

8. Imaging group's new development research plan:

The imaging group has been undertaking collaborative projects with other IFReC groups, aiming to apply new and advanced imaging techniques to both humans and small animals. One major goal is to translate techniques currently only feasible in small animals to human subjects. An example is the detection of functional probes, which has already been established in tissues and small animals by a non-invasive imaging method.
It is also expected that combining brain activity studies with immunological imaging techniques will reveal relationships between human psychology and immune reactions.

1. Summary of center project

<Initial plan>

General plan of the project

The aim of this project 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.

<Results/progress/alternations from initial plan>

IFReC operated following matters to realize our plan.

We hired Dr. Daron M. Standley as a new PI last October. He is an expert in Bioinformatics and will be responsible for simulating protein structures based on data from gene and chemistry studies to clarify immune responses. He is also responsible for establishing the bioinformatics group at IFReC for the purpose of integrating the immunology and imaging groups.

As most immune reactions depend on protein-protein interactions, his expertise in this field will greatly contribute to immunology research.

The collaboration between Dr. Standley and Director Akira's laboratory already resulted in the acceptance of their recent article (See 7. Criteria and methods used to evaluate center's global standing).

In addition to Dr. Standley, we are currently recruiting other foreign PIs to add to both our immunology and imaging groups.

Furthermore, besides the cooperative contracts with 6 oversea institutions, we have made an Academic Cooperation Agreement with the Institute for Systems Biology, Seattle, USA to develop imaging data analysis tools and immune response simulations.

2. Research fields

<Initial plan>

Name of the research field of the project

Immunology and Bioengineering

Relevant fields

Biosciences, Precision and mechanical engineering

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

<Results/progress/alternations from initial plan>

There are no alterations from the initial plan.

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. Similar fields already exist in Japan or overseas Basel Institute for Immunology, Basel, Switzerland (1971-2001)	

3. Research objectives

<Initial plan>	<Results/progress/alternations from initial plan>
Research objectives that the project seeks to achieve by the end of the grant period (in 10 years) 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.	-Research objectives There are no alterations from the initial plan.
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	-Research plan to achieve the objectives, and any related achievements We regularly hold joint seminars every 2-3 months to encourage collaborations between the immunology and imaging groups (approx.100 attendees). Further, individual laboratories arrange less formal meetings with other laboratories for the same purpose. For example, Assistant Professor Saito (Director Akira's lab) and Yanagida's team began a collaborative project to detect nucleic acid ligands in a single cell by observing injected fluorescence-labeled nucleic aid. Integrating the specialties from different laboratories is a major part of IFReC's future success. As stated above, the third research group at IFReC is the Bioinformatics group led by Dr. Daron M. Standley.

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.	

4. Management

<Initial plan>	<Results/progress/alternations from initial plan>
1) Composition of administrative staff 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.	1) Composition of administrative staff We have hired staff holding a PhD in Research Management Section last June to be responsible for organizing symposia, seminars, PR and to coordinate meetings between research groups. In addition, We also recruited a new professor (to be the administrative director from April 2009) in order to facilitate fusion between the immunology and imaging groups and to act as a liaison with the University authorities. He is an internationally known figure in muscle energetics research and has ample experience in research management and coordination through his time as Dean of the Faculty of Computer Science and Systems Engineering, Kyushu Institute of Technology and as the Technical Advisor of Core Research for Evolutional Science and Technology (CREST). The administrative department offers bilingual assistance for the following matters: - Immigration matters for foreign researchers - Providing bilingual notices and announcements - Helping grant applications (ex. Successful application by Assistant Professor Coban to the Bill and Melinda Gates Foundation) For IFReC's PR, we frequently update and post our latest research achievements on our website in a manner easily understood by the public. We have also contracted a designer with experience in science publishing in English to prepare the IFReC brochure.
2) Decision-making system Center management committee consisting of center director (Chairman),	2) Decision-making system Major decisions will be made by the director upon considering the opinions of

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 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. 3) Allocation of authority between center director and host institution 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 center director, determine the salary of center director and make evaluation of the center's performance.	the WPI Initiative Program Committee and the Working Group, etc. Matters will be discussed with the Center Management Committee and the Board of Representatives as needed. In this fiscal year, the role of the International Advisory Board is limited to peer reviews. The first comprehensive examination of IFReC by the board is planned for the next fiscal year. 3) Allocation of authority between center director and host institution It is operating in accordance with the initial framework.

