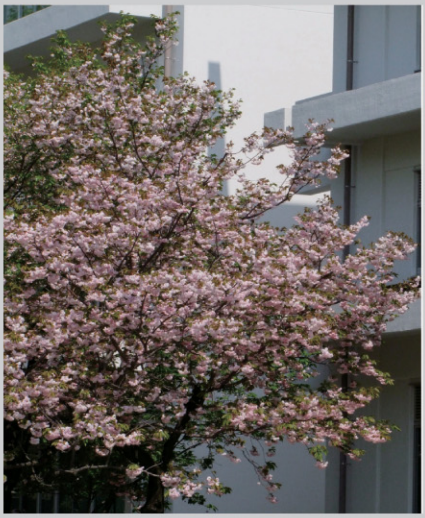
Report of The External Review Committee

Report of The External Review Committee for The Institute of Medical Science, The University of Tokyo

2008



Content

Message

Message from Dean

The predecessor to the Institute of Medical Science was founded as a private institution in 1892 under the name “The Institute for Infectious Disease.” Focused since its foundation on expanding basic research in microbiology and immunology, the institute implemented translational research utilizing the results of its research to develop vaccines and antiserums and applied these effectively in the diagnosis, treatment and prevention of infectious diseases at its affiliated hospital. In 1916, in concert with a change of name to the “Institute for Infectious Disease Affiliated to Tokyo Imperial University,” the institute added practical scientific research to its activities, thereby adding a new facet to its organization as a body engaged in the pursuit of knowledge and education.

Following this, as well as making advances in DNA double helix elucidation and DNA recombinant technologies, the institute’s dramatic advances in molecular biology brought about a revolution in life science. From these radical changes in life science and the necessity to tackle new problems arising from such changes, the Institute for Infectious Disease was reorganized to form the Institute of Medical Science in 1967 and thereafter adopted as its mission “research into and application of scientific principles underlying infectious diseases, cancer and other intractable diseases.”

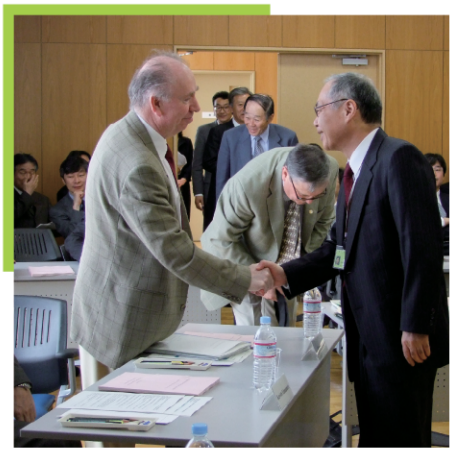
After the reorganization of its existing research departments, the Institute of Medical Science went on to establish new departments and donation laboratories, with the addition of the Human Genome Center in 1991 and the Center for Experimental Medicine in 1998. During the process of reinforcing each rank of the research structure, transition to a larger-department structure was carried out with the goal of overall research structure reorganization, and greater efficiency in research and operation was investigated with the result that reorganization to the current structure was implemented in the year 2000.

Currently, the institute comprises three core departments (Microbiology and Immunology, Cancer Biology and Basic Medical Sciences) active in 17 fields of research and 4 research centers (Human Genome Center, Center for Experimental Medicine, International Research Center for Infectious Diseases, Advanced Clinical Research) active in 19 areas of research and also includes various affiliated institutes as well as a hospital

and laboratory animal facilities. Additionally, the institute has 6 research departments supported by corporate donations. The above are divided into 6 groups (G0 to G5), with core departments and centers as the nucleus of each and with a degree of discretionary power to form units capable of independent operation.

With the advent of all national universities in Japan becoming corporate bodies in 2004, the Institute of Medical Science was incorporated into the organization of the University of Tokyo. (The University of Tokyo corporation)

As a university corporation, the corporation is required to be capable of independent organizational operation and is subject to a 1% cut in the annual budget subsidy provided by the government, giving rise to fierce competition for the acquisition of funding from external sources. Needless to say, this competition in turn produces interdepartmental competition for prioritization of funds within the university corporation itself. Since a university corporation is operated in units of 6 years based on mid-term goals and planning and is subject to provisional assessment at a point past the mid-term in the third year, 2008 is the year for this assessment.



Here at the Institute of Medical Science, we believe that, rather than simply submitting passively to this provisional assessment, we should see this as a positive opportunity to review the status of the institute after its transition to a larger-department structure, and to ensure that we continue to stand at the vanguard in the rapidly-advancing fields of life and medical science. The purpose of the forthcoming assessment is not only to evaluate individual researchers, but also to examine the overall status of the entire Institute of Medical Science and to take on board proposals with a view toward our future. In accordance with these goals, we summarized activity, organization, and operation of the Institute of Medical Science and asked the external evaluation committee for their advice. We are deeply indebted to members of the external evaluation committee who visited us two days for evaluation and spend more days for preparing summary of advice. This is a valuable guidepost to achieve our goals.

Motoharu Seiki

Motoharu Seiki, Dean

General Statement: Current State of IMSUT

1. **Goals and the current state of research**

I. Founding purpose and History

The institute started life as the Institute for Infectious Disease attached to the Great Japan Private Health Association (established in 1892) (First director: Shibasaburo Kitasato) and was reorganized into the current Institute of Medical Science in 1967 after undergoing various name changes including the Institute for Infectious Disease for the Ministry of Home Affairs and the Institute for Infectious Disease Attached to Tokyo Imperial University. In step with improvements in hygiene in post-war society, this organization made advances in leading-edge research into and treatment of not only infectious diseases, but also a wide range of illnesses difficult to treat including cancer and immunological diseases and, at the present time, has adopted as its mission "research into and application of scientific principles underlying infectious diseases, cancer and other intractable diseases" as also stated in the regulations of The Institute of Medical Science, The University of Tokyo. Furthermore, together with the scientific elucidation of diseases, advances in leading-edge treatments based on the concept of "bench to bed" form one of the principle features of the hospital that has been attached to the Institute since its foundation.

With a background in recent years characterized by conspicuous developments in molecular biology, cell biology and bioengineering and by rapid advances in genome science, advances are being made in systemic research into living organisms based on genomics and proteomics. As well as pursuing research into these basic sciences, the Institute of Medical Science has adopted as one of its current critical missions research into personalized medicine based on genome information, research into regenerative medicine, research based on international cooperation into emerging and re-emerging infectious diseases as well as translational research that forms the clinical link with results from the above fields. With respect to the foregoing, founded on creative research activities rooted in the concept of freedom of expression of the individual and based on the results of representative Japanese research to date, the Institute of Medical Science has taken on the burden of carrying out wide-ranging national pro-

jects including “Formation Program of Research Centers for Emerging and Re-emerging Infectious Diseases” and “Project for Leading-edge Treatment Centers through Genomic Science Development ‘21st Century Center of Excellence).”

Furthermore, the Institute of Medical Science is looked on to play a major role as a driving force in making contributions to medical research throughout Japan, acting as a base that both organizes and provides a wide spectrum of research foundations and resources difficult to achieve by individual universities such as a super computer system to support genome research, a field in which the volume of data is increasing at an explosive rate.

II. Current Research

In tandem with the characterization of infectious diseases and cancers, and the promotion of basic biomedical science based on the perspectives of molecular biology and genomic science, within the focal area in line with its goals, the Institute of Medical Science is engaged through its hospital in treatment with the focus on the development of translational research that forms the link between basic and clinical research. The reasons for characterization of each area of research are as follows.

(1) Research into Infectious Diseases: Basic measures to mobilize interdisciplinary research into the drug tolerance of pathogens, new problems arising from dramatically-increasing genome mutations or emerging diseases appearing in civilized society are becoming evermore necessary in today’s world. In response to this situation, the International Research Center for Infectious Diseases and the Advanced Clinical Research Center work in liaison mainly through the Department of Microbiology and Immunology to carry out research into infectious diseases from the perspectives of bacteriology, virology and immunology.

(2) Cancer Research: Because cancer is a genetic disease closely linked to the origins of life, elucidation of the true form of the disease is impossible without an understanding of the principles of life and for this reason, collective research using the knowledge and technology gained from a close study of genomic science is necessary. Cancer is the prime cause of death among Japanese and in response to the social demand for a solution to this threat, the Institute promotes further basic and clinical research into cancer.

(3) Basic Research: To achieve advances of even wider scope and greater depth into the field of biomedical science, the Institute promotes basic research not directly targeting disease. This research gives a fresh perspective to research into diseases and is promoted as an important budding field with the potential for producing new developments.

(4) TR (Translational) Research: The Institute of Medical Science is the only body of its kind in Japan with an attached hospital for research purposes and we believe that this affords us the opportunity to pursue effective TR research with the focus on

clinical applications of basic research. TR research is carried out with the focus on cancer and infectious diseases.

2. Organization and Administration

I. Position and Current Status of the Organization

Reorganization of the Institute of Medical Science in 2000 to establish an organization and research structure capable of appropriate and speedy response to world trends in the field of medical and life sciences was characterized by steps such as transition from the former 23-research-department structure to a 3-core-department organization and the establishment of the new Advanced Clinical Research Center. Subsequent to this, the International Research Center for Infectious Diseases was established in 2005 as a base for leading-edge research into medical and life sciences as well as the training of human resources and this was followed in 2006 by the opening of the Research Center for Asian Infectious Diseases, a joint research facility for research into emerging and re-emerging infectious diseases in China. Furthermore, between these two, the Project Research Center for work on special research themes and the Donations Laboratories Department have been established. Additionally, a Common Research Laboratories Department that includes core laboratories for support of effective development of research has also been opened. As a result, the Institute of Medical Science currently boasts 3 core departments, 4 centers, 4 research facilities including a Medical Proteomics Laboratory, an attached hospital, 5 donation research departments, 7 project research centers and 11 common research facilities (Figure 1).

Moreover, the Institute for Medical Research formed by the foregoing is established as a department of Tokyo University, representing the Institute's promotion of educational research at the same time as reinforcing mutual ties through the free pursuit of cultivation of research frontiers in specialized fields in other departments including graduate courses in physical sciences, agricultural sciences, pharmaceutical sciences and frontier sciences in the area of life sciences as well as graduate courses in medical science.

II. Overall Operation

The Vice Deans of the administrative and accounting organizations work under the Dean in a support capacity while management of the Institute is handled by the Faculty Meeting, the Faculty General Meeting, the Management Meeting (also referred to as the Executive Department Meeting), the Department Head Meeting and 6 group meetings (Department Meetings and Center Meetings) as well as sundry committees. Together with the leadership of the Dean, the Management Meeting is responsible for organization, decisions and proposals regarding items within the scope of the discretion of the Dean relating to management and operation of the Institute. The Department Head Meeting is responsible for examination and determination of important items relating to the management and operation of the Institute while the Group Meeting provides a venue for communication and approval of items decided by the Department Head Meeting and debate made by members of group meetings (See Figure 2). The functions of each of the foregoing meetings are detailed below.

Figure 1 Current Organization of the Institute.

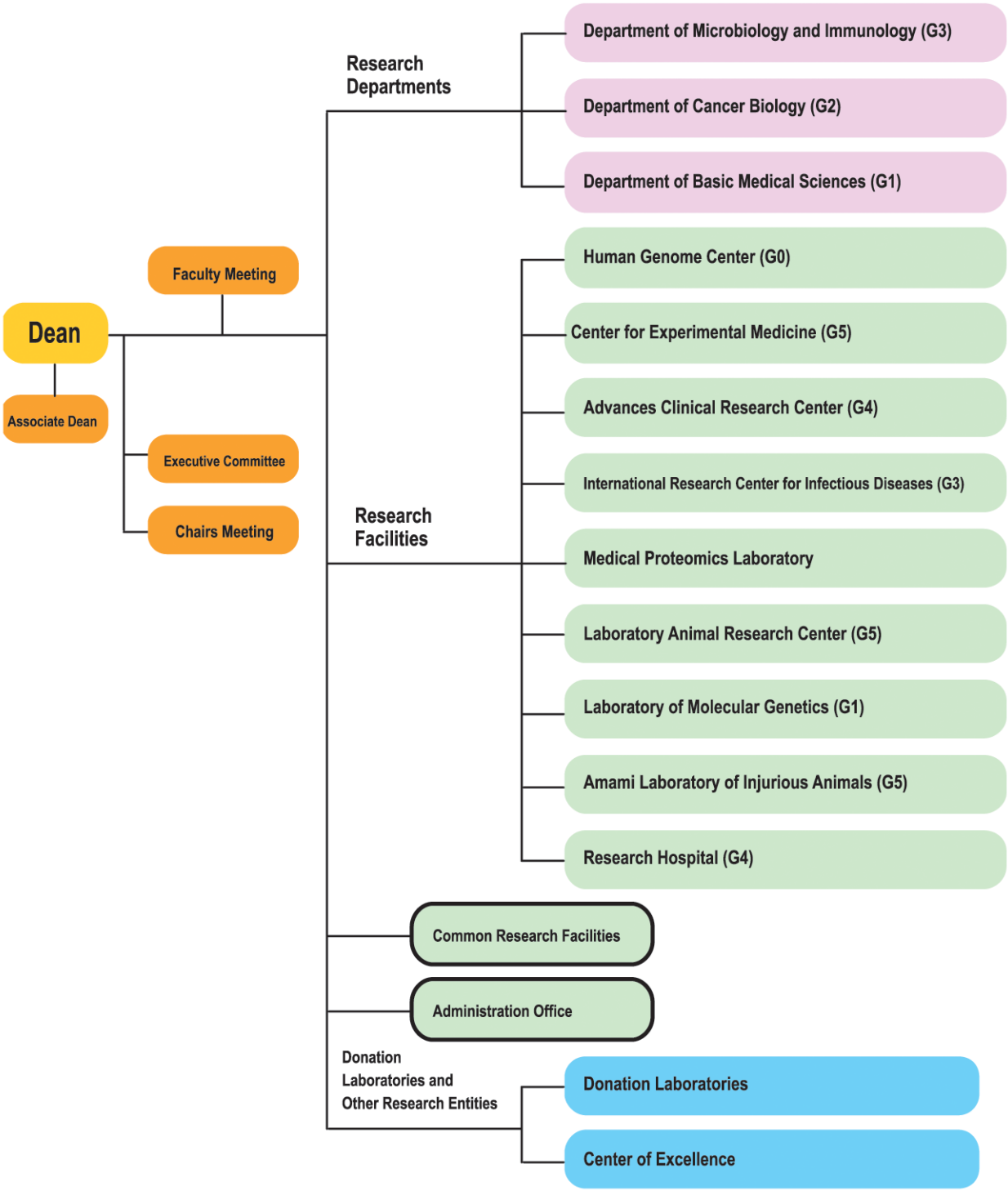
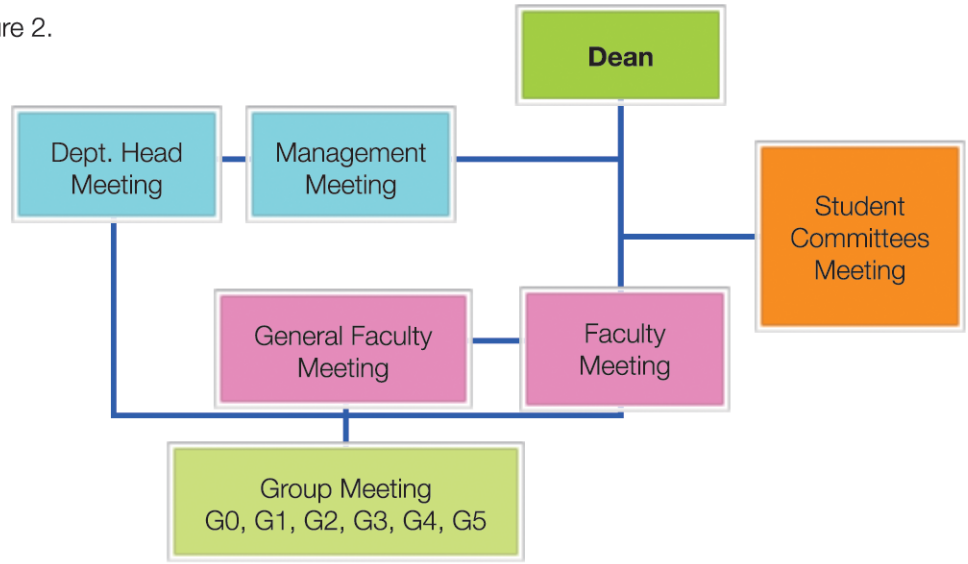


Figure 1. Continued.