5. Researchers and center staffs

i) “Core” to be established within host institution

Principal investigators

	At beginning	Planned for end of FY 2007	Final goal (around Apr. 2010)	Results at end of FY 2007	Results at end of FY 2008
Researchers from within host institution	10	10	10	10	11
Foreign researchers invited from abroad	1	2	5	1	1
Researchers invited from other Japanese institutions	6	6	7	7	8
Total principal investigators	17	18	22	18	20

All members

	At beginning	Planned for end of FY 2007	Final goal (around Apr. 2010)	Results at end of FY 2007	Results at end of FY 2008
Researchers <Number of foreign researchers among them and their percentage> [Number of female researchers among them and their percentage]	49 < 12, 24%>	82 < 25, 30%>	147 < 47, 32%>	52 < 8, 15%> [7, 13%]	89 < 24, 27%> [18, 20%]
Principal investigators <Number of foreign researchers among them and their percentage> [Number of female researchers among them and their percentage]	17 < 1, 6%>	18 < 2, 11%>	22 < 5, 23%>	18 < 1, 6%> [0, 0%]	20 < 2, 10%> [0, 0%]
Other researchers <Number of foreign researchers among them and their percentage> [Number of female researchers among them and their percentage]	32 < 11, 34%>	64 < 23, 36%>	125 < 42, 34%>	34 < 7, 21%> [7, 21%]	69 < 22, 32%> [18, 26%]
Research support staffs	28	34	44	3	23
Administrative staffs	9	15	15	13	15
Total	86	131	206	68	127

ii) Satellites **<Initial plan>** Institution (1) RIKEN Research Center for Allergy and Immunology **-Role** RIKEN Research Center for Allergy and Immunology contributes to improve imaging technique of the center. **-Personnel composition and structure** Takashi Saito, Cell Signaling research group Tomohiro Kurosaki, Lymphocyte Differentiation research group **-Collaborative framework** Researchers in the center and RIKEN Research Center for Allergy and Immunology visit each other and exchange information on a regular basis in order to improve the level of imaging technique. We offer employment expenses to hire several Postdocs to above institution.	<Results/progress/alternations from initial plan> Institution (1) RIKEN Research Center for Allergy and Immunology -Role joint research on imaging acquired immune responses. -Personnel composition and structure Prof. Takashi Saito and 1 other staff (Cell Signaling research group) Prof. Tomohiro Kurosaki and 3 other staffs (Lymphocyte Differentiation research group) -Collaborative framework We have placed PIs and IFReC staff at RIKEN for joint research. Prof. Saito' s laboratory: Research on imaging single cells with special focus on T cells and T cell receptors (TCR) Prof. Kurosaki's laboratory: Research on signal transduction inside B cells and its visualization Institution (2) Kyoto University, Institute for Frontier Medical Sciences -Role joint research on imaging acquired immune responses. -Personnel composition and structure Prof. Shimon Sakaguchi and 8 other staffs -Collaborative framework We placed a PI and IFReC staff at Kyoto for joint research.
iii) Partner institutions **<Initial plan>** Institution (1) National Institutes of Health Institution (2) New York University Institution (3) California Institute of Technology Institution (4) Harvard Medical School Institution (5) Stanford University School of Medicine Institution (6) University of California San Francisco **-Role** Partner institutions contribute to improve imaging technique of the center. **-Personnel composition and structure** Ronald Germain, Deputy Chief, Laboratory of Immunology and Chief, Lymphocyte Biology Section, NIAID Michael Dustin, Professor, Skirball Institute of Biomolecular Medicine Scott Fraser, Director, Biological Imaging Center, Beckman Institute Ulrich H. von Andrian, Professor, Department of Pathology Mark Davis, Professor, Department of Microbiology and Immunology Jason Cyster, Professor, Department of Microbiology and Immunology	<Results/progress/alternations from initial plan> We concluded an Academic Cooperation Agreement with the Institute for Systems Biology, Seattle, USA, along with contracts with 6 other overseas institutions. Institution (1) National Institutes of Health -Role joint research on imaging data analysis and modeling immune responses. -Personnel composition and structure Ronald N. Germain, Deputy Chief, Laboratory of Immunology and Chief, Lymphocyte Biology Section, National Institute of Allergy and Infectious Diseases (NIAID) -Collaborative framework Based on a cooperative contract, the institute employed Dr. Hai Qi as a Postdoc in January 2009 financed by IFReC. He attended the 2nd IFReC international symposium (see 6. Summary of Center's research environment) to give a talk. As part of the symposium, he visited IFReC

-Collaborative framework

Researchers in the center and above institutions visit each other and exchange information on a regular basis in order to improve the level of imaging technique. We offer employment expenses to hire several Postdocs to above institutions.

laboratories and participated in seminars. Dr. Qi is a specialist of lymphnode trafficking and immune imaging and is expected to lead collaborations in Immunodynamics with Dr. Miyasaka and in Biofunctional Imaging with Dr. Yoshioka.

We also recruited Dr. Masaru Ishii, who has done outstanding work in bioimaging at NIAID, as an IFReC Associate Professor in last December.

Institution (2) New York University

-Role

joint research on imaging intercellular interactions.

-Personnel composition and structure

Michael Dustin, Professor of the Skirball Institute of Biomolecular Medicine

-Collaborative framework

Based on a cooperative contract, the university employed Dr. Jan Liese as a Postdoc in April 2008 financed by IFReC. He attended the 2nd IFReC international symposium (see 6. Summary of Center's research environment). As part of the symposium, he visited Dr.Akira's laboratory and participated in their seminar.

Dr. Liese is a specialist of TLR, NK, Dendritic cells and is expected to lead collaborative work in Host Defense with Dr. Akira and in Immunochemistry with Dr. Arase.

Institution (3) California Institute of Technology

-Role

joint research on imaging the immune cell.

-Personnel composition and structure

Scott Fraser, Director of Biological Imaging Center, Beckman Institute

-Collaborative framework

Based on a cooperative contract, the institute employed Dr. Luca Caneparo, who specializes in Gastrulation, Retro viral infection, as a Postdoc in April 2008 financed by IFReC. He attended the 2nd IFReC international symposium (see 6. Summary of Center's research environment) and visited several laboratories.

Institution (4) Harvard Medical School

-Role

joint research on imaging the immune cell.

-Personnel composition and structure

Ulrich H. von Andrian, Professor of Immunopathology

-Collaborative framework

Based on a cooperative contract, the school employed Dr. Sarah E. Henrickson as a Postdoc in August 2008 financed by IFReC. She attended

	the 2nd IFReC international symposium (see below) to give a talk. As part of the symposium, she visited IFReC laboratories and participated in seminars. Dr. Henrickson is a specialist of *In vivo* imaging, T-cell priming and Dendritic cells and is expected to lead collaborations in Mucosal Immunology with Dr. Takeda and in Gastrointestinal Immunology with Dr. Jang. Institution (5) Stanford University School of Medicine -Role joint research on single molecular imaging. -Personnel composition and structure Mark Davis, Professor, Department of Microbiology and Immunology -Collaborative framework Based on a cooperative contract, the university employed Dr. Johannes Huppa as a Postdoc in July 2008 financed by IFReC. He attended the 2nd IFReC international symposium (see 6. Summary of Center's research environment) to give a talk. As part of the symposium, he visited IFReC laboratories and participated in seminars. Dr. Huppa is a specialist of T Cell Receptors, Immunological synapses and Bioinformatics and is expected to lead collaborations in Systems Immunology with Dr. Standley and in Cell Signaling with Dr. Saito and other imaging groups. Institution (6) University of California San Francisco -Role joint research on imaging technique of intercellular interactions. -Personnel composition and structure Jason Cyster, Professor of Microbiology and Immunology -Collaborative framework Based on a cooperative contract, the university employed Dr.Tri Giang Phan as a Postdoc in June 2008 financed by IFReC. However, he has had to leave the post for personal reasons. The university is currently seeking his replacement. Institution (7) Institute for Systems Biology -Role joint research on imaging data analysis and modeling of immune responses. -Personnel composition and structure Alan Aderem, Director of Institute for Systems Biology -Collaborative framework We concluded an Academic Cooperation Agreement with the institute to conduct joint research on imaging data analysis and modeling of immune

	responses.