1) The Faculty Meeting comprises full professors and is responsible for matters involving training of young scientists. In some cases, the Meeting also handles important matters exceeding the group level.
2) The General faculty Meeting comprises full professors and associate professors and is responsible for deliberation of important matters pertaining to the Institute as a whole including selection of associate professors, lecturers, deans and heads of facilities as well as the establishment and abolition of regulations.
3) The Management Meeting comprises the Dean, Vice Deans, Hospital Director, Professor in charge of research collaboration and the Head of the Administration Office and is responsible for organization, decisions and proposals pertaining to items within the discretion of the Dean relating to management and operation of the Institute.
4) The Department Head Meeting is comprises the above management meeting members and the heads of 6 group meetings and is responsible for deliberation on important matters pertaining to assistant teaching staff as well as the management and operation of the Institute.

Figure 2.



The members of the Dept. Head Meeting in 2007 are as follows:

Dean	Motoharu Seiki
Vice-dean, in charge of General Affairs Division	Junichiro Inoue
Vice-dean, in charge of Finance Division	Hiroshi Kiyono
Hospital Director	Naohide Yamashita
Professor in Charge of Research Collaboration	Kenji Morita
Head of Administration Office	Masahiro Seki
Chair of Department of Microbiology and Immunology (G3)	Kensuke Miyake
Chair of Department of Cancer Biology (G2)	Tadashi Yamamoto
Chair of Department of Basic Medical Sciences (G1)	Haruo Saito
Director of Human Genome Center (G0)	Yusuke Nakamura
Director of Center for Experimental Medicine (G5)	Yoichiro Iwakura
Director of Advanced Clinical Research Center (G4)	Motoharu Seiki

(3) Research Group Management

As a result of self-examination and review of the organization of the Institute, the various fields of research and facilities have been divided into 6 groups (departments and centers) depending on the area of research. The representative of each research group (referred to as the department chair or center director) assumes chairmanship of group meetings comprising professors and assistant professors from the corresponding group for the purpose of considering issues such as the research organizations and management as well as research activation and promotion as appropriate to the relevant field of specialization. Additionally, decisions from the Department Head Meeting and sundry information from within and outside the school are reported to each of the group meetings to ensure awareness.

(4) Principle of Research Field Independence

Although the recognized numbers of teaching personnel employable in each field of research and facility are not identical, on average management is based on employment of one professor, one associate professor and one or two assistant professors. Each of these fields and facilities is independent from the others and operate on a parallel principle; this concept is the most important consideration to ensure freedom of individual research. While operating in close connection with the activities of the Institute, the Research Hospital where treatment is carried out exists under a management organization different from that of the Institute.

Statistical Data

Statistical Data on IMSUT

Table 1: Teaching Staff (Regular Staff) Structure (Current as of April 1 for each Fiscal Year)

	2004	2005	2006	2007
Professors	31	33	34	31
Associate Professors	20	23	27	22
Lecturers	15	11	11	10
Assistant Professors	74	86	83	71
Educational Affairs Staff	7	-	-	3 (Assistant)
Technicians	158	147	151	157
Office Staff	44	45	41	45
Total	349	345	347	339

Table 2. Externally funded scientists, External Funding (Donation Laboratories, Industry/Academia/Government, Project Promotion)

	2004	2005	2006	2007
Visiting/Project Professors	7	7	7	7
Visiting/Project Associate Professors	9	12	10	10
Visiting/Project Lecturers	1	1	2	2
Assistant Professors Equivalent	21	30	27	28
Researchers	65	60	69	68
Total	103	110	115	115

Figure 3. Number of Students Accepted by the Institute of Medical Science, University of Tokyo (Master's Degree)

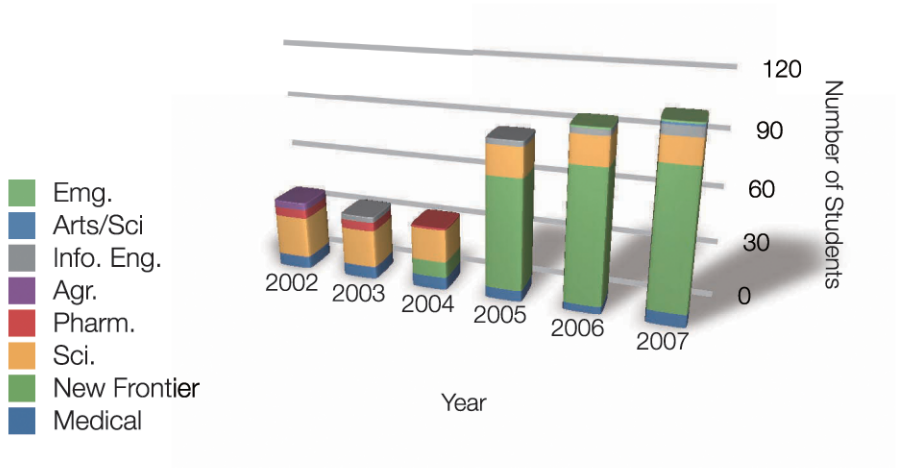


Figure 4. Number of Students Accepted by the Institute of Medical Science, University of Tokyo (Doctorate)

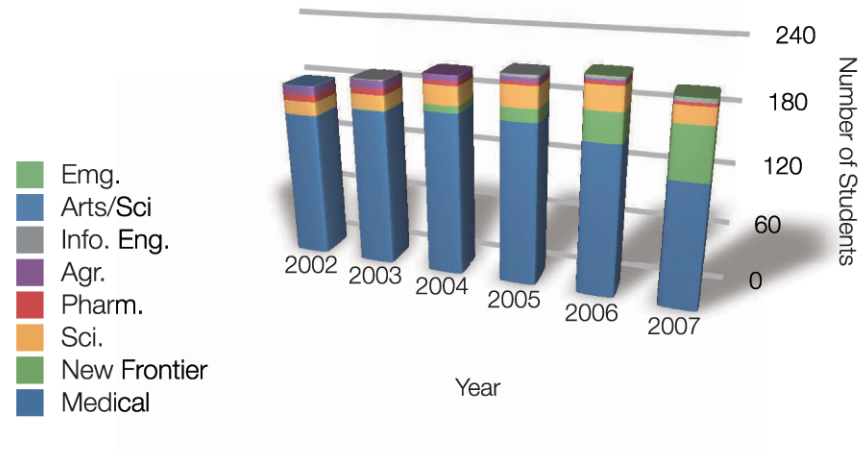


Table 3. External Funding of IMSUT (Thousand Yen)

Item of Expenditure	FY2004	FY2005	FY2006	FY2007*
Research Funds Subsidy	2,291,299	1,814,999	1,922,775	1,689,924
Research Funds Grant	2,349,675	2,637,378	1,754,891	1,750,149
Joint Research	637,106	778,826	641,277	472,573
Donations	289,784	427,826	387,311	245,903
Total	5,567,864	5,659,029	4,706,254	4,158,549

* figures for 2007 are current as of December 2007

External Committee

External Evaluation Committee Members

(alphabetically)

Dr. Ken-ichi Arai
Professor Emeritus, The University of Tokyo
Professor, Laboratory for Systems Biology and Medicine, Research Center of Advanced Science and Technology, The University of Tokyo

Dr. Jerry R. McGhee
Adjunct Professor /Professor Emeritus, Department of Microbiology, Immunobiology Vaccine Center, The University of Alabama at Birmingham

Dr. Tetsuichiro Muto
Professor Emeritus, The University of Tokyo
Medical Director /Hospital Director Emeritus, Japanese Foundation For Cancer Research

Dr. Ira Pastan (Head of the Committee)
Laboratory Chief, National Cancer Institute, NIH

Dr. Charles C. Richardson
Professor, Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School

Dr. John J. Skehel
Professor, Division of Virology, National Institute for Medical Research

Dr. Ken-ichi Yamamura
Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

Dr. Hiroshi Yoshikawa
Professor Emeritus, Osaka University
Professor Emeritus, Nara Institute of Science and Technology

Report of Evaluation Committee for IMSUT

Background

Dr. Tadashi Yamamoto, Chair of the External Evaluation Committee of IMSUT, asked a group of foreign and Japanese scientists to evaluate the research and teaching activities at IMSUT and prepare a written report summarizing their findings. The committee members are alphabetically

Dr. Ken-ichi Arai
Professor Emeritus, The University of Tokyo
Professor, Laboratory for Systems Biology and Medicine, Research Center of Advanced Science and Technology, The University of Tokyo

Dr. Jerry R. McGhee
Adjunct Professor /Professor Emeritus, Department of Microbiology, Immunobiology Vaccine Center, The University of Alabama at Birmingham

Dr. Tetsuichiro Muto
Professor Emeritus, The University of Tokyo
Medical Director /Hospital Director Emeritus, Japanese Foundation For Cancer Research

Dr. Ira Pastan
Laboratory Chief, National Cancer Institute, NIH

Dr. Charles C. Richardson
Professor, Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School

Dr. John J. Skehel
Professor, Division of Virology, National Institute for Medical Research

Dr. Ken-ichi Yamamura
Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

Dr. Hiroshi Yoshikawa
Professor Emeritus, Osaka University
Professor Emeritus, Nara Institute of Science and Technology

IMSUT has undergone a series of changes in recent years, starting with its reorganization in 2000 into larger departments accompanied by the founding of the Advanced Clinical Research Center, and then in 2004 the semi-privatization of all National Universities. A major task of this evaluation is to assess how the institute and its hospital are faring with the reorganization and to give advice on future directions.

The review was held at IMSUT on April 21 and 22, 2008. Prior to the meeting the committee members received detailed documents summarizing the research and teaching activities of the institute, and additional documents at the meeting.

On the first day the committee members were presented with an overview of IMSUT by the dean and heads of various departments. On the second day the committee was divided into 3 groups, which listened to research presentations from staff members from the different research areas. At the conclusion of these activities the review committee met privately to discuss their views about the institute and made suggestions that are incorporated into this report.

Report

1. THE most important finding is that the research activities of IMSUT are judged to be outstanding and at a level comparable to the very best research institutions in the world. IMSUT has an important mission to carry out innovative original research and also to help develop advanced medicine and new therapies at the national and international level. We strongly support that IMSUT be able to continue its mission.

2. The scientists at IMSUT have established collaborations with researchers and research groups in England, France, United States, China and many other countries including nations and economies of the Pacific rim. They have also established a research institute for infectious diseases in China that trains many young Chinese scientists. These activities plus the many symposia and training activities they participate in have established IMSUT as a prominent hub of research activities in Japan and Asia Pacific rim.

3. Many of the research findings from both the basic and translational research groups have the potential to be developed into new therapies or diagnostic methods. We support further consideration of the proposal to establish a Vaccine Research Institute and we were generally supportive of the planned initiative in Systems Biology. We recommend that the institute develop an approach that encourages the wider dissemination of their discoveries so those interested in developing these new discoveries could have an opportunity to do so. We realize IMSUT is a small institution and many of the discoveries will need to be developed employing a translational research (TR) platform outside of the institute in collaboration with TR groups of various institutions and industry.

4. An effort should be made to improve communication among staff members, postdoctoral fellows and students by activities such as frequent (weekly) seminars for all the staff and perhaps a yearly retreat with a few lectures and many posters. In addition IMSUT might build a coffee shop/lounge where scientists could meet on an informal basis.

5. There are currently about 350 graduate students of various backgrounds. IMSUT has an excellent training program for students teaching them how to use the knowledge received in their graduate training to do productive research. One unique feature is the emphasis placed on teaching students to communicate in English. The training program for non-MD students could also take advantage of research activities at the research hospital.

6. IMSUT should 1) increase the number of female researchers in the staff members, 2) increase research positions to hire young independent researchers, 3) increase post doctoral fellow and visiting scholar positions to attract researchers from abroad, and 4) develop career paths for young researchers in an international atmosphere.

7. The research hospital, which is a unique resource, is currently not sufficiently utilized and a way should be found to solve this problem, perhaps by some type of reorganization. IMSUT should seriously think about its strategy to accomplish two hospital-related objectives; i.e., to develop an open research hospital promoting TR, and to strengthen the financial basis for the hospital's operation. IMSUT hospital should be regarded as a common asset for TR shared by other institutions and pharmaceutical industry. Designation of IMSUT research hospital as a special zone for the development of frontier medicine might be considered. IMSUT hospital should take all out efforts

to seek financial support from both public and private sectors.

Some specific suggestions are:

a. Recruiting a strong leader with experience in clinical research programs that could creatively use the hospital resources and recruiting or identifying clinical scientists who have programs that could utilize the hospital.

b. Developing relationships with drug companies, diagnostic companies and biotechnology ventures, which wish to do first in man or other innovative trials at IMSUT. Designate certain numbers of beds for such translational initiatives and seek funding from public and private sectors.

c. Developing relationships with clinicians at other institutions who have clinical programs that could use the hospital facilities in a productive way.

8. IMSUT organizes, sponsors and participates in many research symposia such as the HGC, International Center for Infectious Diseases, East Asia Symposia, A-IMBN/AMBO/EMBO Joint Training & Workshops etc, but the name IMSUT is not used in these activities and the institution does not get sufficient recognition. In the 1990's, IMSUT International Symposia for Biomedical Research had been organized with themes such as cell signaling, neurobiology, stem cells etc. One way to gain international recognition is to sponsor a yearly symposium at IMSUT utilizing scientists at IMSUT and prominent foreign scientists as speakers; such meetings such as IMSUT International Symposia for Genomic Medicine and Cell Therapy would bring significantly more international attention to the institution.

In addition, IMSUT should develop an effective office of communications and technology transfer to communicate discoveries at the institution to the public and to pharmaceutical companies for commercial development.

The communication office could also help IMSUT scientists obtain international recognition by providing information about IMSUT scientists to various award and prize committees.

9. Since the semi-privatization of IMSUT, the amount of government support has been decreasing by about 2% per year and if continued will adversely affect in a serious manner the success of the institute. The committee recognized that IMSUT is truly a unique and international institution conducting outstanding innovative biomedical research with its research hospital for TR. To achieve its mission and to realize its potential, the review committee strongly believes that IMSUT merits continued strong support directly from the Japanese government and should not be subjected to a decreasing budget. A solution to prevent the current series of budget decreases that we strongly support is to make IMSUT a line item in the Japanese Health Research budget so it does not suffer from such budget cuts and can continue its excellent research activities.

The committee also recommends that IMSUT should have the mechanism and resources to nominate its dean and hospital director from outside if necessary.

June 17 ,2008
Ira Pastan

東京大学医科学研究所外部評価報告書

平成20年6月17日
外部評価委員長　Ira Pastan

背景

東京大学医科学研究所（以下、医科研と略す）外部評価準備委員会・委員長・山本雅教授からの依頼により、国内外計8名の科学者が医科研の研究活動及び教育活動への評価審査を行った。評価委員メンバーはアルファベット順で以下の8人である。

新井賢一博士	東京大学名誉教授 東京大学先端科学技術研究センターLSBM特任教授
Dr. Jerry R. McGhee	Adjunct Professor/Professor Emeritus, The University of Alabama at Birmingham
武藤徹一郎博士	東京大学名誉教授 癌研有明病院メディカルディレクター・名誉院長
Dr. Ira Pastan	Laboratory Chief, National Cancer Institute, NIH
Dr. Charles C. Richardson	Professor, Harvard Medical School
Dr. John H. Skehel	Professor, National Institute for Medical Research
山村研一博士	熊本大学教授
吉川寛博士	大阪大学名誉教授 奈良先端科学技術大学院大学名誉教授

医科研は、2000年に改組が認められ、従来の23研究部から3部門（感染・免疫部門、癌・細胞増殖部門、基礎医科学部門）になるとともに、先端医療研究センターを新設した。また、2004年には国立大学法人法により東京大学が法人化するなど、近年さまざまな変化を遂げてきた。今回の外部評価では、医科研と附属病院がこれらの変化にどう対処しているかを評価するとともに、今後の方向性について提言することを目的とする。

評価会は2008年4月21日ー22日、医科研にて行われた。評価委員には事前に医科研の研究及び教育活動の詳細をまとめた冊子が配布されており、評価会当日にはさらに追加資料が配布された。

初日には清木所長より医科研の概要紹介、各部門長より各部門の紹介がなされ、2日目には評価委員が3グループに分かれ、各研究分野の研究者から研究内容の説明を受けた。これらすべてが終了後、評価委員メンバーのみの意見交換の場が設けられ、そこで交換された医科研に対する提言がこの評価報告書の内容となっている。

評価報告書

1. まず最重要事項として、医科研の行っている研究内容は大変素晴らしく、世界でも最高レベルの研究機関であるという結論に至ったことを述べておきたい。医科研には、革新的且つ創造的な研究を行うとともに全国または国際レベルで最新創薬・治療技術の開発に貢献するという重要な任務がある。我々は、医科研がこういった任務を継続して遂行できるよう、強力にサポートしていきたい。

2. イギリス、フランス、アメリカ、中国、その他環太平洋諸国を含む多くの国々の研究者と協力関係を築いている。また、中国・北京にアジア感染症研究拠点を構え、中国の若手研究者育成にも尽力している。これらの活動に加え、多くのシンポジウムや教育活動にも参加しており、日本及びアジア環太平洋諸国における研究活動の中心的役割を果たしている。

3. 基礎研究及びトランスレーショナル・リサーチ（以下、TRと略す）の研究成果の多くは、新しい治療法や診断法への発展の可能性を秘めている。これまでに進められているシステム生物学的研究計画の推進を強く支持するとともに、ワクチン開発研究センター設立計画のさらなる前進にも期待している。また、ＴＲ推進に向けた課題として、個々の研究者自身の研究成果を広く宣伝していく仕組みを作り、それら成果が発展または応用の機会を得やすい環境を整備していくことが挙げられる。比較的小規模な研究機関であるため、他機関または企業のTRチームと連携し、外部のTR基盤を活用しながら研究を展開していく必要がある。

4. 学生、ポスドク、教職員間の相互のコミュニケーションが足りないように思われる。定期的（毎週など）に全員参加型のセミナー開催、1年に1回は講演やポスター発表を企画したリトリートを開催するなど、交流の場を設けるようにした方がよい。また、研究者同士の非公式な交流の場としてカフェ、ラウンジなどを設けるのも良いだろう。

5. 医科研には、現在約350名の様々な経歴を持った大学院生が在籍している。大学院で学んだ知識をいかに実りのある研究に結びつけるかを学べる、優れたトレーニングプログラムもあり、また珍しい特徴として、英語でのコミュニケーション能力の強化に重点を置いていることが挙げられる。医師免許を持たない学生を対象としたトレーニングプログラムにも、附属病院における研究活動を巧みに活用できるようになっている。

6. 医科研がこれから進めていくべきこととして、以下の項目があげられる。 1) 女性研究者の増員　2)若手自立研究者雇用枠の拡大　3) 外国人研究者が応募しやすい、PD特別研究員や客員研究員枠の拡大4)若手研究者が国際的な場でキャリアを築いて行ける環境の整備

7. 医科研が他の研究機関と異なる点として、独自に附属病院を持っていることが挙げられる。しかし、この附属病院が充分に活用されていないのが実情であり、組織の再編成など、何らかの解決策を講じる必要がある。TR推進を目的とした病院の開放、病院運営のための財政基盤の強化など、病院が目標としていることを達成

するための戦略も早急に立てなければならない。附属病院を最先端医療特区として位置づけることを考慮しながら、他の研究機関や医薬産業とシェアし、TRのための共通財産とするべきである。また、政府と民間それぞれから最大限の財的支援を得られるよう、努力する必要もあろう。

具体的な提案策：

a. 病院資源を独創的に活用できる臨床研究の経験を持つ有能なリーダーの採用および病院を活用できるプログラムを持つ臨床研究者の採用（または特定）。

b. 医科研における臨床治験、またはその他の革新的臨床試験の実施を希望する製薬会社、診断薬会社、バイオ技術ベンチャー企業との提携強化。また、そのようなＴＲ実践のためのベッド数確保、政府及び民間からの財的支援の獲得。

c. 病院施設を有意義に利用できる臨床プログラムを持つ他機関の臨床医との関係構築。

8. 医科研はヒトゲノム解析センター、国際感染症センターなどを運営し、さらに東アジアシンポジウム、 A-IMBN/AMBO/EMBO Joint Training & Workshops など、多くのシンポジウムを主催・支援または出席している。しかし、こういった活動において「東京大学医科学研究所」という名前が充分前面に出ておらず、医科研の存在が充分に認知されていない。90年代には、細胞シグナリング、神経生物学、幹細胞などをテーマとした東大医科研バイオメディカル･リサーチ国際シンポジウムも開催している。国際的な評価を得るための方法として、医科研で毎年シンポジウムを開催し、所内の研究者や優秀な外国人研究者をスピーカーとして起用することなどが考えられる。 ゲノム医療や細胞療法をテーマとした国際シンポジウムならば、海外から充分な注目を集められるであろう。

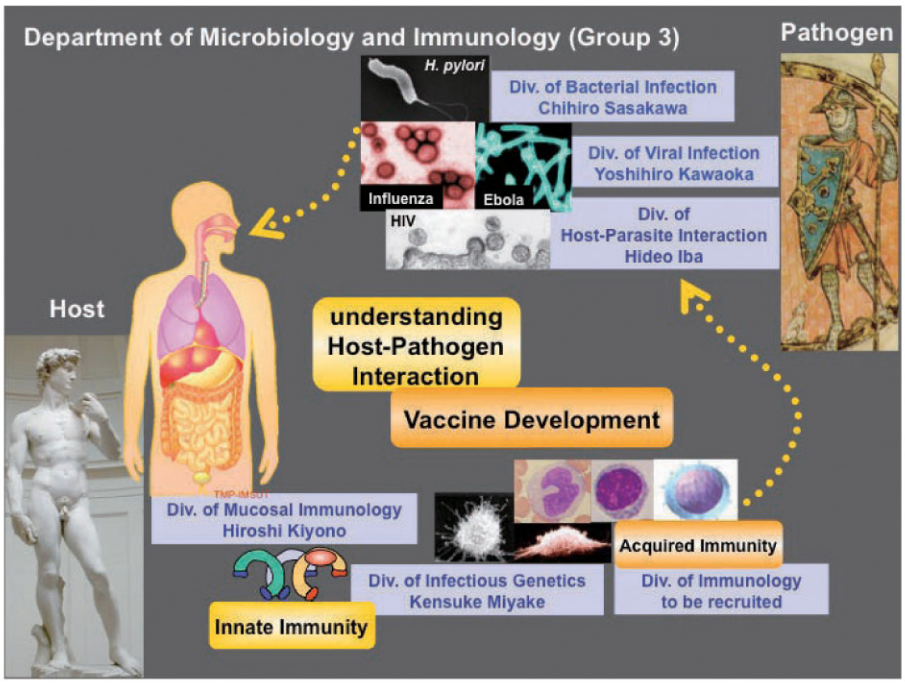
また、情報交換や技術移転を専門に行う部門を作り、研究所での成果を一般社会や製薬会社に公開するなどして商業化していくことにも力を入れていくべきである。更にこの部門から医科研の研究者に関する情報を様々な賞の審査委員会に発信することで、研究者が国際的評価を得やすくなる。

9. 大学の法人化により、政府からの医科研への財的サポートが毎年約２％ずつ減少している。もしこれが続けば、医科研の発展に深刻なマイナス影響を及ぼすであろう。我々評価委員は、医科研及びTRのための附属病院が優秀且つ革新的な生物医学研究を行う、他とは異なるユニークで国際的な研究機関であることを今回確かに認識した。与えられた使命を全うし、またあらゆる可能性の実現化を図るためには、医科研は日本政府から直接強力なサポートを受けるべきであり、予算の削減はふさわしくない、と確信している。近年の研究予算減少をくい止めるためには、医科研が日本政府の対疾患研究予算に直結してサポートされる対象機関として位置づけられ、予算削減の対象となることなく、優れた研究を続けられるようになることを我々は強く提案する。また、必要に応じて外部から所長・病院長を採用できるシステムをつくることも提案する。

Current state by Department

Current State and Future Outlook by Departments & Research Centers

Department of Microbiology and Immunology



Chair: Kensuke Miyake

(1) Missions

Research activities in our department focus on pathogenic mechanisms of infectious diseases. We try to understand: how microorganisms are pathogenic in the host; how the immune system discriminates between microbes and self; and how the immune system responds to pathogens. Our mission is to control infectious and related immune diseases through these basic research activities.

(2) Research activities and future perspectives

In this country, many people are concerned with the threats of newly arising or reemerging infectious diseases like SARS and avian flu and of bacteria resistant to multiple antibiotics. These threats of infectious diseases are expected to remain important over the next decade due to increased global traffic, global warming, and a rapid demographic increase in the aged. Furthermore, rapid changes in diet and environment have increased allergic and autoimmune diseases, which are expected to continue to increase. Considering this situation, our department has been driving basic research on infectious diseases and host immune responses. We also have made every effort toward development of vaccines and a novel therapy based on the findings obtained from basic research.

Currently, research projects focusing on *Shigella, Helicobacter pylori*, enteropathogenic *E.coli*, influenza virus, Ebola virus, and HIV are under way. These projects try to understand the host-pathogen relationship from molecular interactions to in vivo phenomena. Concerning host immune responses, the studies focus on pathogen sensors in the innate immune system and the mucosal immune system in the gut and the airway as well as on the acquired immune system. Vaccines acting specifically on the mucosal immune system have also been developed.

To understand infectious diseases, mutual communication is critical between research focused on pathogens and and that focused on host immune responses. Along this line, our department encourages communication among bacteriology, virology, and immunology not only

in our department but also across the country. It is important to establish a nationwide network for microbiology and immunology. We have already made this effort by establishing a close relationship with the institute for microbial diseases in Osaka University. This effort is to be extended to other research institutes in Japan as our institute tries to play a central role in this network for microbiology and immunology. Also, through communication with researchers in Asia and pan-pacific areas, we are trying to establish ourselves as an internationally recognized institute for microbiology and immunology throughout this region. Finally, it is also important to establish a link with the hospital in this institute in order to encourage translational research for development of vaccines and new therapies for infectious diseases.

(3) Members

Division	Professor	Associate Prof.	Lecturer
Bacterial infection	Chihiro Sasakawa		Michinaga Ogawa Hitomi Mimuro Masato Suzuki
Virology	Yoshihiro Kawaoka	Taisuke Horimoto	Hideo Goto Masayuki Shimojima Kiyoko Iwatsuki-Horimoto Yuko Sakai-Tagawa
Mucosal Immunology	Hiroshi Kiyono		Jun Kunisawa Yoshikazu Yuki Shintaro Sato
Infectious Genetics	Kensuke Miyake		Sachiko Akashi-Takemura Takahisa Furuta Shin-ichiro Saitoh
Host-parasite Relationship	Hideo Iba		Shigeru Minoguchi Taketoshi Mizutani Nobutake Yamamichi
Immunology	No current plan to fill up		

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Watanabe, H., Mizutani, T., Haraguchi, T., Yamamichi, N., Minoguchi, S., Yamamichi-Nishina, M., Mori, N., Kameda, T., Sugiyama, T., and Iba, H. SWI/SNF complex is essential for NRSF-mediated suppression of neuronal genes in human nonsmall cell lung carcinoma cell lines. Oncogene 25, 470-479 (2006)

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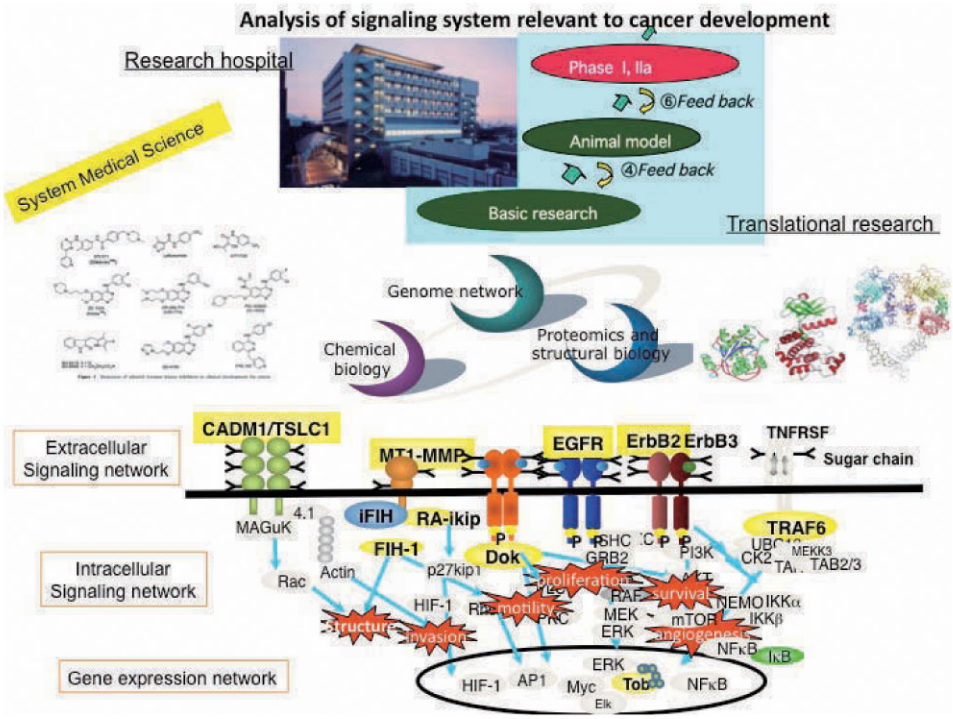
Department of Cancer Biology

Chair: Tadashi Yamamoto

(1) Missions and history

In 1967, the Institute for Infectious Disease, founded by Shibasaburo Kitasato in the late 19th century, was reorganized into the Institute of Medical Science. That the incidence of infectious diseases was decreasing in those days largely affected the reorganization. In contrast the cases of cancer were increasing. The faculties of the University thought that we need to have a research institute where people can study the problems of cancers as well as other intractable diseases. Consequently, the number of laboratories for cancer research in the institute increased. This Department has now seven independent divisions: Oncology, Cancer Cell Research, Cancer Genomics, Molecular Pathology, Cellular and Molecular Biology, Biochemistry, and Genetics. Scientists in these divisions have been conducting basic cancer research employing the approaches of molecular biology and genome sciences.