6. Summary of center's research environment

<Initial plan>	<Results/progress/alternations from initial plan>
1) Environment in which researchers can devote themselves to their research 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 a 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.	1) Environment in which researchers can devote themselves to their research We hired staff holding a PhD in Research Management Section (Project Management) to manage symposia, seminars, PR and coordinate meetings between research groups. In addition, we recruited a new professor (to be the administrative director from April 2009) with ample research management and coordination experience (See 4. Management for details). As a result of these appointments, the Director, Vice Directors and staff in their laboratories have devoted far less time to bureaucratic work unrelated to their research.
2) Startup research funding 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.	2) Startup research funding IFReC provided start-up budget from WPI's direct budget to Prof. Tomohiro Kurosaki, who was invited from RCAI, RIKEN and Prof. Shimon Sakaguchi, who was invited from Kyoto University and Associate Prof. Masaru Ishii, who was invited from NIH. They were allocated start-up budget to purchase necessary equipment for the laboratories and they will receive space in the new research building. We will allocate start-up budget to Associate Prof. Daron M. Standley, when he moves in the new research building.
3) 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.	3) Postdoctoral positions through international solicitations Through public advertisements posted on Nature, the IFReC website, and such, we received nearly 40 applications. Ultimately we hired 4 Postdocs out of them. We will continuously employ excellent young researchers and aggressively recruit foreign PIs.
4) 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	4) Administrative personnel who can facilitate the use of English in the work process We prepared a guide book to inform foreign researchers about daily life in Japan and Osaka, information about schools for children, and about the procedures at IFReC. We provide bilingual assistance for various administrative matters and bilingual notices and announcements.

members with PhD degree, and accounting section and general affairs section each consisting of a senior supervisor with rich administrative experiences in the University, several bilingual or English-speaking full-time and part-time personnel.	
5) Rigorous system for evaluating research and system of merit-based compensation The center director will organize the International Advisory/Review Board consisting of several renowned immunologists. The International Advisory/Review Board will conduct evaluation of research groups' performance every or every other year. The center director will determine principal investigators' salaries based on the evaluation by the International Advisory/Review Board.	5) Rigorous system for evaluating research and system of merit-based compensation In this fiscal year, the role of the International Advisory Board is limited to peer reviews. The first comprehensive examination by the board is planned for the next fiscal year.
6) Equipment and facilities, including laboratory space, appropriate to a top world-level research center The main research building (nine floors and 9,400 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.	6) Equipment and facilities, including laboratory space i) Facility The budget for the Integrated Life Science Building (10 story-building, 9,258.03 sq.m), scheduled to finish in the end of June 2009, was originally 2.5 billion yen. However, Osaka University has subsidized an additional 46 million yen to make up for the extra costs caused from the layout change of the building. Osaka University also supported approximately 0.4 billion yen for moving costs to the new building. The university has also made a budget request for facility subsidies to repair old building, which will be required after moving to the new building. Further, the 1.05 billion yen cost of the Animal Resource Center for Infectious Diseases C (4-story building, 2,481.75 sq.m), for which construction started in November 2008 and has an expected completion date of the end of July 2009, has received a 450 million yen subsidy from the university to purchase equipment, such as animal breeding cages. ii) Equipment We purchased fundamental equipment for IFReC a Cell sorter, Multi-photon laser-scanning microscope, and machinery used to customize. The equipment will be installed by the end of the 2008 fiscal year.
7) International research conferences or symposiums held regularly to bring world's leading researchers together 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	7) International research conferences or symposiums held regularly to bring world's leading researchers together The Second International Symposium of IFReC was held on 12-13 February, 2009. There were sessions for discussion between guest speakers and staff from each IFReC laboratory. Posdocs from the cooperative overseas

Institute for Microbial Diseases, Osaka University. 8) Other measures, if any Based on advices and/or suggestions by the International Advisory/Review Board, the center director will set up research environment suitable for international researchers.	institutes also participated. Moreover, we will also co-host a symposium with the Singapore Immunology Network in June 2009 in Singapore. 8) Other measures, if any i) Helping foreign staff find international schools for their childrens' education. ii) We established a system to provide travel costs and research expenses with senior foreign researchers and young researchers invited to IFReC in a short or long term.