(2) Outline of research and prospect

1. Clarification of the roles of cancer related genes such as oncogenes and protooncogenes in tumor development through the analysis of their structure, expression, and function in normal cells as well as in cancer cells.
2. Studies on signal transduction and gene expression involved in cell growth and differentiation.
3. Clarification of the roles of inositol-phospholipid signaling in the control of cell growth, motility, and architecture.
4. Studies on cell-cell interactions, cell attachment, cell motility, and the cytoskeleton. Clarification of the roles of protein glycosylation in these processes is included.
5. Establishment of molecular mechanisms in tumor angiogenesis, cancer cell invasion, and metastasis.
6. Molecular pathological studies of malignant lymphomas, solid tumors such as breast cancer

and lung cancer, and retrovirus-associated neoplasms.

We will continue the current on-going studies by employing new methodologies such as imaging, proteomics and bioinformatics, and deepen our understanding of the mechanisms of intercellular signaling and intracellular signaling that are relevant to both normal biological events and cancer development. Especially, communication between cancer cells and surrounding normal cells that include niche function and immunity will be an obligatory subject to be addressed. Our studies will be performed by aggressively introducing structural biology and chemical biology, which is essential not only for understanding intracellular signaling but also for developing therapeutic compounds. To facilitate these studies, two specific strategies are planned. First a research program focusing on specific cancers, namely breast cancer and lung cancer, will be targeted for collaborative studies within the department. Second, by collaborating with research facilities within the institute such as the Medical Proteomics Laboratory, Center for Experimental Medicine, Human Genome Center, we will try to establish system biological approaches for cancer science.

(3) Members

Division	Professor	Associate Prof.	Lecturer
Oncology	Tadashi Yamamoto		Miho Ohsugi Toru Suzuki Takanobu Nakazawa
Cancer Cell Research	Motoharu Seiki		Naohiko Kashikawa
Molecular Pathology	Yoshinori Murakami	Akihiko Ito	Mika Sakurai
Cellular & Molecular Biology	Jun-ichiro Inoue		Taishin Akiyama Jin Gohda Noritake Yamaguchi
Genetics	Yuji Yamanashi		Ryuichi Mashima
Biochemistry		Seiichi Takasaki	
Cancer Genomic	(No current plan to fill up)		

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(Oncology)

Ohsugi M, Adach K, Horai R, Kakuta S, Sudo K, Kotaki H, Tokai-Nishizumi N, Sagara H, Iwakura Y, and Yamamoto T, Chromokinesin Kid-Mediated Anaphase Chromosome Compaction Safeguards Mouse Early Embryos Against Multinuclear Formation. Cell 132: 771-782, 2008

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Kawai, T., Sato, S., Ishii, K.J., Coban, C., Hemmi, H., Yamamoto, M., Terai, K., Matsuda, M., Inoue, J., Uematsu, S., Takeuchi, O., and Akira, S. Interferon-α induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. Nat. Immunol. 10, 1061-1068 (2004).

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Department of Basic Medical Sciences

Chair: Haruo Saito

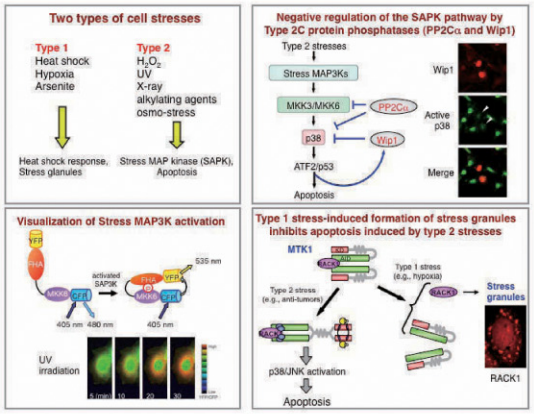
(1) Mission

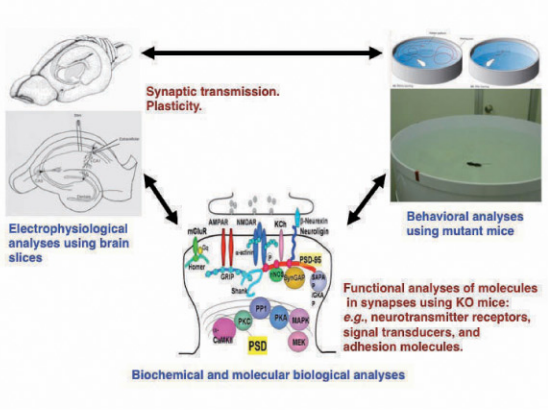
An important mission of the Institute is to develop new fields in basic life science, and apply the results to advanced clinical research. In order to elucidate the causes and mechanisms of diseases, and to develop more effective therapies, it is essential to understand the life processes at the molecular levels. As one of the three basic research departments, this department is established to explore and advance fundamental and creative life sciences without regards to specific diseases or research fields. Thus, this department has been a collection of diverse and unique research groups with free ideas in research directions. At the same time, this department has supporting roles in aiding the research of other departments. In the past, several projects have been launched from this department, including the Human Genome Center and the Center for Experimental Medicine.

(2) Research areas and perspective

In this department, fundamental questions pertinent to basic life processes are studied at the levels of molecule, cell, and individual animal. A brief summary of each laboratory is as follows.

Division of Molecular Cell Signaling studies the cellular responses to extracellular stress stimuli, such as radiation and anti-tumor drugs using mammalian and yeast cells with cell biological, biochemical, and molecular genetic approaches, with an ultimate goal of developping more effective anti-tumor therapies.





The major research interest of the Division of Neuronal Network is the molecular mechanisms of higher brain functions in mammals such as emotion, and learning and memory. The Division is especially focusing on the roles of functional molecules localized in synapses, for instance, neurotransmitter receptors, signal transduction molecules and adhesion molecules, in neuronal information processing, with electrophysiological, biochemical, molecular biological and behavioral approaches.

Division of Bio-molecular Imaging aims to study the dynamic actions of proteins , by observing and analyzing 3D structures of single molecules in living cells, using advanced technologies of electron and light microscopy, such as quick-freeze deep-etch replica electron microscopy and one-molecule FRET method.

Division of Molecular Biology studies various functions of non-coding RNAs for comprehensive understanding of human genome RNA function. The division also aims to uncover natural aptamers, and to develop artificial aptamers that would be highly beneficial to the development of RNA medicine.
Laboratory of Molecular Genetics has two main activities. First is to develop adenovirus vectors for gene therapy. Second is administrative oversight and assistance to institute laboratories that conduct researches involving biohazardous materials and/or recombinant DNA technology.
Division of Stem Cell Engineering (Tooth Regeneration) conducts research aiming to regenerate tooth using the methods of tissue engineering.
Division of Molecular and Developmental Biology (Oriental-Tomy-Softbank) studies molecular mechanisms underlying the intracellular signal transduction that governs self renewal and differentiation of stem cells, employing neural, dental, lymphoid and hematopoietic cell lineages as well as pluripotent embryonic stem cells.

(3) Members

Division	Professor	Associate Prof.	Lecturer
Molecular Cell Signaling	Haruo Saito	Mutsuhiro Takekawa	Kazuo Tatebayashi Taichiro Tomida
Neuronal Network	Toshiya Manabe	Yuko Sekino	Ayako M. Watabe Yuji Kiyama
Molecular Biology	Yoshikazu Nakamura	Koichi Ito Yasuko Yamamura	Shoji Ohuchi
Biomolecular Imaging	Eisaku Katayama		Jun Kozuka
Chromatin Regulation	Osamu Nureki	Ryuichiro Ishitani	Hiroshi Nishimasu
Molecular Neurobiology	No Current plan to fill up		
Laboratory			
Molecular Genetics	Izumu Saito		Yumi Kanegae Saki Kondo
Donation Laboratory			
Stem Cell Engineering (Hitachi Plant Tech., Denics, Ar Blast)	Minoru Ueda	Hideaki Kagami	Masak Honda
Molecular & Developmental Biology (Oriental, Tomy Softbank)	Sumiko Watanabe		Shinya Satoh
Molecular Neurobiology	No Current plan to fill up		

Selected Publications

(Molecular Cell Signaling)

Tatebayashi, K., Tanaka, K., Yang, H.-Y., Yamamoto, K., Matsushita, Y., Tomida, T., Imai, M., and Saito, H. (2007) Transmembrane mucins Hkr1 and Msb2 are putative osmosensors in the SHO1 branch of yeast HOG pathway. EMBO J., 26: 3521-3533.

Takekawa, M., Tatebayashi, K., and Saito, H. (2005) Conserved docking site is essential for activation of mammalian MAP kinase kinases by specific MAP kinase kinase kinases. Mol. Cell, 18: 295-306.

Reiser, V., Raitt, D.C., and Saito, H. (2003) Yeast osmosensor Sln1 and plant cytokinin receptor Cre1 respond to changes in turgor pressure. J. Cell Biol., 161: 1035-1040.

(Neuronal Network)

Bongsebandhu-phubhakdi, S. & Manabe, T. The neuropeptide nociceptin is a synaptically released endogenous inhibitor of hippocampal long-term potentiation. J. Neurosci. 27, 4850-4858 (2007).

Suto, F., Tsuboi, M., Kamiya, H., Mizuno, H., Kiyama, Y., Komai, S., Shimizu, M., Sanbo, M., Yagi, T., Hiromi, Y., Chédotal, A., Mitchell, K. J., Manabe, T. & Fujisawa, H. Interactions between plexin-A2, plexin-A4 and semaphorin 6A control lamina-restricted projection of hippocampal mossy fibers. Neuron 53, 535-547 (2007).

Nakazawa, T., Komai, S., Watabe, A. M., Kiyama, Y., Fukaya, M., Arima-Yoshida, F., Horai, R., Sudo, K., Ebine, K., Delawary, M., Goto, J., Umemori, H., Tezuka, T., Iwakura, Y., Watanabe, M., Yamamoto, T. & Manabe, T. NR2B tyrosine phosphorylation modulates fear learning as well as amygdaloid synaptic plasticity. EMBO J. 25, 2867-2877 (2006).

(Molecular Biology)

Kong, C., Ito, K., Walsh, M., Wada, M., Liu, Y., Kumar, S., Barford, D., Nakamura, Y., Song, H.: Crystal Structure and Functional Analysis of the Eukaryotic Class II Release Factor eRF3 from S. Pombe. Mol. Cell, 14: 233-245 (2004).

Polacek, N., Gomez, M., Ito, K., Xiong, L., Nakamura, Y., Mankin, A.: The critical role of the universally conserved A2602 of 23S ribosomal RNA in the release of the nascent peptide during translation termination. Mol. Cell, 11: 103-112 (2003).

Ito, K., Fujiwara, T., Toyoda, T., Nakamura, Y.: Elongation factor G participates in ribosome disassembly by interacting with ribosome recycling factor at their tRNA-mimicry domains. Mol. Cell, 9: 1263-1272 (2002).

(Biomolecular Imaging)

Yoshida S, Handa Y, Suzuki T, Ogawa M, Suzuki M, Tamai A, Abe A, Katayama E, & Sasakawa C. Microtubule-Severing Activity of Shigella is Pivotal for Intercellular Spreading. Science, 314, 985-989 (2006).

Tanaka H, Homma K, Hikkoshi-Iwane A, Katayama E, Ikebe R, Saito J, Yanagida T, & Ikebe M. The motor domain, not a long neck domain, determines the large step of myosin-V. Nature, 415, 192-195 (2002).

Tamano K, Katayama E, Toyotome T, & Sasakawa C. Shigella Spa32 is an essential secretory protein for functional type III secretion machinery and uniformity of its needle length. J. Bacteriol. 184, 1244-1252 (2002).

(Chromatin Regulation)

T. Sengoku, O. Nureki, A. Nakamura, S. Kobayashi, and S. Yokoyama. Structural basis for RNA unwinding by the DEAD-box protein Drosophila Vasa.Cell, 125, 287-300 (2006).

R. Ishitani, O. Nureki, N. Nameki, N. Okada, S. Nishimura, and S. Yokoyama. "Alternative tertiary structure of tRNA for recognition by a posttranscriptional modification enzyme. Cell, 113, 383-394. (2003).

H. Ogiso, R. Ishitani, O. Nureki, S. Fukai, M. Yamanaka, J. –H. Kim, K. Saito, M. Shirouzu, and S. Yokoyama. Crystal structure of human epidermal growth factor in complex with the extracellular domains of the receptor. Cell, 110, 775-787 (2002).

(Molecular Genetics)

Shibata H, Takano H, Ito M, Shioya H, Hirota M , Matsumoto H , Kakudo Y, Ishioka C, Akiyama T, Kanegae Y, Saito I, & Noda T. α-Catenin is essential in intestinal adenoma formation. Proc Natl Acad Sci U S A. 104, 18199-18204, 2007.

Haruta M, Kosaka M, Kanegae Y, Saito I, Inoue T, Kageyama R, Nishida A, Honda Y, & Takahashi M. Induction of photoreceptor-specific phenotypes in adult mammalian iris tissue. Nat Neurosci. 4, 1163-1164, 2001.

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(Molecular& Developmental Biology)

Nakada, C., Sato, S., Tabata, Y., Arai, K., Watanabe, S. (2006) A novel forkhead transcription factor regulating midbrain formation through suppression of shh expression in zebrafish. Mol. Cell Biol, 26, 7246-7257

Saito, R., Tabata, Y., Muto, A., Arai, K., Watanabe, S. (2005) Melk-like-kinase plays a role for haematopoiesis in zebrafish. Mol. Cell. Biol. 25, 6682-6693

Watanabe, S., Zeng, R., Aoki, Y., Itoh, T., Arai, K. (2001) Initiation of polyoma virus origin dependent DNA replication through STAT5 activation by human granulocyte-macrophage colony-stimulating factor (GM-CSF). Blood 97, 1266-1273

(Stem Cell Enginnering)

Honda MJ, Tsuchiya S, Sumita Y, Sagara H, Ueda M. The sequential seeding of epithelial and mesenchymal cells for tissue-engineered tooth regeneration. Biomaterials. 2007 28(4):680-9.

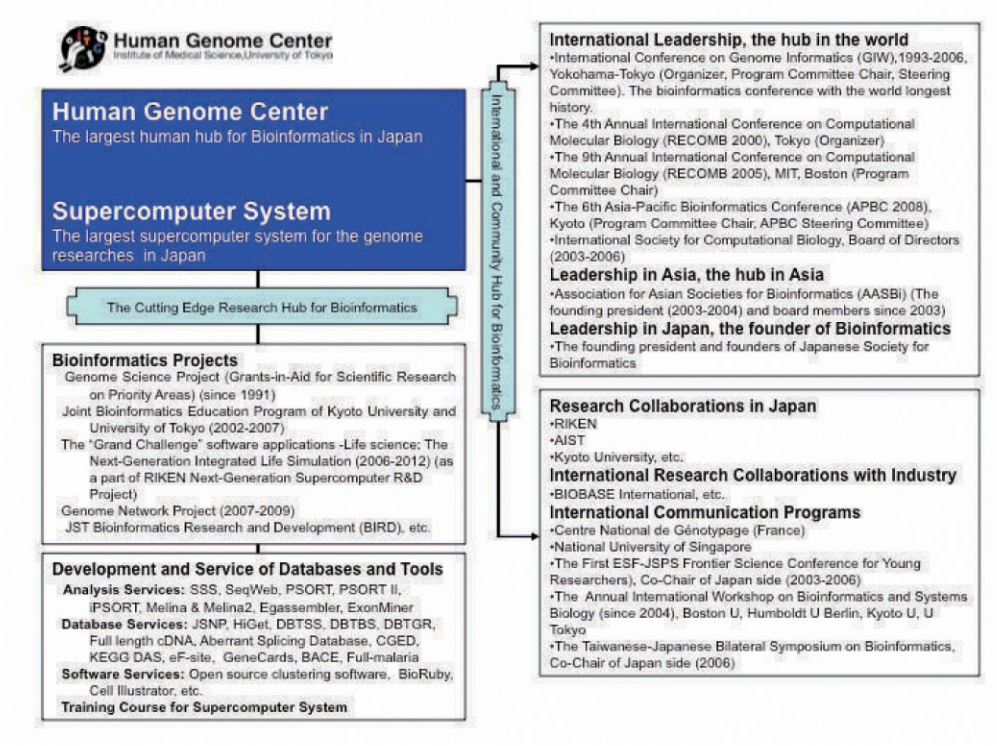
Sumita Y, Honda MJ, Ohara T, Tsuchiya S, Sagara H, Kagami H, Ueda M. Performance of collagen sponge as a 3-D scaffold for tooth-tissue engineering. Biomaterials. 2006 27(17):3238-48.

Honda M, Morikawa N, Hata K, Yada T, Morita S, Ueda M, Kimata K. Rat costochondral cell characteristics on poly (L-lactide-co-epsilon-caprolactone) scaffolds. Biomaterials. 2003 24(20):3511-9.

Human Genome Center

Director:

Yusuke Nakamura



(1) Mission and history

The human genome research is aimed at greatly contributing to human welfare by developing novel methods of diagnosis, prevention, and care of human diseases. Such research is also important as an infrastructure indispensable for the development of basic biology. Thus, the Human Genome Center (HGC) was founded on 1991 in the campus of the Institute of Medical Science, the University of Tokyo, as a national center for the human genome project, which would be crucial for the future progress of both medicine and biology. The center was first started from a single laboratory in 1991 and seven laboratories have joined subsequently One notable feature of HGC is that the majority of its laboratories are so-called dry labs, which are not equipped with the facility for wet experiments. This is based on the strategy of making this center with its relatively small size competitive enough in the world.

(2)Research activities and future direction

Within each laboratory, not only is leading-edge research conducted in each field of the international genome study but also the genome research activities in Japan are supported. For example, members of the laboratories of Molecular Medicine and Genome Technology have provided various materials to other researchers, have held training courses on genome technology, and have taught experimental techniques to young visiting scientists in Japan. These two laboratories are leading systematic expression analysis of human cancers and whole-genome SNP association studies for various diseases in Japan (JSNP database for SNP information by this group. In addition, the Biobank Japan project was conducted by the HGC, the Biobank collected DNAs and sera from nearly 300,000 cases covering 47 diseases, and is considered to be the biggest biobank in the world. Members of HGC have also contributed in maintaining and constructing international databases, in distributing genome information to the genome science

community, and in holding training courses on its usage. Therefore, our center not only plays a leading role in the progress of the human genome project in Japan but also functions as a corresponding door for international activities in database construction, mapping, and sequencing of the human genome. We will continue our efforts in maintaining our leading research activity, in supporting a number of genome scientists, and in releasing the fruits of our achievements to the world. The dry labs in HGC cover a wide range of expertise: from relatively classical computer analyses of genomic nucleotide sequences (Lab. of functional analysis in silico) and the development of algorithms for these purposes (Lab. of sequence analysis) to genome statistics exploiting large-scale SNP information (Lab. of functional genomics), construction of systems-biology oriented databases (Lab. of genome database), and analyses of inter-gene interaction networks (Lab. of DNA information analysis). Of course, collaboration between theoretical studies and experimental studies is essential especially in biosciences. Although there have been many such collaborations with Japanese and/or foreign laboratories, further efforts should be paid to enhance collaboration toward the establishment of molecular medicine. For example, Prof. Miyano (Lab. DNA information analysis) has started a new project for applying next-generation supercomputing techniques into the collaboration with RIKEN SNP center as the team leader of the data analysis fusion subproject in a big national project. Keeping such new trends of genome science in mind, the requirements for a new supercomputer system from 2009 are now under investigation.

(3) Members

Laboratory	Professor	Associate Prof.	Lecturer
Genome Detabase	Minoru Kanehisa		Toshiaki Katayama Shuichi Kawashima
DNA Information Analysis	Satoru Miyano	Seiya Imoto	Masao Nagasaki Rui Yamaguchi
Molecular Medicine	Yusuke Nakamura	Yataro Daigo	Kohichi Matsuda Hitoshi Zembutsu
Genome Technology			Rhuji Hamamoto
Sequence Analysis	Minoru Kanehisa	Seiichi Takasaki	Tetsuo Shibuya Michihiro Araki
Functional Genomics	Mark G. Lathrop	Ryo Yamada	
Functional Analysis in Silico	Kenta Nakai	Kengo Kinoshita	(Rui Yamashita)
Department of Public Policy		Kaori Muto	
Division of System Biomedical Technology		Noriko Goto	

Selected Publications

(Genome Database/Sequence Analysis)

Hu Z, Mellor J, Wu J, Kanehisa M, Stuart JM & DeLisi C. Toward scalable multidimensional maps of the cell. Nat. Biotech. 25, 547-554 (2007).

Kotera M, Okuno Y, Hattori M, Goto S & Kanehisa M. Computational assignment of the EC numbers for genomic-scale analysis of enzymatic reactions. J. Am. Chem. Soc. 126, 16487-16498 (2004).

Kanehisa M & Bork P. Bioinformatics in the post-sequence era. Nature Genetics 33, 305-310 (2003).

Kanehisa M, Araki M, Goto S, Hattori M, Hirakawa M, Itoh M, Katayama T, Kawashima S, Okuda S, Tokimatsu T, Yamanishi Y. KEGG for linking genomes to life and the environment. Nucleic Acids Res. 2008 Jan;36(Database issue):D480-4.

Kanehisa M, Goto S, Hattori M, Aoki-Kinoshita KF, Itoh M, Kawashima S, Katayama T, Araki M, Hirakawa M. From genomics to chemical genomics: new developments in KEGG. Nucleic Acids Res. 2006 Jan 1;34(Database issue):D354-7.

Murphy E, Rigoutsos I, Shibuya T, Shenk TE. Reevaluation of human cytomegalovirus coding potential. Proc Natl Acad Sci U S A. 2003 Nov 11;100(23):13585-90.

(DNA Information Analysis)

Hirose, O., Yoshida, R., Imoto, S., Yamaguchi, R., Higuchi, T., Charnock-Jones, D.S., Print, C., Miyano, S.. Statistical inference of transcriptional module-based gene networks from time course gene expression profiles by using state space models. Bioinformatics. 24(7): 932-942, 2008.

Yoshida, R., Higuchi, T., Imoto, S., Miyano, S.. ArrayCluster: an analytic tool for clustering, data visualization and module finder on gene expression profiles. Bioinformatics. 22(12):1538-1539, 2006.

De Hoon, Michiel J. L., Makita, Y., Nakai, K., Miyano, S.. Prediction of transcriptional terminators in Bacillus subtilis and related species. PLoS Computational Biology. 1(3): e25, 2005.

(Molecular Medicine)

M. Kubo, J. Hata, T. Ninomiya, K. Matsuda, K. Yonemoto, T. Nakano, T. Matsushita, K. Yamazaki, Y. Ohnishi, S. Saito, T. Kitazono, S. Ibayashi, K. Sueishi, M. Iida, Y. Nakamura, and Y. Kiyohara: A nonsynonymous SNP in PRKCH increases the risk of cerebral infarction. Nature Genetics, 39:212-217, 2007

The International HapMap Consortium:, A haplotype map of the human genome. Nature, 437:1299-1320, 2005

T. Kimura, S. Takeda, Y. Sagiya, M. Gotoh, Y. Nakamura and H. Arakawa: Impaired function of p53R2 in Rrm2b-null mice causes severe renal failure through attenuation of dNTP pools. Nature Genetics, 34:440-445, 2003

(Functional Analysis in Silico)

Sierro, N., Makita, Y., de Hoon, M., and Nakai, K., DBTBS: a database of transcriptional regulation in Bacillus subtilis containing upstream intergenic conservation information, Nucl. Acids Res. 36, D93-D96 (2008)

Tsuritani, K., Irie, T., Yamashita, R., Wakaguri, H., Kanai, A., Mizushima-Sugano, J., Sugano, S., Nakai, K., and Suzuki, Y., Distinct class of putative "non-conserved" promoters in humans: comparative studies of alternative promoters of human and mouse genes, Genome Res. 17(7), 1005-1014 (2007)

Kimura, K., Watanabe, A., Suzuki, Y., Ota, T., Nishikawa, T., Yamashita, R., Yamamoto, J., Sekine, M., Tsuritani, K., Ishii, S., Sugiyama, T., Saito, K., Isono, Y., Irie, R., Kushida, N., Yoneyama, T., Otsuka, R., Kanda, K., Yokoi, T., Kondo, H., Wagatsuma, M., Murakawa, K., Ishida, S., Ishibashi, T., Takahashi-Fujii, A., Tanase, T., Nagai, K., Kikuchi, H., Nakai, K., Isogai, T., and Sugano, S., Diversification of transcriptional modulation: large-scale identification and characterization of putative alternative promoters of human genes, Genome Res. 16, 55-65 (2006).

(Functional Genomics)

Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, Depner M, von Berg A, Bufe A, Rietschel E, Heinzmann A, Simma B, Frischer T, Willis-Owen SA, Wong KC, Illig T, Vogelberg C, Weiland SK, von Mutius E, Abecasis GR, Farrall M, Gut IG, Lathrop GM, Cookson WO. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007 Jul 26;448(7152):470-3.

Yamamoto K, Yamada R. Lessons from a genomewide association study of rheumatoid arthritis. N Engl J Med. 2007 Sep 20;357(12):1250-1.

Menzel S, Garner C, Gut I, Matsuda F, Yamaguchi M, Heath S, Foglio M, Zelenika D, Boland A, Rooks H, Best S, Spector TD, Farrall M, Lathrop M, Thein SL. A QTL influencing F cell production maps to a gene encoding a zinc-finger protein on chromosome 2p15. Nat Genet. 2007 Oct;39(10):1197-9.

(Department of Public Policy)

Ishiyama I, Nagai A, Muto K, Tamakoshi A, Kokado M, Mimura K, Tanzawa T, Yamagata Z. Relationship between public attitudes toward genomic studies related to medicine and their level of genomic literacy in Japan. Am J Med Genet A. 2008 Jul 1;146A(13):1696-706.

Muto K. Truth telling and predictive genetic testing - Huntington's Disease in Japan, In Predictive & Genetic Testing in Asia: social- science perspectives on the ramification of choice. (University of Amsterdam Press, The Netherlands), 2008 (in press).

(Division of System Biomedical Technology)

Murakami M, Iwai S, Hiratsuka S, Yamauchi M, Nakamura K, Iwakura Y, Shibuya M. Signaling of vascular endothelial growth factor receptor-1 tyrosine kinase promotes rheumatoid arthritis through activation of monocytes/macrophages. Blood. 2006 108(6):1849-56.

Yamamoto S, Yoshino I, Shimazaki T, Murohashi M, Hevner RF, Lax I, Okano H, Shibuya M, Schlessinger J, Gotoh N. Essential role of Shp2-binding sites on FRS2alpha for corticogenesis and for FGF2-dependent proliferation of neural progenitor cells. Proc Natl Acad Sci U S A. 2005 102(44):15983-8.

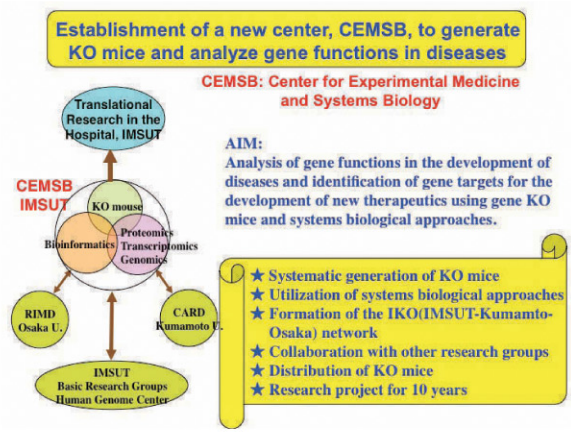
Gotoh N, Ito M, Yamamoto S, Yoshino I, Song N, Wang Y, Lax I, Schlessinger J, Shibuya M, Lang RA. Tyrosine phosphorylation sites on FRS2alpha responsible for Shp2 recruitment are critical for induction of lens and retina. Proc Natl Acad Sci U S A. 2004 Dec 7;101(49):17144-9.

Center for Experimental Medicine

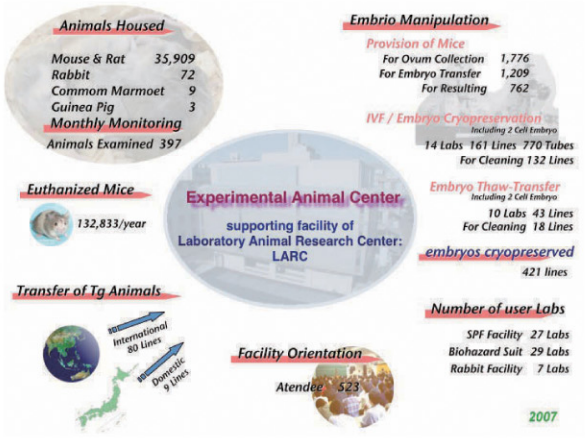
The Center for Experimental Medicine Director: Yoichiro Iwakura

The Laboratory Animal Research Center Director: Chieko Kai

(1) Objective and History



The recent development of transgenic techniques has made it possible to directly analyze the functions of a particular gene in a living animal. These techniques have also made it possible to produce various animal models for human diseases as well as tools to analyze pathogenic mechanisms. The Center for Experimental Medicine (CEM) was established in April of 1998 for a term of 10 years in order to facilitate the research in this field. We are also providing services such as generation, cryopreservation, and distribution of gene-manipulated mice, to researchers outside the CEM.



The Laboratory Animal Research Center (LARC) was established in 1965 in order to facilitate and modernize research using experimental animals. Initially, embryo manipulation techniques were developed in the LARC; IMSUT established CEM in 1998 to facilitate research using these techniques. The Amami Laboratory of Injurious Animals was also established in 1965, and is involved in breeding and studies on infectious diseases of primates. Stem cell biology is being studied in the Leading Project for Realization of Regenerative Medicine in close collaboration with the Laboratory of Stem Cell Therapy, CEM.

(2) Activity

1. Research activity of the CEM

Since CEM was established 10 years ago, we have established systems to generate gene-manipulated mice and to preserve frozen mouse embryos, and distributed these technologies to many laboratories both inside and outside of IMSUT. We have generated 178 lines of gene manipulated mice (138 KO and 40 transgenic (Tg); including collaboration), analyzed these gene functions in living animals, and published 382 original papers.

2. Research activity of the LARC

The LARC has been studying the molecular biology of mononegaviruses and published 30 original papers over the past 5 years. In these studies, Kai's group has established a novel system which allows generation of morbilliviruses and Nipah virus from cDNA and studied the roles of virus components and host factors in viral replication, pathogenicity and species specificity. They are developing attenuated and/or multivalent vaccines, using their novel techniques of genetic engineering.

3. Research activity of the Amami Laboratory of Injurious Animals

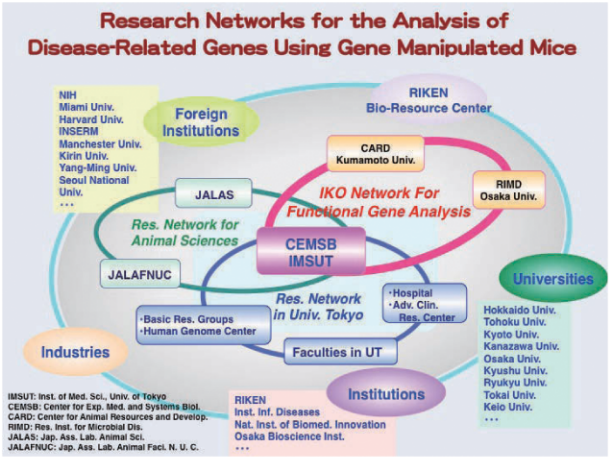
The Amami Laboratory of Injurious Animals has been equipped with BSL2 and BSL3 animal experiment rooms, and the pathogenicity of human infectious microorganisms that otherwise cannot be studied without the use of non-human primates is being studied.