7. Criteria and methods used to evaluate center's global standing

<Initial plan> **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	<Current assessment> List of research accomplishments and publications by IFReC staff. (1)Prof. Sakaguchi won The 2008 Keio Medical Science Prize. (2)Prof. Kishimoto and Prof. Hirano won The Crafoord Prize 2009. (3)The following are articles published in major academic journals including 3 major scientific journals from April 2008 to present. Director Akira and other staffs - Nat. Immunol. 9: 684-91, 2008 - Nature 456: 264-8, 2008 - Nat. Immunol. 9: 769-76, 2008 - Nature 451: 725-9, 2008 - J Exp Med. 2008 14:86-92 Prof. Kinoshita and other staffs - Nature Cell Biology, 10:1135-1145, 2008. Prof. Arase and other staffs - Cell 132:935-944. Prof.Hirano and other staffs - Immunity, 29, 628-636, 2008. Prof. Takeda and other staffs - Nature 455: 808-812, 2008. Prof. Sakaguchi and other staffs - Science 322: 271-275, 2008. - Cell. 133: 775-787, 2008. Prof. Saito and other staffs - Nature Immunology 9, 1179- 188, 2008 - Immunity 29: 589-601, 2008. Prof. Kurosaki and other staffs

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.	- Nat. Immunol. 9, 81-88 (2008). - Immunity 29:33-43 (2008). Associate Prof. Ishii and other staffs - Nature, Feb.8, 2009 (Epub). Associate Prof. Standley and other staffs - Nature, in press

8. Securing competitive research funding

<Initial plan>	<Results/progress/alternations from initial plan>
i) Past record 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** 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.	Actual performance in FY2008 (estimated amount) 1) Contract research expenses: 619,875,512 yen 2) Joint research expenses：32,156,259 yen 3) Donations for research：103,217,400 yen 4) Management expenses grant：62,911,753 yen 5) Grants-in-aid for scientific research：369,156,000 yen 6) Health and Labor Sciences Research Grants：51,102,000 yen 7) WPI indirect costs：349,339,800 yen 8) Other indirect costs：4,108,000 yen Total :1,591,866,724 yen Notes: 1) All WPI indirect costs from this project will be used for the center. 2) Construction of the Integrated Life Science Building (10 story-building, 9,258.03 sq.m), scheduled to finish in the end of June 2009, is currently

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. Notes: 1) Most of the Indirect cost from this project will be used for the Research Center. 2) The main research building (9,400 square m) will be constructed by March 2009 with University budget and external donation in total of 20.8 million dollars or 2.5 billion yen, and 80% of its space will be used for the Research Center for 9.5 years. (Annual contribution will be 20.8 million dollars or 2.5 billion yen x 0.8 / 9.5 = 1.8 million dollars or 210 million yen).	budgeted at 2,546 million yen. 3) The Animal Resource Center for Infectious Diseases C (4-story building, 2,481.75 sq.m), scheduled to complete in the end of July 2009, is currently budgeted for 1,050 million yen.

9. Other important measures taken to create a world premier international research center

<Initial plan>	<Results/progress/alternations from initial plan>
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** 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. **Other important measures to be taken in creating a world premier international research center** **Global COE Program:** 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	For further development of IFReC and maintenance of research center after the termination of WPI program, we are examining the possibility of further systematic reforms. For instance, the following are being considered. - Establishing a salary system for IFReC's exclusive use - Giving titles to IFReC staff - Not setting any limitations on the terms of employment, in the case they are transferred after termination of WPI program - Making it possible to offer tenure positions in order to employ excellent researchers

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.	