4. Research activity of the Leading Project for Realization of Regenerative Medicine

In this project, they are trying to expand hematopoietic stem cells ex vivo, to identify tissue-specific stem cells, and to elucidate the mechanisms of stem cell regeneration.

5. Research supporting activity

The CEM has generated 106 gene manipulated mouse lines (102 KO, 4 Tg) in collaboration with researchers outside of our research center. The center has supplied disease models and research tool mice 634 times to 415 laboratories including 29 pharmaceutical companies (384 times inside Japan and 250 times to foreign countries).



In the LARC, more than 30,000 mice, mainly transgenics or knockouts, are kept for the researchers of IMSUT, and the technical staff support their breeding, cryopreservation of embryos, and microbiological cleaning of the infected mice. The Laboratory of Stem Cell Therapy also provides support for FACS analyses.

(3) Members

Laboratory	Professor	Associate Prof.	Lecturer
Department of Stem Cell Therapy (Laboratory of Stem Cell therapy Laboratory of Developmental Stem Cell Biology Laboratory of Stem Cell Regulation)	Hiromitsu Nakauchi	Ema Hideo Koichi Hattori	Koji Eto Makoto Otsu Akihide Kamiya Nobukazu Watanabe (Beate Heissig)

Laboratory	Professor	Associate Prof.	Lecturer
Cell Biology	Yoichiro Iwakura		Shigeyu Kakuta Shinobu Saijo Noriyuki Fujikado
Gene Expression & Regulation	Nobuaki Yoshida		Mitsuharu Sato Hirotake Ichise Taeko Ichise
Laboratory Animal Research Center	Chieko Kai		Misako Yoneda Hiroki Sato
Amami Laboratory of Injurious Animals	Chieko Kai	Shosuke Hattori	Takeshi Kuraishi

Selected Publications

(Stem Cell Therapy)

Choudhury AR, Ju Z, Djojosubroto MW, Schienke A, Lechel A, Schaetzlein S, Jiang H, Stepczynska A, Wang C, Buer J, Lee HW, von Zglinicki T, Ganser A, Schirmacher P, Nakauchi H, Rudolph KL. Cdkn1a deletion improves stem cell function and lifespan of mice with dysfunctional telomeres without accelerating cancer formation. Nature Genet. 39:99-105, 2007

Iwama A, Oguro H, Negishi M, Kato Y, Morita Y, Tsukui H, Ema H, Kamijo T, Yuko Kato-Fukui, Koseki H, van Lohuizen M, and Nakauchi H. Enhanced self-renewal of hematopoietic stem cells mediated by the polycomb gene product, Bmi-1. Immunity. 21: 843-51. 2004

Zhou S, et al. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nature Med 7:1028-34, 2001

Tadokoro Y, Ema H, Okano M, Li E, Nakauchi H. De novo DNA methyltransferase is essential for self-renewal, but not for differentiation, in hematopoietic stem cells. J Exp Med. 2007 Apr 16;204(4):715-22.

Ema H, Nakauchi H."Homing to Niche," a new criterion for hematopoietic stem cells? Immunity. 2004 Jan;20(1):1-2.

Iwama A, Oguro H, Negishi M, Kato Y, Morita Y, Tsukui H, Ema H, Kamijo T, Katoh-Fukui Y, Koseki H, van Lohuizen M, Nakauchi H. Enhanced self-renewal of hematopoietic stem cells mediated by the polycomb gene product Bmi-1. Immunity. 2004 Dec;21(6):843-51.

Jin DK, Shido K, Kopp HG, Petit I, Shmelkov SV, Young LM, Hooper AT, Amano H, Avecilla ST, Heissig B, Hattori K, Zhang F, Hicklin DJ, Wu Y, Zhu Z, Dunn A, Salari H, Werb Z, Hackett NR, Crystal RG, Lyden D, Rafii S. Cytokine-mediated deployment of SDF-1 induces revascularization through recruitment of CXCR4+ hemangiocytes. Nat Med. 2006 May;12(5):557-67.

Rafii S, Lyden D, Benezra R, Hattori K, Heissig B.Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? Nat Rev Cancer. 2002 Nov;2(11):826-35. Review.

Heissig B, Hattori K, Dias S, Friedrich M, Ferris B, Hackett NR, Crystal RG, Besmer P, Lyden D, Moore MA, Werb Z, Rafii S.Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand. Cell. 2002 May 31;109(5):625-37.

(Cell Biology)

Aujla, S. J., Fei, M., Pociask, D. A., Reinhart, T. A., Edeal, J., Gaus, K., Kreindler, J. L., Dubin, P. J., Zheng, M., Pilewski, J. M., Myerburg, M. M., Mason, C. A., Iwakura, Y., and Kolls, J. K. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nature Med., 14, 275-281 (2008).

Ohsugi, M., Adachi, K., Horai, R., Kakuta, S., Sudo, K., Kotaki, H., Tokai-Nishizumi, N., Sagara, H., Iwakura, Y., and Yamamoto, T. Kid-mediated chromosome compaction ensures proper nuclear envelope formation. Cell, 132, 771-782 (2008).

Fujikado, N., Saijo, S., Yonezawa, T., Shimamori, K., Ishii, A., Sugai, S., Kotaki, H., Sudo, K., Nose, M., and Iwakura, Y. Dcir deficiency causes development of autoimmune diseases in mice due to excess expansion of dendritic cells. Nature Med., 14, 176-180 (2008).

(Gene Expression & Regulation)

Honda ., Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, Shimada N, Ohba Y, Takaoka A, Yoshida N & Taniguchi T.IRF-7 is the master regulator of type-I interferon dependent immune responses. Nature. 434, 772- 777 (2005)

Yamazaki D, Suetsugu S, Miki H, Kataoka Y, Nishikawa S.-I, Fujiwara T, Yoshida N & Takenawa T. WAVE2 is required for directed cell migration and cardiovascular development. Nature 424, 452 – 456 (2003)

Fukami K, Nakao K, Inoue T, Kataoka Y, Nakamura K, Katsuki M, Yoshida N & Takenawa T. Requirement of phosholipase Cδ4 for the first step of fertilization. Science 292, 920-923 (2001)

(Laboratory Animal Research Center)

Hagiwara K, Sato H, Inoue Y, Watanabe A, Yoneda M, Ikeda F, Fujita K, Fukuda H, Takamura C, Kozuka-Hata H, Oyama M, Sugano S, Ohmi S, and Kai C. Phosphorylation of measles virus nucleoprotein upregulates the transcriptional activity of minigenomic RNA. Proteomics in press.

Sato H, Masuda M, Kanai M, Tsukiyama-Kohara K, Yoneda M and Kai C. Measles virus N protein inhibits host translation by binding to eIF3-p40. J Virol 81(21), 11569-11576, 2007.

Yoneda M, Guillaume V, Ikeda F, Sakuma Y, Sato H, Wild T F and Kai C. Establishment of Nipah virus rescue system. Proc Natl Acad Sci USA 103(44), 16508-16513, 2006.

(Amami Laboratory of Injurious Animals)

Zheng Y, Watanabe M, Kuraishi T, Hattori S, Kai C, Shibuya M.Chimeric VEGF-ENZ7/PlGF specifically binding to VEGFR-2 accelerates skin wound healing via enhancement of neovascularization. Arterioscler Thromb Vasc Biol. 2007 Mar;27(3):503-11.

Takahashi H, Hattori S, Iwamatsu A, Takizawa H, Shibuya M. A novel snake venom vascular endothelial growth factor (VEGF) predominantly induces vascular permeability through preferential signaling via VEGF receptor-1. J Biol Chem. 2004 Oct 29;279(44):46304-14.

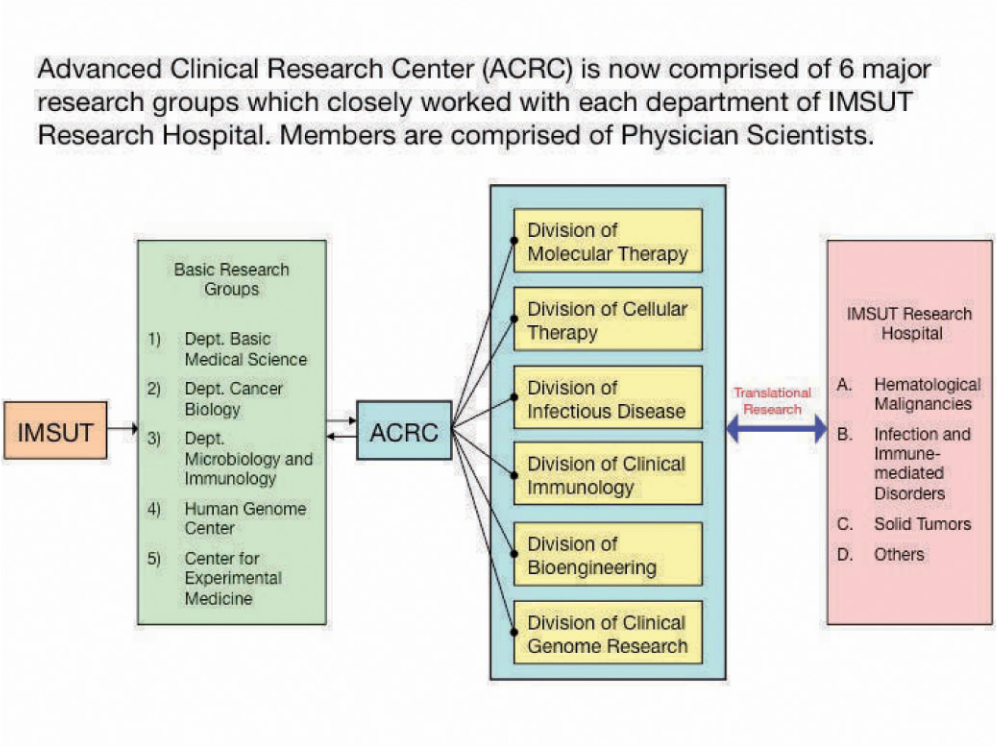
Sun Y, Nonobe E, Kobayashi Y, Kuraishi T, Aoki F, Yamamoto K, Sakai S. Characterization and expression of L-amino acid oxidase of mouse milk. J Biol Chem. 2002 May 24;277(21):19080-6

Advanced Clinical Research Center

Director: Motoharu Seiki

(1) The purpose and current status of the ACRC

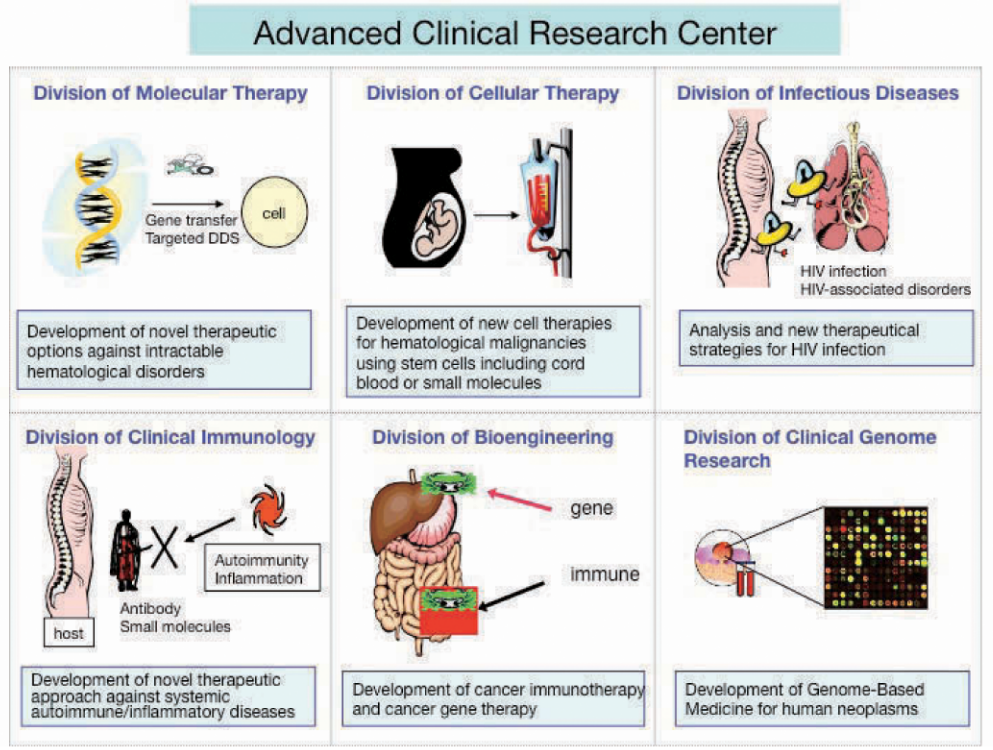
The Advanced Clinical Research Center (ACRC) was founded in the year 2000 and is comprised of research groups that collaborate with basic research groups to translate research products and concepts into clinical practice at the IMSUT Research Hospital. The ACRC also carries out clinical research on designated project diseases such as hematological malignancies, cancers, HIV/AIDS and Immune-mediated disorders. The ACRC aims to translate its own research outcomes into early clinical trials and also to undertake feedback experiments based on its own clinical experiences.



For this purpose, the ACRC attempts to develop novel therapies against the above disorders utilizing Genome medicine, cell therapy, gene therapy, and molecular targeting therapy. Moreover, each division performs research in order to utilize effectively the products and concepts of basic research for application at the bedside. In addition, each division performs their research to solve problems of the bedside as well as to propose ideas to the basic researchers based on bedside problems.

To accomplish this purpose, each division needs to work together closely and collaborate in parallel with basic researchers inside and outside the institute.

(2) Research synopsis of the ACRC



(3) Members

Division	Professor	Associate Prof.	Lecturer
Molecular Therapy	Arinobu Tojo	Satoshi Takahashi	Yasushi Suda Jun Ooi
Cellular Therapy	Toshio Kitamura	Kohichiro Tsuji	Toshiyuki Kawashima Jiro Kutaura
Infectious Diseases	Aikichi Iwamoto		Takeshi Fujii Tomohiko Koibuchi Ai Kawana-Tachikawa
Bioengineering	Hideaki Tahara	Kenji Nakano	Marimo Sato Masahisa Jinushi
Clinical Immunology	Chikao Morimoto	Hirotoshi Tanaka	Satoshi Iwata Hitroto Yamazaki Tadanori Yomochi
Clinical Genome Research	Yoichi Furukawa		Kiyoshi Yamaguchi

Selected Publications

(Melecular Therapy)

Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N, Oiwa-Monna M, Fukuno K, Uchiyama M, Takasugi K, Iseki T, Tojo A, Yamaguchi T, & Asano S. Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem cell transplantation from related donors in adult patients with hematological malignancies after myeloablative conditioning regimen. Blood. 109:1322-30, 2007

Takahashi S, Iseki T, Ooi J, Tomonari A, Takasugi K, Shimohakamada Y, Yamada T, Uchimaru K, Tojo A, Shirafuji N, Kodo H, Tani K, Takahashi T, Yamaguchi T, & Asano S.: Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematological malignancies. Blood, 104:3813-3820, 2004

Ooi J, Iseki T, Takahashi S, Tomonari A, Takasugi K, Shomohakamada Y. Yamada T, Ishii K, Ohno N, Nagamura F, Uchimaru K, Tojo A, & Asano S: Unrelated cord blood transplantation for adult patients with de novo acute myeloid leukemia. Blood, 103: 489-491, 2003

(Cellular Therapy)

Miyanishi M, Tada K, Koike M, Uchiyama Y, Kitamura T, & Nagata S. Identification of TIM4 as a phosphatidylserine receptor for engulfment of apoptotic cells. Nature 450, 435-440, 2007.