10. Host institution's commitment

<Initial plan>	<Results/progress/alternations from initial plan>
-Provision in host institution's mid-to-long-term plan 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" programs, 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	-Provision in host institution's mid-to-long-term plan Osaka University has declared that it "offers its utmost support to enhance a research environment to enable IFReC to attain outstanding achievements".

the WPI Initiative programs, 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 (1) Competitive grants obtained by researchers participating in the project and in-kind contributions, etc.	-Concrete Measures (1) Competitive grants obtained by researchers participating in the project and in-kind contributions, etc.
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. Notes: 1) Most of the Indirect research expenses from this program will be used for the WPI. 2)The main research building (9,400 m2 of space) will be constructed by March 2009 with University budget and external donation in total of 20.8 million dollars or 2.5 billion yen, and 80% of its space will be used for the WPI for 9.5 years. (Annual contribution will be 20.8 million dollars or 2.5 billion yen x 0.8 / 9.5 = 1.8 million dollars or 210 million yen.	The amount of financial resources that the host institution ensured for FY2008 1) Personnel expenses for faculty staff who have concurrent positions at the university : 234,921,558 yen 2) Construction expenses for tentative buildings (new research building, animal resource center) : 708,644,695 yen 3) Equipment purchase expenses: 13,346,970 yen 4) Management expenses grant : 62,911,753 yen 5) Contract research expenses and joint research expenses : 652,031,771 yen 6) Donations for research : 103,217,400 yen 7) Grants-in-aid for scientific research : 369,156,000 yen 8) Health and Labor Sciences Research Grants : 51,102,000 yen 9) WPI indirect costs : 349,339,800 yen 10) Other indirect costs : 4,108,000 yen Total : 2,548,779,947 yen Notes: 1) All WPI indirect costs from this project will be used for the center. 2) Total 2,546 million yen for the construction of the Integrated Life Science Building (10 story-building, 9,258.03 sq.m), scheduled to finish in the end of June 2009. 3) Total 1,050 million yen for the construction of the Animal Resource Center for Infectious Diseases C (4-story building, 2,481.75 sq.m), scheduled to be completed the end of July 2009.
(2) System under which the center's director is able to make substantive personnel and budget allocation decisions	(2) System under which the center's director is able to make substantive personnel and budget allocation decisions
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	Osaka University allows the center director to determine employment and annual salaries of staffs. Moreover, this also applies to budget use, start-up budget size, etc.

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) Support for the center director in coordinating with other departments at host institution when recruiting researchers, while giving reasonable regard to the educational and research activities of those departments	(3) Support for the center director in coordinating with other departments at host institution when recruiting researchers, while giving reasonable regard to the educational and research activities of those departments
When 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.	It is operating according to the initial framework.
(4) Revamping host institution's internal systems to allow introducing of new management methods (e.g., English-language environment, merit-based pay, top-down decision making) unfettered by conventional modes of operation	(4) Revamping host institution's internal systems to allow 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.	As mentioned in " 9. Other important measures taken to create a world premier international research center ", we are examining the possibility of further systematic reforms for IFReC after the termination of the WPI program. For instance, the following are being considered. - Establishing a salary system for IFReC's exclusive use -Giving titles to IFReC staff -Not setting any limitations on the terms of employment, in the case they are transferred after termination of WPI program -Making it possible to offer tenure positions in order to employ excellent researchers

The aforementioned items will undergo examination as necessary by related departments of Osaka University.	
(5) Accommodation of center's requirements for infrastructural support (facilities, e.g., laboratory space; equipment; land, etc.)	(5) Accommodation of center's requirements for infrastructural support (facilities, e.g., laboratory space; equipment; land, etc.)
A new research building of nine floors with 9,400m² 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.	1) Due to unexpected obstacles in the ground, completion of the new research building will be delayed to the end of June 2009. It was originally planned to finish March 2009. 2) Making use of the university lending system, we ensured 1,050 million yen for the construction of the Animal Resource Center for Infectious Diseases C (4-story building, 2,481.75 sq.m), scheduled to be completed in the end of July 2009. 3) Osaka University will replace an old university residence on the Suita campus with lodging for foreign researchers and their families for short and long term stays. This is hoped to be available from April 2010. 4) The immunology group can access to the Research Institute of Microbial Diseases as well as facilities and equipment at Graduate School of Medicine, Osaka University. 5) The imaging group can access to use facilities and equipment at the Graduate School of Frontier Biosciences, Osaka University.
(6) Support for other types of assistance	(6) Support for other types of assistance
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".	The "one stop service office" (Support Office for International Students and Scholars) established in October 2007, officially started its operation in the 2008 fiscal year. This office helps foreign researchers on immigration issues like applying for the Certificate of Eligibility for Status of Residence (CESR) required to obtain a visa and accommodation assistance by managing the Residence Reservation System (RRS). There were approx.130 users for CESR and approx.500 users for RRS since the support office began its operations.