Ozawa T, Sako Y, Sato M, Kitamura T, & Umezawa Y. A genetic approach to identifying mitochondrial proteins. Nat Biotechnol 21, 287-293, 2003.

Minoshima Y, Kawashima T, Hirose K, Tonozuka Y, Kawajiri A, Bao Y-C, Deng X, Tatsuka M, Narumiya S, May WS Jr, Nosaka T, Senba K, Inoue T, Satoh T, Inagaki M, & Kitamura, T. Phosphorylation by Aurora B converts MgcRacGAP to a RhoGAP during cytokinesis. Dev Cell 4, 549-560, 2003.

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Furutsuki, T., Hosoya, N., Kawana-Tachikawa, A., Tomizawa, M., Odawara, T., Goto, M., Kitamura, Y., Nakamura, T., Kelleher, A.D., Cooper, D.A., and Iwamoto, A. Frequent transmission of CTL-escape HIV-1 in highly HLA-A24 -positive Japanese population. J. Virol. 78:8437-8445, 2004.

Kawana-Tachikawa, A., Tomizawa, M., Nunoya, J., Shioda, T., Kato, A., Nakayama, E.E., Nakamura, T., Nagai, Y., and Iwamoto, A. An efficient and versatile mammalian viral vector system for MHC class I/peptide complexes. J. Virol. 76:11982-11988, 2002.

Watanabe, N., Tomizawa, M., Tachikawa-Kawana, A., Goto, M., Ajisawa, A., Nakamura, T., and Iwamoto, A. Quantitative and qualitative abnormalities in HIV-1-specific T cells. AIDS 15:711-715, 2001.

(Bioengineering)

Kaiga T, Sato M, Kaneda H, Iwakura Y, Takayama T, and Tahara H. Systemic Administration of IL-23 Induces Potent Anti-tumor Immunity Primarily Mediated through Th1-type Response in Association with the Endogenously Expressed IL-12. J Immunol 178:7571-80, 2007

Wada S, Tsunoda T, Baba T, Primus FJ, Kuwano H, Shibuya M, Tahara H. Rationale for anti-angiogenic cancer therapy with vaccination using epitope peptides derived from human vascular endothelial growth factor receptor 2 (VEGFR2). Cancer Research, 65: 4939-4946, 2005.

Nakahara S, Tsunoda T, Baba T, Asabe S, Tahara H. Dendritic cells stimulated with a bacterial product, OK-432, efficiently induce cytotoxic T lymphocytes specific to tumor rejection peptide. Cancer Research 63:4112-8, 2003

(Clinical Immunology)

Shimizu N, Ouchida R, Yoshikawa N, Hisada T, Watanabe H, Okamoto K, Kusuhara M, Handa H, Morimoto C, Tanaka H. HEXIM1 forms a transcriptionally abortive complex with glucocorticoid receptor without involving 7SK RNA and positive transcription elongation factor b. Proc Natl Acad Sci U S A. 102, 8555-60(2005).

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Kobayashi S, Ohnuma K, Uchiyama M, Iino K, Iwata S, Dang NH, Morimoto C. Association of CD26 with CD45RA outside lipid rafts attenuates cord blood T-cell activation. Blood. 103, 1002-10(2004)

(Clinical Genome Research)

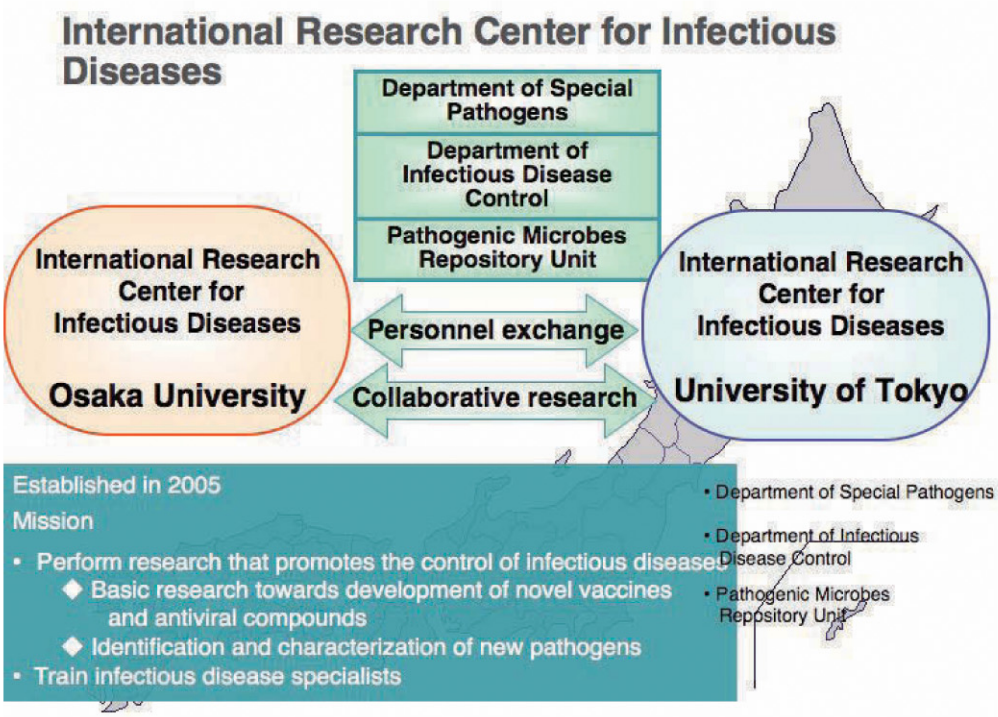
Tsuge M, Hamamoto R, Silva FP, Ohnishi Y, Chayama K, Kamatani N, Furukawa Y, & Nakamura Y. VNTR Polymorphism of E2F-1 binding element in the 5' flanking region of SMYD3 is a risk factor for human cancers. Nature Genet 37(10): 1104-1107, 2005

Hamamoto R, Furukawa Y, Morita M, Iimura Y, Silva FP, Li M, Yagyu R, & Nakamura Y. SMYD3 encodes a histone methyltransferase involved in the proliferation of cancer cells. Nature Cell Biol 6(8): 731-740, 2004

Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junien C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, & Matsumoto N. Heterozygous TGFBR2 mutations in Marfan syndrome. Nature Genet 36(8): 855-860, 2004

International Research Center for Infectious Diseases

Director: Yoshihiro Kawaoka



(1) Missions and history

SARS and avian influenza serve as warnings of the threats posed by emerging infectious diseases. The global impact of these and other emerging infectious diseases prompted the establishment of a research environment aimed at preventing and mitigating the consequences of global disease-causing agents. Although vaccines play a major role in the control of infectious diseases, basic research towards the identification of causative agents and the development of treatment measures are essential to managing emerging infectious diseases. Accordingly, academic institutions have a compelling responsibility to provide such information to be used to establish control measures by responsible government agencies.

In view of this, the Institute of Medical Sciences, University of Tokyo and the Research Institute for Microbial Diseases, Osaka University jointly established the International Research Center for Infectious Diseases in 2005, with the express purpose of training infectious disease specialists and undertaking research to promote the control of infectious diseases. As a foundation to this charge, the Center sponsors cutting edge biomedical research in infectious diseases, including the identification and characterization of new pathogens and the development of novel vaccines.

(2) Research activities and future perspectives

To accomplish the missions described above, the International Research Center for Infectious Diseases at the Institute of Medical Sciences, University of Tokyo comprises the following departments and units:

i. Department of Special Pathogens

Studies in this department focus on the control of known diseases caused by highly pathogenic organisms and on the characterization of newly emerging pathogens, in collaboration with scientists abroad.

ii. Department of Infectious Disease Control

Work undertaken by this department includes the development of measures for disease prevention, including vaccines, as well as the establishment of treatment regimens for infectious diseases that lack recognized therapies. This work is also conducted in collaboration with research centers located in other countries.

iii. Pathogenic Microbes Repository Unit

To promote research in infectious diseases, a pathogen repository is an essential resource. Therefore, the Pathogenic Microbes Repository Units of both the Institute of Medical Sciences, University of Tokyo and the Research Institute for Microbial Diseases, Osaka University have been centralized to promote operational efficiency.

To pursue our missions more efficiently, we have begun to establish nationwide and worldwide networks for research in infectious diseases. We have already established close relationships among the Department of Microbiology and Immunology in our institute, the international research center for infectious diseases in the institute for microbial diseases in Osaka University, and the IMSUT research center for infectious diseases in China. This effort will be extended to other research institutes in Japan and all over the world.

(3) Members

Department/Unit	Division	Professor	Associate Professor	Lecturer
Special Pathogens		Yoshihiro Kawaoka Chieko Kai		Kentaro Fujita Takeshi Kuraishi Takehsi Noda Hideaki Ebihara
Infectious Diseases Control		Chihiro Sasakawa Aikichi Iwamoto		
	Microbial Infection	Tetsuro Matano		Hiroaki Takeuchi
	Viral Infection		Yasushi Kawaguchi	
	Bacteriology		Ichiro Nakagawa	
Pathogenic Microbes Repository Unit		Chihiro Sasakawa Aikichi Iwamoto		Min Soo Kim

Selected Publications

(Department of Special Pathogens)

Yoneda, M., Guillaume, V., Ikeda, F., Sakuma, Y., Sato, H., Wild, T. F. and Kai, C. Establishment of a Nipah virus rescue system. Proc. Natl. Acad. Sci., USA, 103(44), 16508-16513, 2006.

Sato,H., Masuda, M., Kanai, M., Tsukiyama-Kohara, K., Yoneda, M. and Kai, C. Measles virus N protein inhibits host translation by binding to eIF3-p40. J. Virol., 81(21), 11569-11576, 2007.

Yamada S, Suzuki Y, Suzuki T, Le MQ, Nidom CA, Sakai-Tagawa Y, Muramoto Y, Ito M, Kiso M, Horimoto T, Shinya K, Sawada T, Kiso K, Usui T, Murata T, Lin Y, Hay A, Haire LF, Stevens DJ, Russell RJ, Gamblin SJ, Skehel JJ, Kawaoka Y. Hemagglutinin mutations responsible for the binding of H5N1 influenza A viruses to human-type receptors. Nature 444:378-382, 2006.

Darwyn K, Jones, SM, Shinya K, Kash JC, Copps J, Ebihara H, Hatta Y, Kim JH, Halfmann P, Hatta M, Feldmann F, Alimonti JB, Fernando L, Li Y, Katze MG, Feldmann H, Kawaoka Y. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. Nature 445:23, 2007.

(Department of Infectious Diseases Control)

Iwai H., Kim M., Yoshikawa Y., Ashida H., Ogawa M., Fujita Y., Muller D., Kirikae T., Jackson PK., Kotani, S. and Sasakawa C. A bacterial effector targets Mad2L2, an APC inhibitor, to modulate host cell cycling. Cell. 130: 611-623. 2007.

Handa Y., Suzuki M., Ohya K., Iwai H., Ishijima N., Koleske AJ., Fukui Y. and Sasakawa C. Shigella IpgB1 promotes bacterial entry through the ELMO–Dock180 machinery. Nat Cell Biol. 9: 121-128. 2007.

Fujii T, Nakamura T, Iwamoto A. Pneumocystis pneumonia in patients with HIV infection: clinical manifestations, laboratory findings, and radiological features. J Infect Chemother. 2007 13:1-7.

Hosoya N, Miura T, Kawana-Tachikawa A, Koibuchi T, Shioda T, Odawara T, Nakamura T, Kitamura Y, Kano M, Kato A, Hasegawa M, Nagai Y, Iwamoto A. Comparison between Sendai virus and adenovirus vectors to transduce HIV-1 genes into human dendritic cells. J Med Virol. 2008 80:373-82.

(Division of Microbial Infection)

Kawada, M., Tsukamoto, T., Yamamoto, H., Takeda, A., Igarashi, H., Watkins, D.I., and Matano, T. Long-term control of simian immunodeficiency virus replication with central memory CD4+ T-cell preservation after non-sterile protection by a cytotoxic T lymphocyte-based vaccine. J. Virol. 81:5202-5211, 2007.

Matano, T., Kobayashi, M., Igarashi, H., Takeda, A., Nakamura, H., Kano, M., Sugimoto, C., Mori, K., Iida, A., Hirata, T., Hasegawa, M., Yuasa, T., Miyazawa, M., Takahashi, Y., Yasunami, M., Kimura, A., O'Connor, D.H., Watkins, D.I., and Nagai, Y. Cytotoxic T lymphocyte-based control of simian immunodeficiency virus replication in a preclinical AIDS vaccine trial. J. Exp. Med. 199:1709-1718, 2004.

(Division of Viral Infection)

T. Satoh, J. Arii, T. Suemaga, J. Wang, A. Kogure, J. Uehori, N. Arase, I. Shiratori, S. Tanaka, T. Satoh, J. Arii, T. Suemaga, J. Wang, A. Kogure, J. Uehori, N. Arase, I. Shiratori, S. Tanaka, Y. Kawaguchi, P. G. Spear, L. L. Lanier and H. Arase. (2008) PILRa is a herpes simplex-1 entry co-receptor that associates with glycoprotein B. Cell 132: 1-10.

Asai, A. Kato, K. Kato, M. Kanamori-Koyama, K. Sugimoto, T. Sairenji, Y. Nishiyama, and Y. Kawaguchi. (2006) Epstein-Barr Virus Protein Kinase BGLF4 Is a Virion Tegument Protein That Dissociates From Virions in a Phosphorylation Dependent Process and Phosphorylates the Viral Immediate-Early Protein BZLF1. J. Virol. 80: 5125-5134.

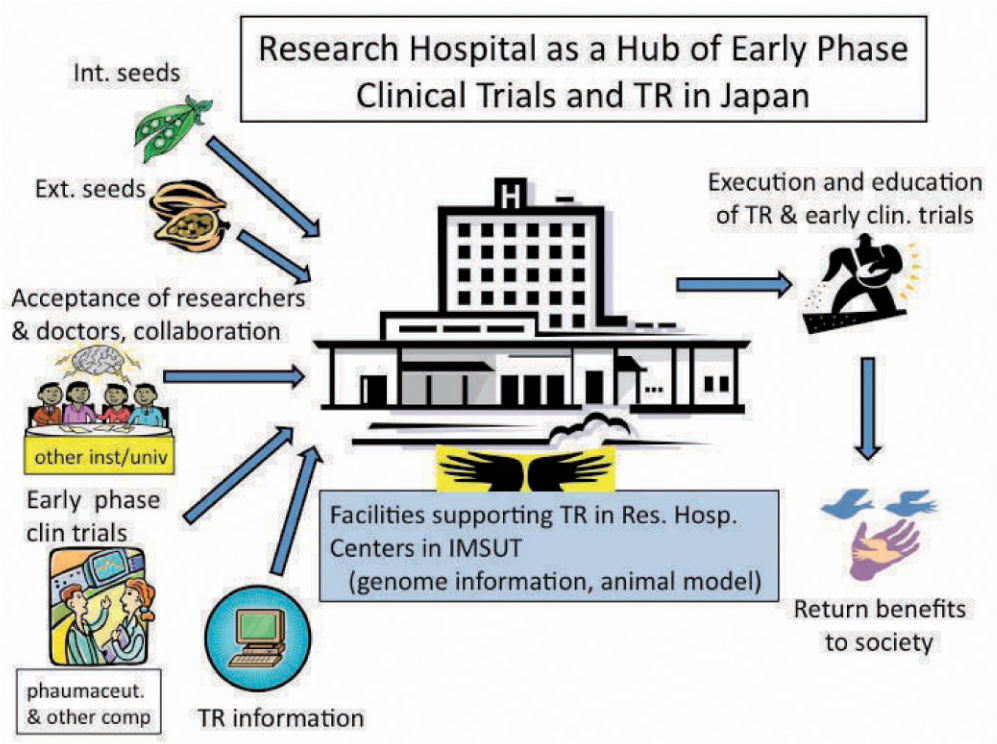
(Division of Bacteriology)

Kato T, Kawai S., Nakano K, Inaba H., Kuboniwa M, Nakagawa I., Tsuda K., Omori H, Ooshima, T., Yoshimori T, Amano A. (2007). Virulence of Porphyromonas gingivalis is altered by substitution of fimbria gene with different genotype. Cell Microbiol. 9:753-65..