11. FY 2008 funding

(Exchange Rate: JPY/USD=120)

Cost Items	Details	Costs (ten thousand dollars)
Personnel	Center director and Administrative director	26
	Principal investigators (no. of persons): 14	111
	Other researchers (no. of persons): 67	278
	Research support staffs (no. of persons): 19	72
	Administrative staffs (no. of persons): 14	75
	Total	562
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons): 0	0
	Cost of dispatching scientists (no. of persons): 4	3
	Research startup cost (no. of persons): 6	35
	Cost of satellite organizations (no. of satellite organizations): 6	27
	Cost of international symposiums (no. of symposiums): 1	13
	Rental fees for facilities	0
	Cost of consumables	2
	Cost of utilities	2
	Other costs	88
	Total	170
Travel	Domestic travel costs	1
	Overseas travel costs	1
	Travel and accommodations cost for invited scientists (no. of domestic scientists): 0 (no. of overseas scientists): 0	0
	Travel cost for scientists on secondment (no. of domestic scientists): 5 (no. of overseas scientists): 2	1
	Total	3
Equipment	Depreciation of buildings	27
	Depreciation of equipment	227
	Total	254
Other research projects	Projects supported by other government subsidies, etc.	52
	Comissioned research projects, etc.	628
	Grants-in-Aid for Scientific Research, etc.	350
	Total	1030
Total		2019

Ten thousand dollars (Exchange Rate: JPY/USD=120)

WPI grant for FY 2008 1262

Costs of establishing and maintaining facilities in FY 2008 521

Establishing new facilities
(Number of facilities: 2 , 11,740 m²) Costs paid: 521

Others 0

Cost of equipment procured in FY 2008 474

Name of equipment: Cell sorting system
Number of units: 1 Costs paid: 46

Name of equipment: Multi-photon laser-scanning microscopy
Number of units: 2 Costs paid: 168

Name of equipment: Development of machines for imaging in vivo
Number of units: 1 Costs paid: 27

Name of equipment: Extension of MRI channel
Number of units: 1 Costs paid: 11

Name of equipment: Highly secured isolated containment type animal casing unit
Number of units: 1 Costs paid: 27

Name of equipment: Individually ventilated caging system for experimental animals
Number of units: 1 Costs paid: 49

Name of equipment: P2A/BSL2 animal breeding and experimentation system
Number of units: 1 Costs paid: 16

Others 130

12. Efforts to improve points indicated as requiring improvement in follow-up review and results of such efforts	
-Points specified as needing improvement	-Efforts to improve and results
(1) The final goal/outcome of IFReC should be more clearly stated in order to strengthen its appeal to young scientists, researchers from other disciplines, and tax payers. Scientifically, it seems unclear what enigmas in immunology IFReC will try to solve.	(1) The scientific aim of this project is to create new concepts and strategies that will result in revolutionary methods for various immunology disciplines, with the ultimate goal of developing effective vaccines and advanced immune therapies for various infectious diseases and novel treatment for cancers and autoimmune diseases. To achieve this, we seek to combine immunology with imaging techniques in order to reveal the dynamic interactions of immune cells and their activation *in vivo*. For and through these activities, IFReC, with generous support from the host institution Osaka University, aspires to become an internationally visible and influential research center that attracts the best researchers from all over the world.
(2) Though it may be early to say at this stage, IFReC seems not to be succeeding in assembling a heterogeneous group of scientists from around the world and from multiple disciplines. IFReC should make a serious effort to meet the WPI objective of creating a research center where first-class immunologists come from all over the world to engage in research for years. (3) To achieve the goal mentioned in (2), IFReC will need to be creative in recruiting foreign PIs and postdoctoral fellows. For example, IFReC may request its US satellite institutions to encourage postdoctoral applicants to consider IFReC as an alternative step in their career paths. Organizing IFReC symposia in other countries would be another way to advertise IFReC's activities and to recruit PIs as well as postdoctoral fellows.	(2)(3) We have allocated funding to invite experienced senior foreign researchers or young researchers for relatively short terms (3-6months) covering their financial costs including travel, daily, and research expenses. In the IFReC international symposium held in Feb. 2009, we intentionally asked researchers in non-immunological fields to give presentations and have designed an environment that encourages research exchange. We have invited all speakers to participate in seminars at separate IFReC laboratories after the symposium. Also, we will co-host an international symposium with the Singapore Immunology Network in June 2009 in Singapore to promote research exchange and increase IFReC's international visibility. In following years, we also plan to hold symposia with immunological societies in the United States and Europe and establish a summer school in cooperation with other research institutes.
(4) Although the integration of imaging technology into immunology is an attractive approach, it is recommended that IFReC incorporate other new, cutting-edge technologies, such as structural biology, genomics, epigenetics and chemical biology, by recruiting outstanding scientists from those disciplines so as to strengthen IFReC as a genuine World Premier Center for Immunology.	(4) Dr. Daron M. Standley, employed as of Oct. 1st, 2008, a specialist in Bioinformatics, is our leader in the field of computer simulating protein structures using gene data and protein chemistry to model immune responses. He is working with the Laboratory of Functional Analysis *in silico,* Institute of Medical Science, University of Tokyo (Computing Science), the University of Exeter (Evolutionary Genetics), the University of London (Biochemistry) and the Protein Data Bank. Dr. Standley has already submitted a paper as a result of his collaborative work with Dr. Akira's laboratory (Matsushita, Takeuchi, Standley, Akira and others. Nature, in press).

(5) Along these lines, the current satellite institutions are all specialized in immunology and imaging, which is similar to IFReC. Active cooperation and interaction with institutions specialized in different technologies/disciplines, such as epigenetics and advanced neuro-imaging, should be considered as being more beneficial to the IFReC program.	(5) Imaging group has been already collaborating with international top level neuro-imaging and information technology groups such as National Institute of Information and Communications Technology (NICT) and Advanced Telecommunications Research Institute International (ATR).
(6) From the viewpoint of both the project's initial objective and clinical application of its results, it is advisable that IFReC integrate clinical researchers into its staff.	(6) To apply our imaging of the immune system to clinical studies, we have invited Prof. Hatazawa (clinical researcher), Department of Nuclear Medicine, Osaka University Graduate School of Medicine, as concurrent staff. He has been conducting collaborative research with Prof. Kishimoto. Prof. Hatazawa has made great contributions to the field of immunology, including his development of radioligands that bind to Interleukin 6, which is often involved in autoimmune diseases, and the ability to observe the dynamics of accumulated IL-6 in animal models.
(7) As an imperative, the team for developing new imaging techniques needs to be strengthened.	(7) We have recruited Dr. Masaru Ishii, an accomplished bioimagist at the National Institute of Health, to be a new PI in our imaging group. He has produced remarkable results in the field of born marrow imaging (Nature, Feb 8, 2009). We also are negotiating with other foreign candidates for PI positions within the imaging group. Through support from Osaka University, we expect construction of the imaging center to be completed in several years. After completion, we will actively promote collaborative projects with private companies.
(8) Under the administrative Director, Dr. Norio Furushiro, a strong and well-trained support staff needs to be put in place to reduce the administrative duties of Drs. Shizuo Akira and Toshio Yanagida.	(8) We recruited staff holding a PhD in Research Management Section to manage symposia, seminars, PR and coordinate meetings between research groups (See page 1 for details). We also recruited a new professor (to be the administrative director from April 2009) with a long career in scientific research to be responsible for management and coordination. He is expected to facilitate the fusion between the immunology and imaging groups and act as a liaison with university authorities. As a result of these appointments, the Director, Vice Directors and staff in their laboratories have devoted far less time to bureaucratic work unrelated to their research. Our goal is to have an Administrative Department of exceptional quality and efficiency.