Nakagawa, I., Amano, A., Mizushima, N., Yamamoto, A., Yamaguchi, H., Kamimoto, T., Nara, A., Funao J, Nakata M, Tsuda K, Hamada S, Yoshimori T. (2004) Autophagy defends cells against invading group A Streptococcus. Science. 2004 306: 1037-40.

Research Hospital

Director: Naohide Yamashita



(1) Summary of the Research Hospital

Research Hospital is located in the campus of the Institute of Medical Science, the University of Tokyo. The aim of Research Hospital is to develop new therapies against intractable diseases. To accomplish this we have the following three philosophies.

1. We treat patients in a warmhearted fashion and perform total care.
2. We develop new therapies based on ethics, science and safety.
3. We respect the rights of the patients as much as possible by providing clarity.

Since its initially establishment as a hospital to treat infectious diseases, Research Hospital has applied the products obtained through basic research toward the development of new therapies and has made fruitful results, including the production of vaccines against microorganism, bone marrow transplantation against leukemia, and the discovery as well as clinical application of granulocyte colony-stimulating factor. To perform stem cell transplantation using cord blood, the bank of cord blood cell was necessary. Therefore Research Hospital pioneered a model public cord blood cell bank in a building of the hospital ten years ago.

(2) Research activities and future plans

We are carrying out hematopoietic stem cell transplantation using cord blood cells in adult leukemia patients. The number of cord blood cell transplantations (CBT) is increasing year by year and the clinical outcome is quite excellent in comparison with other institutions/hospitals. The reasons for excellent results are being investigated in

collaboration with other institutes/hospitals.

Clinical studies (translational research) that have been performed recently include GM-CSF gene therapy against renal cell carcinoma, regeneration of alveolar bones using auto bone marrow stem cells, and active immune therapy against HIV infection. The following subjects are current candidates for translational research. They are aimed toward progress to phase 1 clinical trials supported by pharmaceutical companies within 5 years.

(1) Treatment of malignant mesothelioma using anti-CD26 antibody
(2) Suppression of GVHD using selective amplification of regulatory T cells
(3) Effective diagnosis of genetic colon cancers without polyposis
(4) Cancer immunotherapy against malignancies using domestic viral vectors
(5) Generation of platelets from human ES cells and its clinical application
(6) Treatment of hemophilia-related osteo-arthropathy using auto bone marrow mesenchymal stem cells
(7) Identification of new inhibitors against JAK-STAT
(8) Treatment of ischemia using cord blood cells

Subjects shown in (7) and (8) were proposed from universities other than the Institute of Medical Science (external seeds).

(3)Members

Department	Professor	Associate Prof.	Lecturer
Advanced Medical Science	Nahohide Yamashita		Takeshi Nakaoka Nayuki Iso-O Hideaki Ohno Tokumitsu Watanabe
Hematology/Oncology	Arinobu Tojo	Satoshi Takahashi Kaoru Uchimaru	Jun Ooi Yasushi Soda Koichiro Yuji Nobuhiro Ohno Nobuhiro Ysukada
Infectious Diseases Control & Applied Immunology	Aikichi Iwamoto		Takashi Odawara Tokiomi Endo
Rheumatology and Allergy	Chikao Morimoto	Hirotoshi Tanaka	Osamu Hosono Hiroshi KAwasaki Kei Ohnuma Nirotada Yoshikawa
Pediatric Hematology-Oncology		Koichiro Tsuji	Yasuhiro Ebihara
Surgery	Hideaki Tahara	Masaru Shinozaki Kenji Nakano	Akihiko Itoh Akira Kanamoto Masahisa Jinushi Giichiro Tsurita keisuke Hata
Radiology		Yusuke Inoue	Shigeru Kiryu Makoto Watanabe

Department	Professor	Associate Prof.	Lecturer
Applied Genomics	Yoichi Furukawa Yoshinori Murakami		Naoyuki Tahakashi
Clinical Trial Safety Management	Nahohide Yamashita	Fumitaka Nagamura	Seiichiro Kobayashi
Cell Processing and Transfusion	Arinobu Tojo		Takiko Nagamura-Inoue
Laboratory Medicine		Naoki Oyaizu	
Surgical Center		Mieko Chinzei	Sashiko Imamura
Core Favilities for Therapeutic Vectors	Hideaki Tahara		Hisako Katano
Exploratory Research (Ain Pharmaciez)		Masahiro Kami	Yuji Tanaka Tomoko Matsumura

Selected Publications

(Advanced Medical Science)

Fujita, S., Sato, Y., Sato, K., Eizumi, K., Fukaya, T., Kubo, M., Yamashita, N. and Sato, K. Regulatory dendritic cells protect against cutaneous chronic graft-versus-host disease mediated through CD4+CD25+Foxp3+ regulatory T cells. Blood 110: 3793-3803, 2007

Fujita, S., Seino, K., Sato, K., Sato, Y., Eizumi, K., Yamashita, N., Taniguchi, M., and Sato, K. Regulatory dendritic cells act as regulators of acute lethal systemic inflammatory response. Blood, 107:3656-64, 2006

Sato, K., Yamashita, N., Yamashita, N., Baba, M. and Matsuyama, T. Regulatory dendritic cells protect mice from murine acute graft-versus-host disease and leukemia relapse. Immunity. 18:367-79, 2003

(Hematology/Oncology)

Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N, Oiwa-Monna M, Fukuno K, Uchiyama M, Takasugi K, Iseki T, Tojo A, Yamaguchi T, & Asano S. Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem cell transplantation from related donors in adult patients with hematological malignancies after myeloablative conditioning regimen. Blood. 109:1322-30, 2007

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Ooi J, Iseki T, Takahashi S, Tomonari A, Takasugi K, Shomohakamada Y. Yamada T, Ishii K, Ohno N, Nagamura F, Uchimaru K, Tojo A, & Asano S: Unrelated cord blood transplantation for adult patients with de novo acute myeloid leukemia. Blood, 103: 489-491, 2003

(Infectious Diseases Control & Applied Immunology)

Yamada T, Watanabe N, Nakamura T, Iwamoto A.
Antibody-dependent cellular cytotoxicity via humoral immune epitope of Nef protein expressed on cell surface.J Immunol. 2004 Feb 15;172(4):2401-6.

Tani K, Azuma M, Nakazaki Y, Oyaizu N, Hase H, Ohata J, Takahashi K, OiwaMonna M, Hanazawa K, Wakumoto Y, Kawai K, Noguchi M, Soda Y, Kunisaki R, Watari K, Takahashi S, Machida U, Satoh N, Tojo A, Maekawa T, Eriguchi M, Tomikawa S, Tahara H, Inoue Y, Yoshikawa H, Yamada Y, Iwamoto A, Hamada H, Yamashita N, Okumura K, Kakizoe T, Akaza H, Fujime M, Clift S, Ando D, Mulligan R, Asano S. Phase I study of autologous tumor vaccines transduced with the GM-CSF gene in four patients with stage IV renal cell cancer in Japan: clinical and immunological findings. Mol Ther. 2004 Oct;10(4):799-816.

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(Rheumatology and Allergy)

Shimizu N, Ouchida R, Yoshikawa N, Hisada T, Watanabe H, Okamoto K, Kusuhara M, Handa H, Morimoto C, Tanaka H. HEXIM1 forms a transcriptionally abortive complex with glucocorticoid receptor without involving 7SK RNA and positive transcription elongation factor b. Proc Natl Acad Sci U S A. 102, 8555-60(2005).

Ohnuma K, Yamochi T, Uchiyama M, Nishibashi K, Yoshikawa N, Shimizu N, Iwata S, Tanaka H, Dang NH, Morimoto C. CD26 up-regulates expression of CD86 on antigen-presenting cells by means of caveolin-1. Proc. Natl. Acad. Sci. USA. 101, 14186-91(2004).

Kobayashi S, Ohnuma K, Uchiyama M, Iino K, Iwata S, Dang NH, Morimoto C. Association of CD26 with CD45RA outside lipid rafts attenuates cord blood T-cell activation. Blood. 103, 1002-10(2004)

(Surgery)

Kaiga T, Sato M, Kaneda H, Iwakura Y, Takayama T, and Tahara H. Systemic Administration of IL-23 Induces Potent Anti-tumor Immunity Primarily Mediated through Th1-type Response in Association with the Endogenously Expressed IL-12. J Immunol 178:7571-80, 2007

Wada S, Tsunoda T, Baba T, Primus FJ, Kuwano H, Shibuya M, Tahara H. Rationale for anti-angiogenic cancer therapy with vaccination using epitope peptides derived from human vascular endothelial growth factor receptor 2 (VEGFR2). Cancer Research, 65: 4939-4946, 2005.

Nakahara S, Tsunoda T, Baba T, Asabe S, Tahara H. Dendritic cells stimulated with a bacterial product, OK-432, efficiently induce cytotoxic T lymphocytes specific to tumor rejection peptide. Cancer Research 63:4112-8, 2003

(Applied Genomics)

Silva FP, Hamamoto R, Kunizaki M, Tsuge M, Nakamura Y, Furukawa Y. Enhanced methyltransferase activity of SMYD3 by the cleavage of its N-terminal region in human cancer cells. Oncogene. 2008 Apr 24;27(19):2686-92.

Kidokoro T, Tanikawa C, Furukawa Y, Katagiri T, Nakamura Y, Matsuda K. CDC20, a potential cancer therapeutic target, is negatively regulated by p53. Oncogene. 2008 Mar 6;27(11):1562-71.

Kunizaki M, Hamamoto R, Silva FP, Yamaguchi K, Nagayasu T, Shibuya M, Nakamura Y, Furukawa Y. The lysine 831 of vascular endothelial growth factor receptor 1 is a novel target of methylation by SMYD3. Cancer Res. 2007 Nov 15;67(22):10759-65.

(Pediatric Hematology-Oncology)

Shinoda G, Umeda K, Heike T, Arai M, Niwa A, Ma F, Suemori H, Luo HY, Chui DH, Torii R, Shibuya M, Nakatsuji N, Nakahata T. alpha4-Integrin(+) endothelium derived from primate embryonic stem cells generates primitive and definitive hematopoietic cells. Blood. 2007 Mar 15;109(6):2406-15.
Masuya M, Moussa O, Abe T, Deguchi T, Higuchi T, Ebihara Y, Spyropoulos DD, Watson DK, Ogawa M. Dysregulation of granulocyte, erythrocyte, and NK cell lineages in Fli-1 gene-targeted mice. Blood. 2005 Jan 1;105(1):95-102.
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(Radiology)
Abe O, Yamasue H, Aoki S, Suga M, Yamada H, Kasai K, Masutani Y, Kato N, Kato N, Ohtomo K. Aging in the CNS: comparison of gray/white matter volume and diffusion tensor data. Neurobiol Aging. 2008 Jan;29(1):102-16.
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(Laboratory Medicine)
Nagayama S, Fukukawa C, Katagiri T, Okamoto T, Aoyama T, Oyaizu N, Imamura M, Toguchida J, Nakamura Y.Therapeutic potential of antibodies against FZD 10, a cell-surface protein, for synovial sarcomas.Oncogene. 2005 Sep 15;24(41):6201-12.
Yoshiura K, Nakaoka T, Nishishita T, Sato K, Yamamoto A, Shimada S, Saida T, Kawakami Y, Takahashi TA, Fukuda H, Imajoh-Ohmi S, Oyaizu N, Yamashita N.
Carbonic anhydrase II is a tumor vessel endothelium-associated antigen targeted by dendritic cell therapy. Clin Cancer Res. 2005 Nov 15;11(22):8201-7.
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Medical Proteomics Laboratory

Professor: Jun-ichiro Inoue, Ph.D.
Associate Professor: Shinobu Imajoh-Ohmi, Ph.D.
Assistant Professor: Hiroshi Sagara, Ph.D.
Project Assistant Professor: Masaaki Oyama, Ph.D.

(1) Mission:

Development of proteomics technology for systematic understanding of diseases.

(2) Overview:

Proteins play important roles in cellular activities and their individual malfunctioning leads to a variety of diseases. Although recent advances in genomics technology have enabled us to obtain a comprehensive view of disease-related genes at the genome and transcriptome level, a systematic view of their translated proteins is yet to be fully described. Advanced technologies in molecular imaging and mass spectrometry greatly help us to analyze complex cellular systems or mechanisms controlled by dynamic behaviors of these cellular proteins. The overall view of functional protein networks through these technologies would substantially contribute to systematic understanding of the regulatory mechanisms that give rise to each biological effect.

Laboratory Head:
Jun-ichiro Inoue

(3) Staff:

Laboratory	Professor	Associate Prof.	Lecturer
Medical Proteomic Laboratory	Jun-ichiro Inoue		
Proteomics Information Analysis Group I (Medical Proteomics Laboratory)		Shinobu Imajoh-Ohmi	
Proteomics Information Analysis Group II (Medical Proteomics Laboratory)			Masaaki Oyama
Fine Structure Analysis Group (Medical Proteomics Laboratory)			Hiroshi Sagara

(4) Research Emphasis:

The mission of our laboratory is to develop technologies for protein research that enable us to analyze complex cellular systems leading to a variety of diseases such as cancer and infection. We mainly focus on research endeavors to develop advanced technologies regarding mass spectrometry and electron microscopy for precise measurement of dynamic behaviors of functional proteins, also In addition, we provide support for various protein biochemical analyses including peptide synthesis.

Selected Publications

(Proteomics Information Analysis Group I)

Xiang Y, Sekine T, Nakamura H, Imajoh-Ohmi S, Fukuda H, Yudoh K, Masuko-Hongo K, Nishioka K, Kato T. Fibulin-4 is a target of autoimmunity predominantly in patients with osteoarthritis. J Immunol. 2006 Mar 1;176(5):3196-204.

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(Proteomics Information Analysis Group II)

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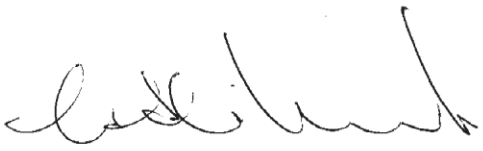
Postscript

In the process of preparing for the external review of this year, we learned a lot about ourselves. Before the review committee even convened, we somehow found, albeit subjectively, how productive we have been over the last few years and where the Institute stands During the days of the committee meeting itself, we explained to the reviewers what we are and discussed our most pressing challenges today and down the road. Discussion is vital here too, just as it is in research; only through discussion can we formulate what we should do next. Thank to the reviewers, the summary of the discussion is provided in the form of a report based on objective analysis. The report carries great weight, because it is summarized as a consensus of leading scientists from different research fields and different nations. With great appreciation to the reviewers, we will turn to this report as a critical guide for strengthening our Institute.



June 26, 2008.

Tadashi Yamamoto

Chair of the Preparation Committee
for External Review of IMSUT